Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Platelet-Aggregation Inhibitors
AHFS Class 201218
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I. Overview

Platelet-aggregation inhibitors, also known as antiplatelet agents, play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases.[1-3] Antiplatelet agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes, angina, intermittent claudication, myocardial infarction, stroke and transient ischemic attack. The antiplatelet agents are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. National and international treatment guidelines recommend them either as monotherapy or in combination therapy depending on the patient's risk for thromboembolic events.[4-21]

The platelet-aggregation inhibitors exert their pharmacologic effects through several different mechanisms of action. Aspirin irreversibly inhibits platelet cyclooxygenase-1.[1-3] Inhibition of this enzyme prevents the formation of thromboxane A2 from arachidonic acid and leads to a reduction in platelet activation. While aspirin also exhibits analgesic, anti-inflammatory and antipyretic activity, this review focuses primarily on its antiplatelet properties.

In addition to thromboxane A2, platelets also produce adenosine diphosphate (ADP). The attachment of ADP to receptors on the surface of platelets causes them to aggregate. The thienopyridines, ticlopidine and clopidogrel, block the ADP receptors, preventing the attachment of ADP and subsequent platelet adhesion and aggregation.[1-3] The mechanism of action for dipyridamole is not completely elucidated but may involve its ability to increase concentrations of adenosine, which is a platelet-aggregation inhibitor and coronary vasodilator, and of cyclic adenosine monophosphate (cAMP), which decreases platelet activation. Cilostazol and its active metabolites inhibit phosphodiesterase activity and suppress degradation of cAMP in platelets and blood vessels.

Table 1 lists all of the platelet-aggregation inhibitors included in this review. Aspirin, cilostazol, dipyridamole and ticlopidine are available generically. Aspirin is also available over-the-counter. This review encompasses all dosage forms and strengths.

Table 1. Platelet-Aggregation Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
aspirin	chewable tablet, delayed-release tablet, enteric-coated tablet, packet, rectal suppository, sustained-release tablet, tablet	Ecotrin®*‡, Ninoprin®*‡, St. Joseph Aspirin®*‡, Stanback Analgesic®‡, Tasprin®*‡, Zorprin®*	aspirin
aspirin and dipyridamole	extended-release capsule	Aggrenox®	none
cilostazol	tablet	Pletal®*	cilostazol
clopidogrel	tablet	Plavix®	none
dipyridamole	injection, tablet	Persantine®*, Persantine IV®*	dipyridamole
ticlopidine	tablet	Ticlid®*	ticlopidine

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.

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II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the platelet-aggregation inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Platelet-Aggregation Inhibitors

Clinical Guideline	Recommendation
American Heart Association (AHA)/American Stroke Association (ASA) Council on Stroke: **Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack (2006)**[4]	Antithrombotic Therapy for Noncardioembolic Stroke or Transient Ischemic Attack (TIA) (Specifically Atherosclerosis, Lacunar, or Cryptogenic Infarcts) • For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulants are recommended to reduce the risk of recurrent stroke and other cardiovascular events. Aspirin (50 to 325 mg/day), the combination of aspirin and extended-release (ER) dipyridamole, and clopidogrel are all acceptable options for initial therapy. • Compared with aspirin alone, both the combination of aspirin and ER dipyridamole and clopidogrel are safe. The combination of aspirin and ER dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations about choices between antiplatelet options other than aspirin. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, tolerance, and other clinical characteristics. • The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients. • For patients allergic to aspirin, clopidogrel is reasonable. • For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been studied in patients who have had an event while receiving aspirin.
Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy: **Antithrombotic and Thrombolytic Therapy for Ischemic Stroke (2004)**[5,6]	Acute Ischemic Stroke • Early (within 48 hours of stroke onset) aspirin therapy, 160-325 mg once daily (QD), is recommended for patients with ischemic stroke who are not receiving thrombolysis. Noncardioembolic TIA or Stroke • To prevent cerebral ischemic events, an antiplatelet agent is recommended and acceptable options for initial therapy include aspirin 50-325 mg QD; the combination of aspirin 25 mg and ER dipyridamole 200 mg twice daily (BID); or clopidogrel 75 mg QD. • Low doses of aspirin, 50-100 mg QD, are recommended in patients receiving aspirin who are at moderate-to-high risk of bleeding complications. • The authors suggest use of the combination of aspirin and ER dipyridamole 25/200 mg BID over aspirin, and clopidogrel over aspirin. • Clopidogrel is recommended in patients who are allergic to aspirin. • Antiplatelet agents are recommended over oral anticoagulation for most patients with noncardioembolic TIA or stroke. • Oral anticoagulation is suggested over antiplatelet agents in patients with well-documented prothrombotic disorders. Carotid Endarterectomy • Aspirin 81-325 mg QD, prior to and following the procedure, is recommended to prevent cerebral ischemic events.
American College of Cardiology (ACC)/American	Early Hospital Care • Aspirin should be administered as soon as possible after hospital presentation and

Clinical Guideline	Recommendation
Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[7]	continued indefinitely in patients not known to be intolerant of that medication. • Clopidogrel should be administered to unstable angina (UA)/non–ST-elevation myocardial infarction (NSTEMI) patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. • In patients with a history of gastrointestinal bleeding, when aspirin and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (eg, proton-pump inhibitors) should be prescribed concomitantly. • In patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel or an intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitor. • In patients in whom an early initial conservative (eg, noninvasive) strategy is selected, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month and ideally up to 1 year. • In patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. Either an IV GP IIb/IIIa inhibitor or clopidogrel should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). • For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, or who undergo stress testing and are determined to be "low risk", continue aspirin indefinitely. Continue clopidogrel for at least 1 month and ideally up to 1 year. • For patients in whom coronary artery bypass graft (CABG) surgery is selected, continue aspirin. Discontinue clopidogrel 5-7 days before elective CABG. • For patients in whom percutaneous coronary intervention (PCI) is selected, continue aspirin. Administer a loading dose of clopidogrel if not started before diagnostic angiography. • For patients in whom medical therapy is selected after angiography and in whom no significant obstructive coronary artery disease (CAD) was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. For patients in whom evidence of coronary atherosclerosis is present (albeit without flow-limiting stenoses), long-term treatment with aspirin and other secondary prevention measures should be prescribed. • For patients in whom medical therapy is selected after angiography and in whom CAD was found on angiography, continue aspirin. Administer a loading dose of clopidogrel if not given before diagnostic angiography. • For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, continue aspirin indefinitely. Continue clopidogrel for at least 1 month and ideally up to 1 year. <u>Long-Term Medical Therapy and Secondary Prevention</u> • For patients treated medically without stenting, aspirin (75-162 mg per day) should be prescribed indefinitely. Clopidogrel (75 mg per day) should be prescribed for at least 1 month and ideally for up to 1 year. For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. For clopidogrel-allergic patients, use ticlopidine (250 mg twice daily). • For UA/NSTEMI patients treated with bare-metal stents, aspirin 162-325 mg per day should be prescribed for at least 1 month, and then continued indefinitely at a dose of 75-162 mg per day. Clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding, then it should be given for a minimum of 2 weeks). • For UA/NSTEMI patients treated with drug-eluting stents (DES), aspirin 162-325

Clinical Guideline	Recommendation
	mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75-162 mg per day. Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES. • Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors).
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS) (2007)[8]**	• Aspirin is recommended for all patients presenting with NSTE ACS without contraindication at an initial loading dose of 160-325 mg (nonenteric), and at a maintenance dose of 75-100 mg long term. • For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily. Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding. • For all patients with contraindication to aspirin, clopidogrel should be given instead. • In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function. • In patients pretreated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible. • Nonsteroidal anti-inflammatory agents should not be administered with aspirin or clopidogrel. • Interruption of dual antiplatelet therapy with aspirin and clopidogrel during the first 12 months after the initial event is not recommended unless severe, life-threatening bleeding occurs, or surgery is to be performed during which minor bleeding may result in serious consequences.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)[9]**	• Aspirin should be started at 75-162 mg per day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)[10]**	<u>Therapy to Improve Prognosis</u> • Aspirin 75 mg daily is recommended in all patients without specific contraindications (eg, active gastrointestinal bleeding, aspirin allergy or previous aspirin intolerance). Clopidogrel is an alternative antiplatelet agent in patients who cannot take aspirin. • The use of unopposed cyclooxygenase (COX)-2 inhibition is not recommended in patients with stable angina pectoris. • Clopidogrel may be combined with aspirin after coronary stenting or an acute coronary syndrome for a finite period of time, but combination therapy is currently not recommended in stable angina pectoris. • Dipyridamole is not recommended for antithrombotic treatment of stable angina.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) (2007)[11]**	<u>Initial and Hospital Management</u> • Oxygen, morphine, nitroglycerin, angiotensin-converting enzyme inhibitors, ß-blockers, and aspirin may be used in patients presenting with a myocardial infarction. Patients should be considered for reperfusion therapy. • Patients undergoing facilitated PCI may be treated with high dose aspirin, platelet GP IIb/IIIa inhibitors, and/or fibrinolytic therapy. • Clopidogrel 75 mg/day should be initiated with aspirin and continued for 14 days regardless of whether reperfusion is performed. • In patients <75 years of age who receive fibrinolytic therapy or who do not receive

Clinical Guideline	Recommendation
	reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel 300 mg (no data are available to guide decision making regarding an oral loading dose in patients 75 years of age or older). • In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days and preferably for 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. <u>Secondary Prevention</u> • Aspirin therapy is recommended for all patients post-PCI STEMI without aspirin resistance, allergy or increased risk of bleeding at a daily dose of 162-325 mg for at least 1 month after bare metal stent (BMS) implantation, 3 months for sirolimus-eluting stent placement, and 6 months after paclitaxel-eluting stent placement. Thereafter, aspirin should be continued indefinitely at 75-162 mg daily. In patients at risk of bleeding, 75-162 mg daily aspirin is reasonable during the initial period after stent implantation. • Clopidogrel 75 mg daily should be given to all post-PCI patients who receive a DES for at least 12 months, and for a minimum of 1 month and ideally up to 12 months after placement of a BMS (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). • Clopidogrel should be given for at least 14 days to patients not undergoing stent placement (medical therapy alone or PTCA without stenting). • Long-term therapy with clopidogrel 75 mg/day (eg, 1 year) is reasonable in patients regardless of whether or not they receive reperfusion therapy. • Initiating and managing warfarin to an international normalized ratio (INR) of 2.0-3.0 is recommended in post-myocardial infarction patients with atrial fibrillation or flutter when clinically indicated. When therapy with aspirin, clopidogrel, and warfarin is indicated, an INR of 2.0-2.5 is recommended.
National Institute for Health and Clinical Excellence (NICE): **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[12]	• Aspirin is recommended in all patients after a myocardial infarction and should be continued indefinitely. Clopidogrel should not be offered as first-line monotherapy after a myocardial infarction. • Clopidogrel combined with low-dose aspirin for 12 months is recommended in patients who have had a non-ST-segment-elevation acute coronary syndrome who are at moderate-to-high risk of myocardial infarction or death. Thereafter, patients may be treated with low-dose aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy. • Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an ST-segment-elevation myocardial infarction should continue on dual antiplatelet therapy for at least 4 weeks. Thereafter, low-dose aspirin should be continued and clopidogrel discontinued in the absence of indication for dual antiplatelet therapy. • If both clopidogrel and aspirin were not given during the acute phase of a myocardial infarction, this combination should not routinely be initiated. • Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months after an acute myocardial infarction unless another indication for dual antiplatelet therapy exists. After an ST-segment-elevation myocardial infarction, the combination of aspirin and clopidogrel is usually recommended for a shorter duration than 12 months. • Clopidogrel monotherapy is an alternative treatment in patients with aspirin hypersensitivity. • Low-dose aspirin and a proton-pump inhibitor are recommended in patients with comorbid dyspepsia. A full-dose proton-pump inhibitor and low-dose aspirin should be considered in patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori.* • Patients being treated with warfarin for another indication should continue on

Clinical Guideline	Recommendation
	warfarin. Those being treated with moderate-intensity warfarin (INR 2.0-3.0) and are at low risk of bleeding, may be treated with aspirin. The combination of warfarin and clopidogrel is not routinely recommended.
Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy: **Antithrombotic Therapy for Coronary Artery Disease (2004)**[5,13]	<u>Acute Management of Non-ST-Elevation Acute Coronary Syndromes (NSTE ACS)</u> • Aspirin 75-325 mg orally and then daily 75-162 mg is recommended for all patients presenting with NSTE ACS without a clear allergy to aspirin. • Clopidogrel 300 mg bolus orally, followed by 75 mg/day indefinitely is recommended for all NSTE ACS patients with an aspirin allergy. • In addition to aspirin, clopidogrel (bolus 300 mg followed by 75 mg/day for 9-12 months) is recommended in all NSTE ACS patients in whom diagnostic catheterization will be delayed or when coronary bypass surgery will not occur until >5 days following coronary angiography. • In NSTE ACS patients in whom angiography will take place rapidly (≤24 hours), the authors suggest beginning clopidogrel after the coronary anatomy has been determined. • For patients who have received clopidogrel and are scheduled for coronary bypass surgery, the authors recommend discontinuing clopidogrel for 5 days prior to the scheduled surgery. • Currently, there is no evidence to support use of dipyridamole either instead of, or in addition to, aspirin and the thienopyridines in the acute treatment of NSTE ACS. <u>Post-Myocardial Infarction and Post-ACS</u> • Aspirin at initial doses from 160-325 mg, and then 75-162 mg/day continued indefinitely is recommended in patients with ACS with and without ST-segment elevation. • For patients with a history of aspirin-induced bleeding or with risk factors for bleeding, the authors recommend lower doses (≤100 mg) of aspirin. • Long-term administration of clopidogrel 75 mg/day is recommended for patients in whom aspirin is contraindicated or not tolerated. • In most health-care settings, for moderate- and low-risk patients with a myocardial infarction, aspirin alone is recommended over oral vitamin K antagonists (VKAs) plus aspirin. • In health-care settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after myocardial infarction, long-term (up to 4 years) high-intensity oral VKAs (target INR 3.5; range 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral VKAs (target INR 2.5; range 2.0 to 3.0) with aspirin is recommended. • For high-risk patients with myocardial infarction, including those with a large anterior myocardial infarction, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, the authors suggest the combined use of moderate-intensity (INR 2.0 to 3.0) oral VKAs plus low-dose aspirin (≤100 mg/day) for 3 months after the myocardial infarction. <u>Chronic Stable Coronary Artery Disease</u> • Aspirin 75-162 mg/day by mouth is recommended for all patients with chronic stable coronary artery disease. The authors suggest that aspirin be continued indefinitely. • Long-term clopidogrel in addition to aspirin is suggested for patients with stable chronic coronary disease with a risk profile indicating a high likelihood of development of an acute myocardial infarction. <u>Primary Prevention</u> • Aspirin 75 to 162 mg/day is recommended over either no antithrombotic therapy or

Clinical Guideline	Recommendation
	VKAs for patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of >10%). • For patients at particularly high risk of events in whom INR can be monitored without difficulty, the authors suggest low-dose VKAs with a target INR of approximately 1.5.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2003)**[14]	Prophylactic Therapies in the Acute Phase • Aspirin 150-325 mg daily is recommended. Secondary Prevention • Aspirin 75-160 mg daily is recommended. Clopidogrel 75 mg daily may be used if aspirin is not tolerated.
National Institute for Health and Clinical Excellence (NICE): **Clopidogrel and Modified-release Dipyridamole in the Prevention of Occlusive Vascular Events (2005)**[15]	• This guidance applies to people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • The combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischemic stroke or a transient ischemic attack for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin). • Clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease. Aspirin intolerance is defined as either a proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin. • Clopidogrel is licensed in the United Kingdom (UK) for the prevention of atherothrombotic events in people who have had a myocardial infarction (from a few days until less than 35 days), have had an ischemic stroke (from 7 days until less than 6 months), or have established peripheral arterial disease. MR dipyridamole is licensed in the UK for the secondary prevention of ischemic stroke and TIAs, either alone or in combination with aspirin. (MR dipyridamole is not available without aspirin in the United States.)
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (2005)**[16]	Antiplatelet and Antithrombotic Drugs • Antiplatelet therapy is indicated to reduce the risk of myocardial infarction, stroke, or vascular death in individuals with atherosclerotic lower extremity peripheral arterial disease. • Aspirin 75-325 mg/day is recommended as safe and effective antiplatelet therapy. • Clopidogrel 75 mg/day is recommended as an effective alternative antiplatelet therapy. • Warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity peripheral arterial disease. Claudication • Cilostazol 100 mg twice daily is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity peripheral arterial disease and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure).
Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy:	Chronic Limb Ischemia • Lifelong aspirin therapy, 75-325 mg/day, is recommended in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease and in those without clinically manifest coronary or cerebrovascular disease. • Clopidogrel is recommended over ticlopidine.

Clinical Guideline	Recommendation
Antithrombotic Therapy in Peripheral Arterial Occlusive Disease (2004)[5,17]	• Clopidogrel is recommended in comparison to no antiplatelet therapy, but the authors suggest aspirin be used instead of clopidogrel. • Cilostazol is suggested for patients with disabling intermittent claudication who do not respond to conservative measures (risk factor modification and exercise therapy) and who are not candidates for surgical or catheter-based intervention. The authors suggest that clinicians not use cilostazol in those with less-disabling claudication. <u>Vascular Grafts (Prolonging the Patency of Grafts)</u> • Aspirin is recommended in patients undergoing prosthetic infrainguinal bypass. • For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, VKAs plus aspirin are not recommended. VKAs plus aspirin are suggested for those at high risk of bypass occlusion and limb loss. <u>Carotid Endarterectomy</u> • Aspirin 75-325 mg/day is recommended to be given preoperatively and continued indefinitely in patients undergoing carotid endarterectomy. <u>Asymptomatic and Recurrent Carotid Stenosis</u> • Lifelong aspirin 75-162 mg/day is recommended in nonoperative patients with asymptomatic or recurrent carotid stenosis. <u>Lower Extremity Endovascular Procedures</u> • Long-term aspirin 75-162 mg/day is recommended for all patients undergoing lower-extremity balloon angioplasty (with or without stenting).
European Society of Cardiology (ESC), Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents (2004)**[18]	<u>Major Recommendations for Individual Antiplatelet Agents</u> Aspirin • Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75-100 mg for the long-term prevention of serious vascular events in high-risk patients (eg, ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in acute coronary syndromes or in acute ischemic stroke), a loading dose of 160-300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton-pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75-100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (eg, ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal anti-inflammatory drug therapy may benefit from the use of selective COX-2 inhibitors.

Clinical Guideline	Recommendation
	Ticlopidine • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction. Clopidogrel • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of superiority versus aspirin by regulatory authorities. • Clopidogrel 75 mg daily is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial have led to Food and Drug Administration (FDA) approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation. A loading dose of 300 mg clopidogrel should be used in this setting followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with GP IIb/IIIa antagonists. Dipyridamole • Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg twice a day) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.
American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines: **AHA 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention (2007)**[19]	Comprehensive Risk Reduction for Patients With Coronary and Other Vascular Disease After PCI • For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 162-325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 75-162 mg daily. • In patients for whom the physician is concerned about risk of bleeding, 75-162 mg of aspirin is reasonable during the initial period after stent implantation. • For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for at least 12 months (if the patient is not at high risk of bleeding). For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patients is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). • For all post-PCI nonstented STEMI patients, treatment with clopidogrel should continue for at least 14 days. • Long-term maintenance therapy (eg, 1 year) with clopidogrel 75 mg QD is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.
Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy: **Antithrombotic Therapy in**	Prevention of Saphenous Vein Graft Occlusion Following Coronary Artery Bypass Grafting • Aspirin 75-162 mg/day is recommended indefinitely for all patients with coronary artery disease. • Aspirin 75-162 mg/day starting 6 hours after CABG operation is recommended over preoperative aspirin.

Clinical Guideline	Recommendation
Patients With Saphenous Vein and Internal Mammary Artery Bypass Grafts (2004)[5,20]	• In patients in whom bleeding prevents the administration of aspirin at 6 hours after CABG, the authors recommend starting aspirin as soon as possible thereafter. • For patients undergoing CABG, the addition of dipyridamole to aspirin therapy is not recommended. • Clopidogrel 300 mg orally 6 hours after operation followed by 75 mg/day, is recommended for patients with coronary artery disease undergoing CABG who are allergic to aspirin. • Clopidogrel 75 mg/day for 9-12 months following CABG, in addition to aspirin, is recommended in patients who undergo CABG for non-ST-segment elevation ACS. • For patients who have received clopidogrel for ACS and are scheduled for coronary bypass surgery, clopidogrel should be discontinued for 5 days prior to the scheduled surgery. <u>Prevention of Internal Mammary Bypass Graft Occlusion Following CABG</u> • Aspirin 75-162 mg/day is recommended indefinitely for all patients with coronary artery disease who undergo internal mammary artery bypass grafting.
Seventh American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy: **Antithrombotic Therapy in Valvular Heart Disease—Native and Prosthetic (2004)**[5,21]	<u>Prosthetic Heart Valves</u> • For all patients with mechanical prosthetic heart valves, VKAs are recommended. • In patients who have mechanical valves and additional risk factors (eg, atrial fibrillation, myocardial infarction), a target INR of 3.0 (range 2.5-3.5), combined with low doses of aspirin, 75-100 mg/day, is recommended. • For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, aspirin 75-100 mg/day in addition to VKAs, and maintenance of the INR at a target of 3.0 (range 2.5-3.5) is recommended. • In patients with prosthetic heart valves in whom VKAs must be discontinued, low molecular weight heparin or aspirin 80-100 mg/day is recommended.

III. Indications

Table 3 outlines the Food and Drug Administration (FDA)-approved indications for the platelet-aggregation inhibitors. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Platelet-Aggregation Inhibitors[3,22-28]

Indication	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Reduction of Atherothrombotic Events/Vascular Indications						
Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli	✔					
Reduce the combined risk of death and nonfatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris	✔					
Reduce the combined risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris	✔					
Reduce the risk of vascular mortality in patients with a suspected acute myocardial infarction	✔					
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis		✔				
Reduce atherothrombotic events in patients with recent myocardial infarction, recent stroke or established peripheral arterial disease				✔		
Reduce atherothrombotic events in patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or coronary artery bypass graft surgery				✔		
Reduce atherothrombotic events in patients with ST-segment elevation acute myocardial infarction†				✔		
Reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke						✔ (see black box warning)*
Reduce symptoms of intermittent claudication			✔			
Revascularization Procedures						
In patients who have undergone revascularization procedures (ie, coronary artery bypass graft, percutaneous transaminase coronary angioplasty or carotid endarterectomy) when there is a pre-existing condition for which	✔					

Indication	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
aspirin is already indicated						
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation as adjunctive therapy with aspirin						✔
Prevent postoperative thromboembolic complications of cardiac valve replacement as an adjunct to coumarin anticoagulants					✔ (oral)	
Miscellaneous Indications						
Evaluate coronary artery disease (radionuclide myocardial perfusion study)					✔ (injection)	
Fever	✔					
Generalized aches and pains	✔					
Headache	✔					
Migraine	✔					
Relief of signs and symptoms of rheumatic diseases (rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropies and arthritis and pleurisy associated with systemic lupus erythematosus)	✔					

*Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia, agranulocytosis and aplastic anemia, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[28]

†This benefit is not known to pertain to patients who receive primary angioplasty.

IV. Pharmacokinetics

The pharmacokinetic parameters of the platelet-aggregation inhibitors are outlined in Table 4. There are no significant interactions between aspirin and dipyridamole and the pharmacokinetics of the components are unchanged by their coadministration in the fixed-dose combination product.[24]

Table 4. Pharmacokinetic Parameters of the Platelet-Aggregation Inhibitors[3,29-34]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Elimination (%)	Active Metabolites	Serum Half-Life (hours)
Aspirin	50-75	50-80	Hepatic	Renal (6-36)	Yes; salicylate	15-20 minutes (parent compound); 3 hours (300-600 mg doses); 5-6 hours (1 g doses); 10 hours (>1 g doses)
Cilostazol	87-100	95-98	Hepatic, primarily via CYP3A4 (also 1A2, 2C19 and 2D6)	Renal (74); fecal (20)	Yes; 3,4-dehydro-cilostazol and 4'-trans-hydroxy-cilostazol	11-13
Clopidogrel	Not specified; well absorbed	94-98	Hepatic; extensively hydrolyzed	Renal (50); fecal (46)	Yes (not reported)	8
Dipyridamole	Readily, but variable (IR); 37-66 (ER)	91-99	Hepatic	Fecal	None	10-12
Ticlopidine	80-90	98	Hepatic; extensively metabolized	Renal (60); fecal (23)	Yes (not reported)	13 (single dose)

ER=extended-release, IR=immediate-release

V. Drug Interactions

Significant drug interactions with the platelet-aggregation inhibitors are noted in Table 5.

Table 5. Significant Drug Interactions with the Platelet-Aggregation Inhibitors[35]

Drug(s)	Significance Level	Interaction	Mechanism
Aspirin	1	Clopidogrel	Concurrent therapy may increase the risk of life-threatening bleeding (eg, intracranial and gastrointestinal hemorrhage) in high-risk patients with transient ischemic attack or ischemic stroke. Avoid aspirin use in high-risk patients with recent ischemic stroke or transient ischemic attack who are receiving clopidogrel.
Aspirin	1	Heparin	Aspirin can inhibit platelet aggregation and has caused bleeding. The risk of bleeding may be increased when aspirin and heparin are used together. Monitor coagulation parameters and signs of bleeding if the combination is used.
Aspirin	1	Ketorolac	Aspirin may displace ketorolac from protein binding sites and have synergistic side effects. Ketorolac is contraindicated in patients receiving aspirin due to an

Drug(s)	Significance Level	Interaction	Mechanism
			increased risk of serious ketorolac-related side effects.
Aspirin, bismuth subsalicylate, choline magnesium salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	1	Methotrexate	Salicylates may increase the toxic effects of methotrexate by decreasing methotrexate's renal clearance and plasma protein binding. When salicylates are coadministered, the dose of methotrexate may need to be decreased or prolonged regimens of leucovorin rescue may be indicated. Dosage adjustment may also be guided by monitoring methotrexate plasma levels.
Aspirin	1	Nonsteroidal anti-inflammatory drugs (NSAIDs) (celecoxib, diclofenac, etodolac, fenoprofen, flurbi-profen, ibuprofen, indomethacin, ketoprofen, meclo-fenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin)	The pharmacologic effects of some NSAIDs may be decreased and the cardioprotective effect of low-dose uncoated aspirin may be reduced with concurrent administration of NSAIDs and aspirin. Both aspirin and NSAIDs are also gastric irritants. Consider using analgesics that do not interfere with antiplatelet effect (eg, acetaminophen).
Aspirin, methyl salicylate	1	Warfarin	The anticoagulant activity of warfarin and the risk of hemorrhage may be enhanced by the effects of aspirin on the gastric mucosa and platelet function. If concurrent use cannot be avoided, frequently monitor the patient's international normalized ratio (INR) and adjust the warfarin dose accordingly, especially when starting or stopping aspirin therapy.
Aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Angiotensin-converting enzyme (ACE) inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Aspirin inhibits prostaglandin synthesis and may reduce the hypotensive and vasodilator effects of the ACE inhibitor. Monitor blood pressure and hemodynamic parameters if both agents are needed.
Aspirin, bismuth subsalicylate, magnesium salicylate, salsalate, sodium thiosalicylate	2	β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol)	Salicylates may inhibit the synthesis of prostaglandins involved in the antihypertensive activity of β-blockers; therefore, the blood pressure-lowering effects of β-blockers may be reduced. In addition, the beneficial effects of β-blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated; however, the mechanism of this interaction is not known.
Aspirin, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Carbonic anhydrase inhibitors (acetazolamide, methazolamide)	Concurrent administration of carbonic anhydrase inhibitors and salicylates may result in the accumulation of carbonic anhydrase inhibitors and toxicity (eg, central nervous system depression, metabolic acidosis). Aspirin displaces carbonic anhydrase inhibitors from plasma protein binding sites and inhibits renal clearance. Metabolic acidosis may lead to increased penetration of salicylates into the

Drug(s)	Significance Level	Interaction	Mechanism
			central nervous system. Minimize or avoid coadministration of salicylates and carbonic anhydrase inhibitors.
Aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Corticosteroids (beta-methasone, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone)	Corticosteroids may reduce serum salicylate levels by stimulating liver metabolism of salicylates and increasing renal elimination. The effectiveness of salicylates may be decreased. When adding or withdrawing corticosteroids, tailor the salicylate dosage and monitor plasma salicylate concentrations.
Aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Insulin	Salicylates may potentiate the serum glucose-lowering action of insulin by increasing basal insulin concentrations and enhancing the acute insulin response to a glucose load. Blood glucose levels should be monitored and insulin regimens tailored as needed.
Aspirin, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Probenecid	Coadministration of probenecid and aspirin may inhibit the uricosuric action of either drug alone. The mechanism of this interaction is not known but may be due to an alteration in the renal filtration of uric acid. Coadministration should be avoided to allow maximum uricosuria to be attained. Aspirin therapy dosed at nonanti-inflammatory concentrations may be acceptable in patients who require both agents.
Aspirin, bismuth subsalicylate, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Sulfinpyrazone	Salicylates may displace sulfinpyrazone from plasma protein binding sites and may block the inhibitory effects of sulfinpyrazone on tubular reabsorption of uric acid. Patients should be counseled not to take salicylate-containing products on a regular or extended basis since the uricosuria produced by sulfinpyrazone may be suppressed.
Aspirin, choline salicylate, magnesium salicylate, salsalate, sodium salicylate, sodium thiosalicylate	2	Sulfonylureas (acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	Salicylates may increase the hypoglycemic effect of sulfonylureas by several mechanisms. Salicylates reduce basal plasma glucose levels, enhance insulin secretion and inhibit acute insulin responses to glucose. Salicylates may also displace sulfonylureas from protein binding sites. Monitor the patient's blood glucose and if hypoglycemia develops, consider decreasing the sulfonylurea dose. Consider alternative therapy with acetaminophen or an NSAID.
Aspirin, bismuth subsalicylate, magnesium salicylate, salsalate, sodium thiosalicylate	2	Valproic acid	Aspirin may displace valproic acid from protein binding sites and increase the free fraction of valproic acid, leading to toxic effects. Aspirin may also alter the metabolic pathways of valproic acid. Monitor serum valproic acid concentrations (including free fraction if readily available), symptoms of valproic acid toxicity and liver enzymes when aspirin is coadministered with valproic acid.
Cilostazol	2	Clarithromycin, erythromycin	Certain macrolide antibiotics may inhibit the metabolism (CYP3A4) of cilostazol leading to

Drug(s)	Significance Level	Interaction	Mechanism
			increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration with certain macrolide antibiotics.
Cilostazol	2	Omeprazole	Omeprazole may inhibit the metabolism (CYP2C19) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration of omeprazole.
Clopidogrel	2	Ketoconazole	Ketoconazole may inhibit the isozymes (CYP3A4 and CYP3A5) that convert the prodrug clopidogrel to its active metabolite. If possible, avoid coadministration of these agents since the antiplatelet effect of clopidogrel may be inhibited.
Dipyridamole	2	Adenosine	Dipyridamole may potentiate the pharmacologic effects of adenosine by inhibiting the transport or metabolism of adenosine. Following rapid bolus administration of adenosine, profound bradycardia may occur.
Ticlopidine	2	Cyclosporine	Through an unknown mechanism, ticlopidine decreases cyclosporine whole blood concentrations and pharmacologic effects. If ticlopidine therapy is started or discontinued, consider frequent monitoring of cyclosporine blood concentrations. Adjust the dose of cyclosporine or discontinue ticlopidine as indicated.
Ticlopidine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Ticlopidine may inhibit hydantoin metabolism thereby increasing plasma hydantoin concentrations and adverse effects. Monitor hydantoin levels and make dosage adjustments as needed. Also, observe the patient's clinical response when starting, stopping, or changing the dose of ticlopidine.
Ticlopidine	2	Theophyllines (aminophylline, theophylline)	Ticlopidine may impair theophylline elimination. Theophylline levels may increase and lead to toxicity (eg, nausea, vomiting, seizures and arrhythmias). Monitor theophylline serum levels when ticlopidine is added or withdrawn from a patient's regimen and tailor dosages as needed.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Adverse reactions for the platelet-aggregation inhibitors are outlined in Table 6. Many adverse effects of aspirin are dose related and are extremely rare at low dosages.[29] Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. The black box warning for cilostazol and heart failure is summarized in Table 7. The black box warning for ticlopidine concerning hematological adverse events is summarized in Table 8.

Table 6. Adverse Drug Events (%) Reported with the Platelet-Aggregation Inhibitors[29-34]

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Cardiovascular						
Angina pectoris	-	<1	-	-	✔	-
Arrhythmia	-	<1	-	-	-	-
Atrial fibrillation/flutter	✔ (toxicity)	-	<2	1-3	-	-
Cardiac arrest	-	-	<2	-	-	-
Cardiac failure	-	2	-	1-3	-	-
Chest pain	-	-	-	8	-	-
Conduction defect	✔ (toxicity)	-	-	-	-	-
Congestive heart failure	-	-	<2	-	-	-
Coronary artery spasm	✔	-	-	-	-	-
Dysrhythmias	✔	-	-	-	-	-
Edema	✔	-	-	4	-	-
Hypertension	-	-	-	4	-	-
Hypotension	✔	-	<2	-	✔	-
Myocardial infarction/ischemia	-	-	<2	-	-	-
Nodal arrhythmia	-	-	<2	1-3	-	-
Palpitation	-	-	5-10	-	✔	-
Peripheral edema	-	-	7-9	-	-	-
Postural hypotension	-	-	<2	-	-	-
QTc prolongation	-	-	<2	-	-	-
Supraventricular tachycardia	-	-	<2	-	-	-
Syncope	-	1	<2	1-3	-	-
Tachycardia	✔	-	4	-	✔	-
Torsades de pointes	-	-	<2	-	-	-
Ventricular tachycardia	-	-	<2	-	-	-
Central Nervous System						
Agitation	✔	-	-	-	-	-
Amnesia	-	2	-	-	-	-
Anxiety	-	-	-	1-3	-	-
Cerebral edema	✔	<1	-	-	-	-

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Cerebral hemorrhage (includes intracranial and subarachnoid hemorrhage)	-	<1	-	<1	-	<1
Cerebral infarction/ischemia	-	-	<2	-	-	-
Coma	✔	<1	-	-	-	-
Confusion	✔	1	-	<1	-	-
Delirium	✔	-	-	-	-	-
Depression	-	-	-	4	-	-
Dizziness	✔	-	9-10	2-6	14	-
Fatigue	✔	6	-	3	-	-
Fever	-	-	-	1-3	-	-
Flushing	-	-	-	-	✔	-
Hallucination	-	-	<1	-	-	-
Headache	✔	38% (tolerance usually develops)	27-34	3-8	2	-
Hyperthermia	✔	-	-	-	-	-
Insomnia	✔	-	-	1-3	-	-
Ischemic brain infarction	✔	-	-	-	-	-
Lethargy/malaise	✔	2	-	-	✔	-
Nervousness	✔	-	-	-	-	-
Pain	-	6	-	6	-	-
Seizure	-	2	-	-	-	-
Somnolence	-	1	-	-	-	-
Subdural hematoma	-	-	<2	-	-	-
Vertigo	-	-	<3	1-3	-	-
Dermatologic						
Alopecia	-	<1	-	-	✔	-
Angioedema	✔	-	-	-	-	-
Bullous eruption	-	-	-	<1	-	-
Eczema	-	-	-	1-3	-	-
Erythema multiforme	-	-	-	<1	-	<1
Erythema nodosum	-	-	-	-	-	<1
Exfoliative dermatitis	-	-	-	-	-	<1
Extradural hematoma	-	-	<2	-	-	-
Ischemic necrosis	-	-	-	<1	-	-
Lichen planus	-	-	-	<1	-	-
Maculopapular rash	-	-	-	<1	-	<1
Purpura	-	1	-	-	-	2
Pruritus	-	<1	-	3	✔	1

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Rash	✔	<1	-	4	2	5
Stevens-Johnson syndrome	-	-	<2	-	-	<1
Toxic epidermal necrolysis	-	-	-	<1	-	-
Ulceration	-	<1	-	-	-	-
Urticaria	✔	<1	-	<1	-	<1
Endocrine/Metabolic						
Acidosis	✔	-	-	-	-	-
Dehydration	✔	-	-	-	-	-
Diabetes mellitus	-	-	<2	-	-	-
Gout/hyperuricemia	-	-	<2	1-3	-	-
Hypercholesterolemia/increased cholesterol	-	-	4	-	-	>10*
Hyperglycemia	✔	-	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-
Hypoglycemia	✔ (children)	-	-	-	-	-
Hyponatremia	✔ (buffered forms)	-	-	-	-	<1
Pancreatitis	-	<1	-	<1	-	-
Gastrointestinal						
Abdominal distress	-	-	-	-	6	-
Abdominal pain	✔	18	4-5	2-6	-	4
Abnormal stools	-	-	12-15	-	-	1
Anorexia	-	1	-	-	-	-
Bleeding	-	4	-	-	-	-
Chronic diarrhea	-	-	-	-	-	<1
Colitis	✔	-	<2	-	-	-
Colonic ulceration	✔	-	-	-	-	-
Constipation	-	-	-	1-3	-	-
Diarrhea	-	13	12-19	2-5	✔	13
Duodenal ulcer	✔	-	<2	-	-	-
Duodenitis	-	-	<2	-	-	-
Dyspepsia	✔	>10	6	2-5	✔	7
Epigastric discomfort/heartburn	✔	-	-	-	-	-
Esophageal ulcer	-	-	-	-	-	-
Esophageal hemorrhage	-	-	<2	-	-	-
Esophageal stricture	✔	-	-	-	-	-
Esophageal ulcer	✔	-	-	-	-	-
Esophagitis	✔	-	<2	-	-	-

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Flatulence	-	-	2-3	-	-	2
Gastric erosions	✔	-	-	-	-	-
Gastric erythema	✔	-	-	-	-	-
Gastrointestinal hemorrhage	-	1	-	1-3	-	<1
Hematemesis	-	<1	-	-	-	-
Hemorrhoids	-	1	-	-	-	-
Nausea	✔	16	6-7	3	✔	7
Oral mucosal ulcers (aspirin-containing chewing gum)	✔	-	-	-	-	-
Peptic ulcer	6-31	-	<2	-	-	<1
Periodontal abscess	-	-	<2	-	-	-
Rectal bleeding	-	2	<2	-	-	-
Rectal stenosis	✔ (suppository)	-	-	-	-	-
Retroperitoneal hemorrhage	-	-	<2	<1	-	-
Vomiting	✔	8	-	1-3	✔	2
Genitourinary						
Blood urea nitrogen increased	✔	-	-	-	-	-
Cystitis	-	-	<2	1-3	-	-
Hematuria	-	-	-	<1	-	<1
Interstitial nephritis	✔	<1	-	-	-	-
Menorrhagia	-	-	-	-	-	<1
Nephrotic syndrome	-	-	-	-	-	-
Papillary necrosis	✔	<1	-	-	-	-
Proteinuria	✔	-	-	-	-	-
Renal failure	✔	<1	-	-	-	<1
Serum creatinine increased	✔	-	-	-	-	<1
Urinary tract infection	-	-	-	3	-	-
Uterine hemorrhage	-	<1	-	-	-	-
Hematologic						
Agranulocytosis	-	-	<2	<1	-	<1
Anemia	✔	2	<2	1-3	-	-
Aplastic anemia	-	<1	-	<1	-	<1
Bleeding	✔	-	-	Major 4; Minor 5	-	-
Bone marrow suppression	-	-	-	-	-	-
Coagulopathy	✔	-	-	-	-	-
Disseminated intravascular coagulation	✔	<1	-	-	-	-
Eosinophilia	-	-	-	-	-	<1

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Epistaxis	-	-	-	3	-	-
Granulocytopenia	-	-	<2	<1	-	-
Hematoma	-	-	-	1-3	-	-
Hemolytic anemia	✔	-	-	-	-	<1
Hemorrhage	-	-	<2	-	-	-
Hypochromic anemia	-	-	-	<1	-	-
Iron deficiency anemia	✔	-	-	-	-	-
Leukopenia	-	-	<2	<1	-	-
Neutropenia	-	-	-	<1	-	2
Pancytopenia	-	<1	-	<1	-	<1
Polycythemia	-	-	<2	-	-	-
Prothrombin time prolonged	✔	<1	-	-	-	-
Purpura	-	-	-	5	-	-
Thrombocytopenia	✔	<1	<2	<1	✔	<1
Thrombocytosis	-	-	-	-	-	<1
Thrombosis	-	-	<2	-	-	-
Thrombotic thrombocytopenic purpura	-	-	-	-	-	<1
Hepatic						
Acute liver failure	-	-	-	<1	-	-
Bilirubinemia	-	-	-	<1	-	-
Cholelithiasis	-	<1	<2	-	✔	-
Fatty liver	-	-	-	<1	-	-
Hepatic dysfunction	-	-	<2	-	-	-
Hepatic failure	-	<1	-	-	-	-
Hepatic necrosis	-	-	-	-	-	<1
Hepatitis	✔	<1	-	<1	✔	<1
Hepatotoxicity	✔	-	-	-	-	-
Jaundice	✔	<1	-	-	-	<1
Liver dysfunction	-	-	-	-	✔	-
Liver function test abnormalities	-	-	-	<3	-	1
Transaminases increased	✔	-	-	-	-	-
Neuromuscular/Musculoskeletal						
Acetabular bone destruction	✔	-	-	-	-	-
Arthralgia	-	6	-	6	-	-
Arthritis	-	2	-	1-3	✔	-
Arthropathy	-	-	-	-	-	<1
Arthrosis	-	1	-	-	-	-

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Back pain	-	5	6-7	6	-	-
Bursitis	-	-	<2	-	-	-
Fatigue	-	-	-	-	✔	-
Leg cramps	-	-	-	1-3	-	-
Myalgia	-	1	2-3	-	✔	-
Myositis	-	-	-	-	-	<1
Neuralgia	-	-	<2	1-3	-	-
Paresthesia	-	<1	-	1-3	✔	-
Peripheral neuropathy	-	-	-	-	-	<1
Rhabdomyolysis	✔	<1	-	-	-	-
Weakness	✔	2	-	1-3	-	-
Respiratory						
Asthma	✔	-	<2	-	-	-
Bronchiolitis obliterans-organized pneumonia	-	-	-	-	-	<1
Bronchitis	-	-	-	4	-	-
Bronchospasm	✔	<1	-	-	-	-
Cough	-	2	3-4	3	-	-
Dyspnea	✔	<1	-	5	-	-
Epistaxis	-	2	-	-	-	-
Hemoptysis	-	<1	-	<1	-	-
Hemothorax	-	-	-	<1	-	-
Hyperpnea	✔	-	-	-	-	-
Intestinal pneumonitis	-	-	-	<1	-	-
Larynx edema	✔	-	-	-	✔	-
Pharyngitis	-	-	7-10	-	-	-
Pneumonia	-	-	<2	-	-	-
Pneumonitis	-	-	-	-	-	<1
Pulmonary edema	✔	<1	-	-	-	-
Pulmonary hemorrhage	-	-	-	<1	-	-
Respiratory alkalosis	✔	-	-	-	-	-
Rhinitis	-	-	7-12	4	-	-
Rhinosinusitis	✔	-	-	-	-	-
Tachypnea	✔	<1	-	-	-	-
Upper respiratory infection	-	1	-	-	-	-
Other						
Accidental trauma	-	-	-	-	-	-
Allergic reaction	-	<1	-	<1	-	-

Adverse Event	Aspirin	Aspirin and Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Ticlopidine
Allergic vasculitis	-	<1	-	-	-	-
Anaphylactoid reaction/anaphylaxis	-	<1	-	<1	-	<1
Angioedema	-	<1	-	<1	-	<1
Ante-/peri-/postpartum bleeding	✔	<1	-	-	-	-
Blindness	-	-	<2	-	-	-
Cataract	-	-	-	1-3	-	-
Conjunctival bleeding	-	-	-	-	-	<1
Conjunctivitis	-	-	-	1-3	-	-
Deafness	-	<1	-	-	-	-
Fever	-	-	-	<1	-	-
Flu symptoms	-	-	-	8	-	-
Hearing loss	✔	-	-	-	-	-
Hypersensitivity reaction	-	-	-	<1	✔	-
Infection	-	-	10-14	-	-	-
Lower weight infants	✔	<1	-	-	-	-
Ocular/retinal hemorrhage	-	-	<2	<1	-	-
Periorbital edema	✔	-	-	-	-	-
Positive antinuclear antibody	-	-	-	-	-	<1
Prolonged pregnancy and labor	✔	-	-	-	-	-
Reye's syndrome	✔	<1	-	-	-	-
Sepsis	-	-	-	-	-	<1
Serum sickness	-	-	-	<1	-	<1
Stillbirths	✔	<1	-	-	-	-
Systemic lupus erythematosus	-	-	-	-	-	<1
Taste disorder	-	-	-	<1	-	-
Tinnitus	✔	-	-	-	-	-
Tooth disorder	-	-	-	-	-	-
Vasculitis	-	-	-	<1	-	<1

*Increases of 8-10% within 1 month of therapy
- Event not reported or incidence <1%
✔ Percent not specified

Table 7. Black Box Warning for Cilostazol and Congestive Heart Failure[25]

Warning for Congestive Heart Failure
CONTRAINDICATION
Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

Table 8. Black Box Warning for Ticlopidine and Hematological Adverse Reactions[28]

Warning for Hematological Adverse Reactions
WARNING: Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia. *Neutropenia/Agranulocytosis:* Among 2,048 patients in clinical trials in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1,200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population). *TTP:* One case of thrombotic thrombocytopenic purpura was reported during clinical trials in stroke patients. Based on postmarketing data, United States (US) physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2,000 to 4,000 patients exposed. *Aplastic Anemia:* Aplastic anemia was not seen during clinical trials in stroke patients, but US physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4,000 to 8,000 patients exposed. *Monitoring of Clinical and Hematologic Status:* Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks. The incidence of aplastic anemia peaks after about 4 to 8 weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, TTP, or aplastic anemia have arisen after more than 3 months of therapy. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine should be immediately discontinued. The detection and treatment of ticlopidine-associated hematological adverse reactions are further described under WARNINGS.

VII. Dosing and Administration

The usual dosing regimens for the platelet-aggregation inhibitors are summarized in Table 9.

Table 9. Usual Dosing for the Platelet-Aggregation Inhibitors[22-28]

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
Aspirin	Carotid endarterectomy: Oral: 81 mg once daily to 650 mg twice daily, start presurgery; continue therapy indefinitely Chronic stable angina pectoris: Oral: 75-325 mg once daily; continue therapy indefinitely	Fever and ≤12 years: Oral: 40-60 mg/kg/day (divide every 4-6 hours); maximum, 4 g in 24 hours Fever and 12 years and older: Oral: 325-650 mg every 4-	Chewable tablet: 81 mg Delayed-release tablet: 81 mg 325 mg 500 mg 650 mg

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
	Coronary artery bypass graft: Oral: 325 mg starting 6 hours postprocedure; continue for 1 year postprocedure Fever: Oral: 325-650 mg every 4-6 hours as needed; maximum, 4 g in 24 hours Generalized aches and pains: Oral: 326-650 mg every 4 hours; maximum, 3.9 g in 24 hours Headache: Oral: 500-1,000 mg every 4-6 hours; maximum 4 g in 24 hours Migraine: Oral: 1,000 mg one time; maximum, 1,000 mg in 24 hours Ischemic stroke and transient ischemic attack: Oral: 50-325 mg once daily; continue therapy indefinitely Osteoarthritis: Oral: up to 3 g per day in divided doses Percutaneous transaminase coronary angioplasty: Oral: initial, 325 mg daily given 2 hours presurgery; maintenance, 160-325 mg daily; continue therapy indefinitely Prevention of recurrent myocardial infarction: Oral: 75-325 mg once daily; continue therapy indefinitely Rheumatoid arthritis: Oral: initial, 3 g a day in divided doses; increase dose as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/mL Spondyloarthropathies: Oral: up to 4 g per day in divided doses Suspected acute myocardial infarction: Oral: initial, 160-162.5 mg as soon as a myocardial infarction is suspected; maintenance, 160-162.5 mg a day for 30 days postinfarction; after 30 days, consider further therapy based on dosage and administration for prevention of recurrent myocardial infarction	6 hours as needed; maximum, 4 g in 24 hours Generalized aches and pains and 12 years and older: Oral: 326-650 mg every 4 hours; maximum, 3.9 g in 24 hours Juvenile rheumatoid arthritis: Oral: initial 90-130 mg/kg/day in divided doses; increase dose as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg /mL Pain and ≤12 years: Oral: 40-60 mg/kg/day (divide every 4-6 hours); maximum, 4 g in 24 hours Pain and 12 years and older: Oral: 326-650 mg every 4 hours; maximum, 3.9 g in 24 hours	975 mg Enteric-coated tablet: 81 mg 325 mg 500 mg 650 mg Packet: 650 mg Rectal suppository: 60 mg 125 mg 300 mg 600 mg Sustained-release tablet: 800 mg Tablet: 81 mg 325 mg 500 mg

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
	Systemic lupus erythematosis, arthritis and pleurisy: Oral: initial, 3 g a day in divided doses; increase dose as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg /mL Unstable angina pectoris: Oral: 75-325 mg once daily; continue therapy indefinitely		
Aspirin and dipyridamole	Thromboembolic stroke, recurrent: prophylaxis: Capsule, extended-release: 1 capsule twice daily (in the morning and evening) Alternative regimen for patients with intolerable headaches: 1 capsule at bedtime and low-dose aspirin in the morning; return to usual dose as soon as tolerance to headache develops (usually within a week) Note: Aggrenox® capsules are not interchangeable with the individual components of aspirin and Persantine® tablets.	Safety and efficacy in children have not been established.	Capsule, extended-release: aspirin 25 mg and dipyridamole 200 mg
Cilostazol	Intermittent claudication: Tablet: 100 mg orally twice daily; dosage should be reduced to 50 mg twice daily during coadministration with inhibitors of CYP3A4 (eg, erythromycin, diltiazem, itraconazole, ketoconazole) or CYP2C19 (eg, omeprazole)	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Clopidogrel	Non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction): Tablet: initial, 300 mg once; maintenance, 75 mg orally once daily (note: aspirin 75-325 mg once daily should be initiated and continued in combination with clopidogrel) Recent myocardial infarction, recent stroke, or established peripheral arterial disease: Tablet: 75 mg orally once daily ST-segment elevation acute myocardial infarction: Tablet: 75 mg once daily, administered in combination with aspirin, with or without thrombolytics; clopidogrel may be initiated with or without a loading dose	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Dipyridamole	Cardiac valve replacement, adjunct prophylaxis: Tablet: 75-100 mg 4 times daily as an adjunct to warfarin therapy Radionuclide myocardial perfusion study: Injection: 0.142 mg/kg/minute (0.57 mg/kg	Safety and efficacy in children below the age of 12 years have not been established.	Injection: 5 mg/mL Tablet: 25 mg 50 mg 75 mg

Drug	Usual Adult Dosage	Usual Pediatric Dosage	Availability
	total) intravenously over 4 minutes prior to thallium; maximum 60 mg		
Ticlopidine	Coronary artery stent implantation, adjunct: Tablet: 250 mg twice daily together with antiplatelet doses of aspirin for up to 30 days of therapy following successful stent implantation Stroke: Tablet: 250 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 250 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the platelet-aggregation inhibitors are summarized in Table 10.

Table 10. Clinical Efficacy Studies Using the Platelet-Aggregation Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cerebrovascular Conditions (Ischemic Stroke, Transient Ischemic Attack)				
International Stroke Trial[36] Aspirin 300 mg daily vs heparin 5,000 or 12,500 IU BID vs aspirin and heparin vs placebo	Factorial design, MC, OL, RCT Patients with acute ischemic stroke (randomized within 48 hours of stroke onset), 61% of patients were >70 years	N=19,435 Up to 14 days	Primary: Death from any cause within 14 days, death or dependency at 6 months Secondary: Symptomatic intracranial or extracranial hemorrhage, ischemic stroke or other major event within 14 days	Primary: Aspirin-allocated patients experienced slightly fewer deaths within 14 days (9.0% vs 9.4%; *P*=NS). There was a trend toward a reduction in death or dependence at 6 months (62.2% vs 63.5%; *P*=0.07; a difference of 13 per 1,000 patients) and after adjustment for baseline prognosis the benefit from aspirin was significant (*P*=0.03; a difference of 14 per 1,000 patients). More aspirin-allocated patients reported complete recovery from their stroke (17.6% vs 16.6%; *P*=0.07). Secondary: Aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs 3.9%; *P*<0.001) with no significant excess of hemorrhagic strokes (0.9% vs 0.8%), so the reduction in death or nonfatal recurrent stroke with aspirin was significant (11.3% vs 12.4%; *P*=0.02; 11 fewer per 1,000 patients treated). Aspirin was associated with a significant excess of 5 transfused or fatal extracranial bleeds per 1,000 patients (1.1% vs 0.6%; *P*=0.0004), in the absence of heparin the excess was 2 and was not significant. There was no interaction between aspirin and heparin in the main outcomes. (Primary and secondary results for heparin arms are not presented. The authors concluded that neither heparin regimen offered any significant clinical advantage at 6 months.)
CAST[37] Aspirin 160 mg per day vs	MC, PC, RCT Hospitalized patients with acute ischemic stroke (were	N=21,106 Up to 4 weeks	Primary: Death from any cause during the 4-week treatment period, death or	Primary: Patients in the aspirin group experienced a small but significant reduction in both early mortality (3.3% vs 3.9%; *P*=0.04) and recurrent ischemic strokes (1.6% vs 2.1%; *P*=0.01) but slightly more hemorrhagic strokes than placebo (1.1% vs 0.9%; *P*>0.1). At discharge, the aspirin-treated group experienced a smaller proportion of patients who

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	randomized within 48 hours of stroke onset), mean age 63 years		dependence at discharge Secondary: Fatal or nonfatal recurrent stroke, death or nonfatal stroke during the scheduled treatment period	were dead or dependent (30.5% vs 31.6%; *P*=0.08), corresponding to 11.4 fewer per 1,000 patients. Secondary: Fatal and nonfatal recurrent strokes occurred in 3.2% of aspirin-allocated patients vs 3.4% for placebo (*P*=NS). For the combined inhospital end point of death or nonfatal stroke at 4 weeks, there was a 12% proportional risk reduction with aspirin (5.3% vs 5.9%; *P*=0.03), an absolute difference of 6.8 fewer cases per 1,000 patients.
Diener, Cunha et al[38] European Stroke Prevention Study 2 (ESPS 2) Aspirin 25 mg BID alone vs aspirin and ER dipyridamole 25-200 mg BID (Aggrenox®) vs ER dipyridamole 200 mg BID (not available in the United States) vs placebo	DB, PC, MC, RCT Male and female patients who had an ischemic stroke (76%) or TIA (24%) within 3 months prior to study entry, mean age 66.7 years	N=6,602 24 months	Primary: Stroke (fatal or nonfatal), death (all-cause mortality) and combined stroke or death Secondary: TIA, adverse events	Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin alone (*P*=0.013), 37% with the fixed-dose combination product of aspirin and ER dipyridamole (*P*<0.001) and 16% with dipyridamole alone (*P*=0.039). There was no significant difference in all-cause mortality among the active treatment groups (no *P* values reported). In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin alone (*P*=0.016), 24% with the fixed-dose combination (*P*<0.001) and 15% with dipyridamole alone (*P*=0.015). Secondary: Aspirin alone (*P*<0.001), the fixed-dose combination product (*P*<0.001) and dipyridamole alone (*P*<0.01) were significantly effective in preventing TIA compared to placebo. Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients (no *P* values reported). All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin in comparison to placebo or dipyridamole (no *P* values reported).
Leonardi-Bee et al[39] Dipyridamole alone	MA of 5 RCT (including the ESPS 1 and 2),	N=11,036 Follow-up at	Primary: Incidence of combined fatal	Primary: The incidence of recurrent stroke was reduced by dipyridamole as compared with control (OR, 0.82; 95% CI, 0.68 to 1.00; *P*<0.05), and by combined aspirin and dipyridamole vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs dipyridamole and aspirin vs aspirin alone vs control (not specified)/placebo Two formulations of dipyridamole were assessed: conventional (daily dose 150-300 mg) and modified release (daily dose 400 mg). The daily dose of aspirin was 50-1,300 mg.	average age 65.4 years Patients with previous ischemic stroke and/or TIA	15-72 months	and nonfatal stroke Secondary: Nonfatal stroke, combined fatal and nonfatal MI, vascular death, and composite of nonfatal stroke, nonfatal MI and vascular death	aspirin alone (OR, 0.78; 95% CI, 0.65 to 0.93; *P*<0.05), dipyridamole alone (OR, 0.74; 95% CI, 0.60 to 0.90; *P*<0.05), or control (OR, 0.61; 95% CI, 0.51 to 0.71; *P*<0.05). Secondary: The combination of dipyridamole and aspirin also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97; *P*<0.05), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90; *P*<0.05), or control (OR, 0.66; 95% CI, 0.57 to 0.75; *P*<0.05). The combination of dipyridamole and aspirin significantly reduced the incidence of fatal and nonfatal MI compared to control (*P*<0.05) but not compared to monotherapy with aspirin or dipyridamole (*P*>0.05). Vascular death was not altered in any group.
Sacco et al[40] Aspirin and ER dipyridamole 25-200 mg BID (Aggrenox®) vs aspirin 25 mg BID	Post hoc analysis using data from the ESPS 2	N=1,650 Aggrenox® and N=1,649 aspirin	Primary: Rates of annual strokes and combined strokes and vascular events Secondary: Not reported	Primary: Compared to aspirin alone, aspirin plus ER dipyridamole was more effective in reducing the risk of stroke (relative risk reduction, 23%; *P*=0.006) and stroke or vascular events (relative risk reduction, 22%, *P*=0.003). A more pronounced efficacy was observed for patients <70 years; those with hypertension, prior MI, prior stroke or TIA, and any prior cardiovascular disease; and smokers (all *P*<0.01). The greatest relative hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event. Significant hazard reductions were reported for the combined outcome of stroke or vascular events with the greatest reductions found in patients with prior stroke or TIA, previous MI and among current smokers.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The difference in efficacy increased in higher-risk patients. Secondary: Not reported
ESPRIT Study Group[41] ESPRIT Aspirin (30-325 mg daily) and dipyridamole (200 mg BID), either as a fixed-dose combination or free combination (83% of dipyridamole was ER formulation) vs aspirin 30-325 mg daily Median daily aspirin dose was 75 mg in both groups.	MC, OL, RCT Patients with a TIA or minor stroke (were randomized within 6 months of the event), mean age 63 years	N=2,739 Mean follow-up 3.5 years	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (whichever happened first) Secondary: Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	Primary: Primary outcome events occurred in 173 (13%) of patients on aspirin plus dipyridamole vs 216 (16%) on aspirin monotherapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction 1.0% per year; 95% CI, 0.1 to 1.8). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. Secondary: The hazard ratios for death from all causes and all vascular causes were 0.88 (95% CI, 0.67 to 1.17) and 0.75 (95% CI, 0.51 to 1.10). Ischemic events were less frequent in the combination group than in the monotherapy group (HR, 0.81; 95% CI, 0.65 to 1.01). Major bleeding complications arose in 35 patients allocated to aspirin and dipyridamole vs 53 patients allocated to aspirin alone, whereas minor bleeding was reported in 171 patients allocated to the combination regimen vs 168 patients allocated to aspirin (RR, 1.03; 95% CI, 0.84 to 1.25).
Verro et al[42] Dipyridamole (IR and ER formulations) plus aspirin vs	MA of 6 RCT (4 were DB) Patients with a history of noncardioembolic stroke or TIA	N=7,648 Duration varied	Primary: Incidence of nonfatal stroke Secondary: Composite of stroke, MI or	Primary: Dipyridamole plus aspirin significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin alone (RR, 0.77; 95% CI, 0.67 to 0.89; no *P* value reported). Secondary: Dipyridamole plus aspirin significantly reduced the risk of the composite of stroke, MI

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin			vascular death, subset analysis comparing outcomes with IR and ER dipyridamole	or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94; no *P* value reported). Based on 4 trials, IR dipyridamole plus aspirin did not show a statistically significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin alone (no *P* values reported). Based on 2 trials (ESPS 2 and ESPRIT), ER dipyridamole plus aspirin showed a significant reduction in risk for stroke (RR, 0.76; 95% CI, 0.65 to 0.89) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92) compared to aspirin alone (no *P* values reported).
Markus et al[43] CARESS Clopidogrel 300 mg on day 1 and then 75 mg QD on days 2-7 plus aspirin 75 mg QD vs aspirin 75 mg QD	DB, PC, RCT Patients with ≥50% carotid stenosis, mean age 66.4 years for patients on dual therapy and 62.8 years for patents on aspirin monotherapy	N=107 7 days	Primary: Proportion of patients who were MES positive on day 7 Secondary: Proportion of patients who were MES positive on day 2, the rate of embolization on both days 2 and 7 and their percent change from baseline, safety (adverse and cerebrovascular events)	Primary: Intent-to-treat analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day 7, as compared with 72.7% of monotherapy patients (RR reduction, 39.8%; 95% CI, 13.8 to 58.0; *P*=0.0046). Secondary: MES frequency per hour was reduced compared with baseline by 61.4% (95% CI, 31.6 to 78.2; *P*=0.0013) in the dual-therapy group at day 7 and by 61.6% (95% CI, 34.9 to 77.4; *P*=0.0005) on day 2. There were 4 recurrent strokes and 7 TIAs in the monotherapy group vs no stroke and 4 TIAs in the dual-therapy group that were considered treatment emergent and ipsilateral to the qualifying carotid stenosis. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared with the 90 without (*P*=0.0003).
Diener, Bogousslavsky et al[44] MATCH	DB, PC, RCT High-risk patients (mean age 66 years) with recent	N=7,599 18 months	Primary: Composite of ischemic stroke, MI, vascular death or	Primary: There was no significant benefit of combination therapy compared with clopidogrel monotherapy in reducing the primary outcome (15.7% vs 16.7%, respectively; *P*=0.244). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clopidogrel 75 mg per day vs clopidogrel 75 mg and aspirin 75 mg per day	ischemic stroke or TIA and had at least one additional vascular risk factor who were already receiving clopidogrel		rehospitalization for an acute ischemic event Secondary: Death, stroke, individual components and various combinations of the primary end points	There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the secondary outcomes. Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel vs clopidogrel monotherapy (2.6% vs 1.3%; *P*<0.0001). Major and minor bleeding were also significantly higher with combination therapy vs clopidogrel monotherapy (both *P*<0.0001). [Note: Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, with most guidelines advocating for up to 12 months of treatment, the results of MATCH do not suggest a similar risk:benefit ratio for stroke and TIA survivors.]
Kennedy et al[45] FASTER Clopidogrel 300 mg loading dose then 75 mg QD vs placebo and simvastatin 40 mg QD vs placebo All patients were also given aspirin 81 mg QD with a 162 mg loading dose if naïve to aspirin.	Factorial design 2 x 2, DB, PC, RCT Patients aged 40 years and older with TIA or minor stroke, randomized within 24 hours of symptom onset	N=392 90 days	Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis) Secondary: Composite of stroke, MI and vascular death	Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins. Within 90 days, 7.1% of patients on clopidogrel had a stroke compared to 10.8% of patients on placebo (RR, 0.7; 95% CI, 0.3 to 1.2) for an absolute risk reduction of –3.8% (95% CI, –9.4 to 1.9; *P*=0.19). In the simvastatin group, 10.6% of patients had a stroke within 90 days compared to 7.3% of patients on placebo (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% (95% CI, –2.3 to 8.9; *P*=0.25). Two patients on clopidogrel had intracranial hemorrhage compared with none on placebo (absolute risk increase 1.0%; 95% CI, –0.4 to 2.4; *P*=0.5). There was no difference between groups for the simvastatin safety outcomes. Secondary: Clopidogrel was associated with a –3.3% risk difference in the secondary end point compared to placebo (95% CI, –9.3% to 2.7%; *P*=0.28). Simvastatin was associated with a +2.7% risk difference compared to placebo (95% CI, –3.2% to 8.7%; *P*=0.37).
Fukuuchi et al[46] Ticlopidine 200 mg QD vs clopidogrel 75 mg QD	DB, DD, MC, RCT Japanese patients between the ages of 20 and 80 years who	N=1,151 52 weeks	Primary: Safety with emphasis on hematologic changes, hepatic dysfunction, nontraumatic	Primary: During the 52-week study period, 15.1% of ticlopidine patients and 7.0% of clopidogrel patients had at least one primary safety end point (*P*<0.001). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4% vs 1.0%; *P*=0.043) and hepatic dysfunction (11.9% vs 4.2%; *P*<0.001). Study medication was discontinued prematurely due to safety end points in 27% and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	experienced a noncardioembolic cerebral infarction at least 8 days prior to enrollment		hemorrhage and other serious adverse reactions Secondary: Combined incidence of nonfatal or fatal cerebral infarction or MI, or death due to other vascular causes	17% of patients receiving ticlopidine and clopidogrel, respectively (*P*<0.001). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721; no *P* value reported) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6% vs 3.0%, respectively; *P*=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Gent et al[47] CATS Ticlopidine 250 mg BID vs placebo	DB, MC, PC, RCT Patients with ischemic strokes occurring from 1 week to 4 months	N=1,072 Up to 3 years (mean 24 months)	Primary: Event rate per year for stroke, MI, or vascular death Secondary: Adverse events	Primary: The event rate per year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% (*P*=0.006) in the on-treatment analysis and by 23% (*P*=0.020) using the intent-to-treat approach. Ticlopidine reduced the RR of ischemic stroke by 33% (*P*=0.008) in the on-treatment analysis. Ticlopidine was beneficial for both men and women (RR, 28.1%; *P*=0.037 and RR, 34.2%; *P*=0.045, respectively). Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe 2%) and diarrhea (severe 2%).
Hass et al[48] TASS Ticlopidine 250 mg BID vs	Blinded, MC, RCT Patients with recent (within 3 months) minor stroke or TIA	N=3,069 2-6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate was 17% for ticlopidine vs 19% for aspirin; *P*= 0.048). Ticlopidine reduced the risk of stroke after 3 years by 21% (10% for ticlopidine vs 13% for aspirin; *P*=0.024). Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9% vs 2%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin 650 mg BID				*P*<0.01). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al[49] AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American men and women who recently had a noncardio-embolic ischemic stroke (mean age 60.9 years in the ticlopidine group and 61.6 years in the aspirin group)	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI, or vascular death Secondary: Fatal or nonfatal stroke	Primary: There was no statistically significant difference in the percent of patients reaching the primary outcome of recurrent stroke, MI or vascular death between ticlopidine and aspirin (14.7% vs 12.3%, respectively; *P*=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (*P*=0.08). The frequency of laboratory-determined serious neutropenia was 3.4% for ticlopidine vs 2.2% for aspirin (*P*=0.12).
Cerebrovascular and Cardiovascular Conditions				
Antithrombotic Trialists' Collaboration[50] Antiplatelet agents vs control vs one antiplatelet regimen versus another	MA of 287 studies (197 RCT compared antiplatelet therapy vs control and 90 studies compared different antiplatelet regimens) Patients at high risk of occlusive vascular events	N=135,640 Duration varied	Primary: "Serious vascular event" (nonfatal MI, nonfatal stroke or vascular death) Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15% with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg daily) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of at least 150 mg aspirin may be required. Clopidogrel reduced serious vascular event by 10% compared with aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
CAPRIE Steering Committee[51] CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients (mean age 62.5 years) with recent ischemic stroke (within 6 months with at least a week of residual neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease	N=19,185 1-3 years (mean 1.91 years)	Primary: Composite outcome of ischemic stroke, MI or vascular death Secondary: Primary outcome and amputation, vascular death, all-cause mortality, safety	Primary: Intention–to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared with 5.83% with aspirin, for a RR reduction of 8.7% (95% CI, 0.3 to 16.5; *P*=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RR reduction of 9.4% in favor of clopidogrel. For the 6,431 patients admitted to the study with prior stroke, the RR reduction for ischemic stroke, MI, or vascular death was 7.3% in favor of clopidogrel (*P*=0.26), and the RR reduction for the end point of stroke was 8.0% (*P*=0.28). For the 6,302 patients admitted to the study with myocardial infarction, an RR increase of 3.7% was associated with clopidogrel (*P*=0.66). For the 6,452 patients admitted to the study with peripheral arterial disease, an RR of 23.8% was noted in favor of clopidogrel (*P*=0.0028). Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (*P*=0.076). There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90% vs 2.06%; *P*=0.29) and all-cause mortality (3.05% vs 3.11%; *P*=0.71). There were no major differences in terms of safety. Severe rash (*P*=0.017) and severe diarrhea (*P*=0.080) were reported more frequently with clopidogrel and severe upper gastrointestinal discomfort (*P*=0.096), intracranial hemorrhage (*P*=0.23) and gastrointestinal hemorrhage (*P*=0.05) were reported more frequently with aspirin.
DeSchryver et al (Cochrane Database Systematic Review 2007) [52] Dipyridamole with or without other antiplatelet drugs	MA of 29 RCT trials (including Medline 1966 to May 2006) Patients with arterial vascular disease (angina,	N=23,019 Duration varied (but at least 1 month in duration)	Primary: Secondary prevention of vascular death and vascular events (defined as vascular death or any death	Primary: Compared with control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared with control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only statistically significant in patients presenting with cerebral ischemia.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs control (no drug or another antiplatelet drug)	CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)		from an unknown cause, nonfatal stroke or nonfatal MI) Secondary: Not reported	There was no evidence that dipyridamole alone was more efficacious than aspirin. Secondary: Not reported
Cardiovascular Indications (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)				
CURE Trial Investigators[53] CURE Clopidogrel (300 mg immediately, followed by 75 mg once daily) plus aspirin vs placebo plus aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset, mean age 64 years	N=12,562 3-12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome) Secondary: Severe ischemia, heart failure, need for revascularization, safety	Primary: A composite of death from cardiovascular causes, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel and aspirin group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; *P*<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5% in the clopidogrel and aspirin group compared to 18.8% for aspirin alone (RR, 0.86; 95% CI, 0.79 to 0.94; *P*<0.001). Secondary: Significant reductions in nonfatal MI (5.2% vs 6.7%) and trends toward reduction in death (5.1% vs 5.5%) and stroke (1.2% vs 1.4%) with clopidogrel plus aspirin versus aspirin alone were noted (no *P* values reported). The percentages of patients with inhospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also significantly lower with clopidogrel plus aspirin vs aspirin alone (all *P*<0.05). There were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7% vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; *P*=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1% vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; *P*=0.13).
COMMIT Collaborative Group[54] COMMIT Clopidogrel 75 mg plus aspirin 162 mg daily	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI, mean age 61	N=45,852 15 days (mean)	Primary: Composite of death, reinfarction or stroke; death from any cause	Primary: Allocation to clopidogrel plus aspirin produced a highly significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin alone (actual reductions 9.2% vs 10.1%, respectively; *P*=0.002), corresponding to 9 fewer events per 1,000 patients treated for about 2 weeks. There was also a significant 7% proportional reduction in any death in the clopidogrel

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs aspirin 162 mg daily	years		Secondary: Safety	plus aspirin group compared to aspirin alone (7.5% vs 8.1%; *P*=0.03). Secondary: Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel plus aspirin versus aspirin alone, either overall (0.58% vs 0.55%, respectively; *P*=0.59) or in patients older than 70 years or in those given fibrinolytic therapy.
Sabatine et al[55] CLARITY-TIMI 28 Clopidogrel 300 mg loading dose, followed by 75 mg QD vs placebo Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin, and were scheduled to undergo angiography 48 to 192 hours after the start of the study medication.	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI	N=3,491 30 days (study medication given up to and including the day of angiography, or up to day 8 or hospital discharge if no angio-graphy)	Primary: Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography (death or recurrent MI by day 8 or hospital discharge in patients who did not undergo angiography) Secondary: Safety	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel vs 21.7% for placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27% to 47%; *P*<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1% to 11.6%; *P*=0.03). Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.
Bhatt et al[56] CHARISMA Clopidogrel 75 mg QD plus aspirin 75-162 mg QD vs	DB, MC, PC, RCT Patients 45 years of age or older with clinically evident cardiovascular disease (eg,	N=15,603 Median 28 months	Primary: Composite of first occurrence of MI, stroke, or death from cardiovascular causes Secondary:	Primary: The composite of MI, stroke or death from cardiovascular causes was 6.8% with clopidogrel plus aspirin and 7.3% with aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; *P*=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel plus aspirin and 5.5% with aspirin alone (RR, 1.2; 95% CI, 0.91 to 1.59; *P*=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel plus aspirin than aspirin alone (3.9% vs 2.2%; *P*=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel plus aspirin and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin 75-162 mg QD	documented coronary, cerebrovascular or peripheral arterial disease) or multiple atherothrombotic risk factors		First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	7.9% with aspirin alone (RR, 0.88; 95% CI, 0.77 to 1.00; *P*=0.046). Secondary: The secondary end point was reached in 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; *P*=0.04) of patients receiving clopidogrel plus aspirin vs aspirin alone, respectively. The rate of severe bleeding was 1.7% and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; *P*=0.09) for patients receiving clopidogrel plus aspirin vs aspirin alone.
Hart et al[57] CHARISMA Clopidogrel 75 mg QD plus aspirin 75-162 mg QD vs aspirin 75-162 mg QD	DB, MC, PC, RCT Post hoc analysis of participants with a history of atrial fibrillation in the CHARISMA trial; patients 45 years of age or older with clinically evident cardiovascular disease or multiple atherothrombotic risk factors; patients receiving oral anticoagulation were excluded	N=593 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving clopidogrel plus aspirin (35 of 298 patients) and aspirin alone (27 of 285 patients; *P*=0.40). Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; *P*=0.93) or all-cause mortality (29 vs 25 patients; *P*=0.69) among patients receiving clopidogrel plus aspirin and aspirin alone. Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving clopidogrel plus aspirin (2.2% per year) and in 14 patients receiving aspirin alone (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; *P*=0.94). Severe or fatal extracranial hemorrhage occurred in 6 patients given clopidogrel plus aspirin vs 3 patients given aspirin alone (*P*=0.51), while intracranial bleeding occurred in 3 patients vs 1 patients (*P*=0.62), respectively.
Ho et al[58] Clopidogrel (dose not specified)	RETRO cohort Patients (98% males) with ACS discharged on	N=3,137 Duration varied with mean	Primary: Rate of all-cause mortality or acute MI after stopping	Primary: Among medically treated patients, mean duration of clopidogrel treatment was 302 days and death or acute MI occurred in 17.1% of patients, with 60.8% of events occurring during 0 to 90 days, 21.3% during 91 to 180 days, and 9.7% during 181 to 270 days after stopping treatment with clopidogrel.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	clopidogrel from 127 Veterans Affairs hospitals between October 1, 2003 and March 31, 2005, mean age 66 years	follow-up after stopping clopidogrel of 196 days for patients medically treated and 203 days for patients receiving PCI	clopidogrel Secondary: Not reported	In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (IRR, 1.98; 95% CI, 1.46 to 2.69 vs the interval 91-180 days). Among the PCI-treated patients with ACS, mean duration of clopidogrel treatment was 278 days and death or acute MI occurred in 7.9% of patients, with 58.9% of events occurring during 0 to 90 days, 23.4% during 91 to 180 days, and 6.5% during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17 to 2.83). Secondary: Not reported
Procedures and/or Surgery				
Sabatine et al[59] PCI-CLARITY Clopidogrel (300 mg loading dose, followed by 75 mg QD) plus aspirin (150-325 mg on the first day and then 75-162 mg QD) vs placebo plus aspirin (150-325 mg on the first day and then 75-162 mg QD)	DB, MC, PC, RCT Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)	N=1,863 30 days	Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization Secondary: MI or stroke before PCI and the primary end point from randomization to 30 days	Primary: Pretreatment with clopidogrel in patients receiving concurrent aspirin significantly reduced the primary end point following PCI compared to aspirin alone (3.6% vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; *P*=0.008). Pretreatment with clopidogrel and aspirin also reduced the incidence of MI or stroke prior to PCI (4.0% vs 6.2%; OR, 0.62; 95% CI, 0.40 to 0.95; *P*=0.03). Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary outcome (7.5% vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; *P*=0.001). There was no significant excess in the rates of major or minor bleeding in patients receiving dual therapy vs aspirin alone (2.0% vs 1.9%, respectively; *P*>0.99).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mehta et al[60] PCI-CURE Prior to PCI, patients received aspirin with clopidogrel or placebo; after PCI, stented patients received open-label clopidogrel or ticlopidine in combination with aspirin for 2-4 weeks; then clopidogrel or placebo was resumed (for 3-12 months after initial randomization)	DB, RCT Patients with non-ST-elevation ACS from the CURE study undergoing PCI	N=2,658 Average duration of follow-up after PCI was 8 months	Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI (main primary end point); cardiovascular death or MI from time of PCI to scheduled end of trial Secondary: Not reported	Primary: 4.5% of patients in the clopidogrel and aspirin group had the main primary end point compared with 6.4% in the aspirin group (*P*=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization (*P*=0.03) and of cardiovascular death or MI (*P*=0.047). Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (*P*=0.002). At follow-up, there was no significant difference in major bleeding between the groups (*P*=0.64). Secondary: Not reported
Steinhubl et al[61] CREDO Clopidogrel 300 mg loading dose (3-24 hours before PCI), then clopidogrel 75 mg QD through 12 months vs placebo (3-24 hours before PCI), then clopidogrel 75 mg QD through day 28, then placebo through 12 months	DB, MC, PC, RCT Patients undergoing PCI, mean age 62 yeas	N=2,116 12 months	Primary: One-year incidence of the composite of death, MI, or stroke; 28-day incidence of the composite of death, MI or urgent target vessel revascularization Secondary: Components of composite end points, administration of	Primary: Long-term (1 year) clopidogrel and aspirin therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke versus aspirin alone (95% CI, 3.9% to 44.4%; *P*=0.02; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (–18.5%; 95% CI, –14.2% to 41.8%; *P*=0.23). Secondary: A similar level of benefit was found in the individual components of the primary end point at 1 year, although individual outcomes were not significant. Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. In a prespecified subgroup analysis, patients who had received clopidogrel at least 6 hours before PCI experienced a reduction in the relative combined risk of death, MI, or stroke by 38.6% (95% CI, –1.6% to 62.9%; *P*=0.051) compared with no reduction when treatment was given less than 6 hours before PCI (*P*=0.051).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received aspirin 325 mg prior to PCI, then 325 mg QD through day 28, then 81-325 mg QD throughout the study.			clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at 1 year	Risk of major bleeding at 1 year increased, but not significantly (8.8% with clopidogrel vs 6.7% with aspirin alone; *P*=0.07).
Lev et al[62] Clopidogrel 300-600 mg before PCI (N=165) vs clopidogrel 300-600 mg immediately after PCI (N=127) All patients were treated with aspirin 325 mg before PCI and aspirin (dose not specified) and clopidogrel 75 mg QD for 3-12 months after PCI.	PRO Patients with chest pain and STEMI undergoing emergency PCI, mean age 60 years in the pretreatment group and 61 years in the no pretreatment group	N=292 6 months	Primary: Occurrence of TIMI myocardial perfusion grade 3 after PCI Secondary: Incidence of reinfarction, stent thrombosis, target vessel revascular-ization, death	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group than in the no pretreatment group (85% vs 71%; *P*=0.01). Secondary: The incidence of reinfarction at 30 days (0% vs 3.2%, respectively; *P*=0.04) and 6 months (0.6% and 3.9%, respectively; *P*=0.09) was lower in the pretreatment group than in the no pretreatment group. The incidence of stent thrombosis at 30 days (0% vs 2.4%, respectively; *P*=0.08) and 6 months (0% and 3.9%, respectively; *P*=0.02) was lower in the pretreatment group than in the no pretreatment group. The incidence of death and target vessel revascularization were not significantly different between the 2 groups at 30 days (*P*=0.6 and *P*=1.0) or 6 months (*P*=0.7 and *P*=0.9).
Bertrand et al[63] CLASSICS Clopidogrel 300 mg loading dose then 75 mg QD and aspirin 325 mg QD	RCT Patients receiving a stent placement, mean age 60 years	N=1,020 28 days	Primary: Major peripheral or bleeding complications, neutropenia, thrombocyto-penia or early discontinuation due to	Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel group and in 9.1% of patients in the ticlopidine group (RR 0.50; 95% CI, 0.31 to 0.81; *P*=0.005). Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; *P*=NS for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs clopidogrel 75 mg QD and aspirin 325 mg QD vs ticlopidine 250 mg BID and aspirin 325 mg QD			noncardiac adverse event Secondary: Incidence of cardiac events	
Takeyasu et al[64] Cilostazol 200 mg/day and aspirin 81-200 mg/day vs ticlopidine 200 mg/day and aspirin 81-200 mg/day	OL, RCT Patients with ischemic heart disease receiving stents	N=642 6 months	Primary: Rate of stenosis according to qualitative coronary angiography analysis of minimal lumen diameter of artery, safety Secondary: Not reported	Primary: The rates of restenosis (27.8% vs 29.3%; *P*=NS) and target lesion revascularization (22.4% vs 23.5%; *P*=NS) were similar between patients receiving cilostazol and ticlopidine. The rate of subacute thrombosis was significantly greater with cilostazol than ticlopidine (2.5% vs 0.3%; *P*=0.02). There were no differences in the incidence of adverse reactions with the exception of purpura, which was reported more frequently with ticlopidine than cilostazol (1% vs 0.0%; *P*=0.045). Secondary: Not reported
Leon et al[65] Aspirin 325 mg QD vs aspirin 325 mg QD and warfarin (dose adjusted to INR 2.0-2.5) vs aspirin 325 mg QD and ticlopidine 250 mg BID	MC, RCT Patients receiving a stent	N=1,653 30 days	Primary: Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days Secondary: Achievement of <50% residual	Primary: The primary end point was observed in 38 patients: 3.6% assigned to aspirin alone, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (*P*=0.001 for the comparison of all 3 groups). Secondary: Compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis (*P*=0.001) following coronary stenting. Hemorrhagic complications occurred in 10 patients: 1.8% with aspirin alone, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (*P*<0.001 for the comparison of all 3 groups); the incidence of vascular surgical complications was 0.4%, 2.0% and 2.0%, respectively (*P*=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications	There were no significant differences in the incidence of neutropenia or thrombocytopenia among the 3 treatment groups and the overall incidence was 0.3%.
Lee et al[66] DECLARE-DIABETES Aspirin 200 mg daily plus clopidogrel 300 mg loading dose, then 75 mg QD, beginning at least 24 hours before stent placement and continued for at least 6 months vs aspirin plus clopidogrel (as above) plus cilostazol 200 mg immediately after stent placement and continued for 6 months at 100 mg BID	MC, PRO, RCT Diabetic patients who are 18 years of age or older undergoing drug-eluting stent implantation	N=400 9 months	Primary: In-stent late loss at 6 months Secondary: In-segment late loss and restenosis rate at 6 months; stent thrombosis, target vessel revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at 9 months; safety	Primary: At 6 months, the in-stent late loss was significantly lower in the triple therapy versus dual therapy group (0.25±0.53 mm vs 0.38±0.54 mm; *P*=0.025). Secondary: At 6 months, the in-segment late loss (0.42±0.50 mm vs 0.53±0.49 mm; *P*=0.031) and restenosis (8.0% vs 15.6%; *P*=0.033) were significantly lower in the triple therapy versus dual therapy group. At 9 months, there was no difference in the rate of stent thrombosis (0% vs 0.5%; *P*=0.999). Target vessel revascularization was lower in the triple therapy versus dual therapy group (3.5% vs 8.0%; *P*=0.053). At 9 months, major adverse cardiac events tended to be lower in the triple therapy than in the dual therapy group (3.0% vs 7.0%; *P*=0.066). Drug discontinuation was more common in the triple therapy vs dual therapy group (14.5% vs 2.5%; *P*<0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Intermittent Claudication				
Hiatt et al[67] CASTLE Cilostazol 50-100 mg BID vs placebo	DB, MC, PA, PC, RCT Patients ≥17 years with a clinical diagnosis of PAD and symptoms of claudication, mean age 66.5 years for the cilostazol group and 65.9 years for placebo	N=1,435 Up to 3.5 years	Primary: All-cause mortality on treatment (defined as period while taking the study drug and for 30 days after discontinuing therapy) Secondary: Safety	Primary: Long-term adherence to cilostazol was poor with >60% of participants discontinuing therapy by 36 months. There were 18 deaths in patients receiving cilostazol (N=717) and 19 deaths in patients receiving placebo (N=718) (HR, 0.99; 95% CI, 0.52 to 1.88; no *P* value reported). The study was underpowered to meet its primary end point. In the full intent-to-treat population at 36 months, there were 49 deaths for cilostazol patients and 52 deaths for placebo patients (HR, 0.94; 95% CI, 0.64 to 1.39; no *P* value reported). Thus most deaths occurred >30 days after study drug discontinuation. The incidence of cardiovascular deaths was similar between the 2 groups (14 patients in each group). Secondary: Serious bleeding events affected 18 patients taking cilostazol and 22 patients taking placebo (no *P* value reported). The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel or anticoagulants at anytime during the course of the study (no *P* values reported).

Drug regimen abbreviations: BID=twice daily, ER=extended release, IR=immediate release, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, IRR=incidence rate ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PA=parallel arm, PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, IU=international units
Other abbreviations: AAASPS=American Aspirin Stroke Prevention Study, ACS=acute coronary syndrome, CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, CAST=Chinese Acute Stroke Trial, CATS=Canadian American Ticlopidine Study, CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, CARESS=Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis, CASTLE=Cilostazol: A STudy in Long-term Effects, CHARISMA=Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance, CLARITY-TIMI 28=Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 study, CLASSICS=Clopidogrel Aspirin Stent International Cooperative Study, COMMIT=ClOpidogrel and Metoprolol in Myocardial Infarction Trial, CURE=Clopidogrel in Unstable Angina to Prevent Recurrent Events, CREDO=Clopidogrel for the Reduction of Events During Observation, ESPRIT= European/Australasian Stroke Prevention in Reversible Ischemia, ESPS=European Stroke Prevention Study, FASTER=Fast Assessment of Stroke and TIA to prevent Early Recurrence, INR=international normalized ratio, MATCH=Management of ATherothrombosis with Clopidogrel in High-risk patients, MES=microembolic signal, MI=myocardial infarction, NSTEMI=non-ST-elevation myocardial infarction, PCI=percutaneous coronary intervention, PCI-ClARITY=PCI-Clopidogrel as Adjunctive Reperfusion Therapy, PCI-CURE=PCI-Clopidogrel in Unstable angina to prevent Recurrent Events, STEMI=ST-elevation myocardial infarction, TASS=Ticlopidine Aspirin Stroke Study, TIA=transient ischemic attack

Additional Evidence

Dose Simplification:
An evidenced-based medicine literature search did not reveal data pertinent to this topic, or data directly comparing the safety and efficacy of administration of the fixed-dose combination product to administration of the individual components.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Platelet-Aggregation Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
aspirin	chewable tablet, delayed-release tablet, enteric-coated tablet, packet, rectal suppository, sustained-release tablet, tablet	Ecotrin®*‡, Ninoprin®*‡, St. Joseph Aspirin®*‡, Stanback Analgesic®‡, Tasprin®*‡, Zorprin®*	$	$
aspirin and dipyridamole	extended-release capsule	Aggrenox®	$$$$	N/A
cilostazol	tablet	Pletal®*	$$$	$$$
clopidogrel	tablet	Plavix®	$$$$	N/A
dipyridamole	injection, tablet	Persantine®*, Persantine IV®*	$$$$	$$
ticlopidine	tablet	Ticlid®*	$$$$	$

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
N/A=not available.

X. Conclusions

The platelet-aggregation inhibitors play an important role in the treatment and prevention of cerebrovascular and cardiovascular diseases. Aspirin, cilostazol, dipyridamole and ticlopidine are available generically, and aspirin is available in several over-the-counter formulations. Clopidogrel (Plavix®) and the fixed-dose combination product of aspirin and extended-release dipyridamole (Aggrenox®) are not available generically. Aggrenox® is not interchangeable with the commercially available generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.

Aspirin has been the most frequently studied platelet-aggregation inhibitor and is usually the reference drug to which other treatments are compared.[50] Aspirin is the platelet-aggregation inhibitor recommended as first line in most treatment guidelines for general use. Aspirin is recommended as a first-line option for the initial management of noncardioembolic stroke or transient ischemic attack (TIA), acute coronary syndrome, and myocardial infarction, and for primary and secondary prevention in patients with cerebrovascular, cardiovascular and peripheral vascular diseases.[4-14,16-21] Low dose aspirin 75-150 mg daily is an effective antiplatelet regimen for long-term use but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Other platelet-aggregation inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy, or in high-risk patients when dual antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin and clopidogrel is recommended for patients with acute coronary syndrome (non–ST-elevation myocardial infarction and unstable angina) or ST-elevation myocardial infarction, or who undergo percutaneous coronary intervention (PCI) with stenting.[68] At this time, dual antiplatelet therapy with aspirin and clopidogrel is not recommended for primary or secondary prevention of coronary artery disease or atherosclerotic and cardioembolic ischemic strokes.[68] For patients with noncardioembolic ischemic strokes or TIAs, the combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.[4-6] At this time, there are no head-to-head clinical trials comparing the fixed-dose combination product of aspirin and extended-release dipyridamole to clopidogrel for secondary prevention of ischemic strokes. For patients who have had an ischemic stroke while taking aspirin, there is no evidence that increasing the dose provides additional benefit and there are no studies evaluating the effectiveness of other single or combination platelet-aggregation inhibitors in patients who have had an event while receiving aspirin.[4]

Clopidogrel and ticlopidine are adenosine diphosphate (ADP)-receptor antagonists and have been shown to significantly reduce the odds of a serious vascular event in high-risk patients. The CAPRIE study reported that clopidogrel significantly reduced the combined risk of ischemic stroke, myocardial infarction and vascular death by 8.7% compared to aspirin in patients with a recent ischemic stroke, myocardial infarction or established peripheral vascular disease.[51] In a subanalysis of over 6,000 patients who were enrolled in the study based on a recent ischemic stroke, clopidogrel reduced the risk of the composite endpoint by 7.3% and stroke by 8.0% compared to aspirin; however, these differences were not statistically significant.[51] On the basis of the CURE[53], COMMIT[54] and CLARITY[55] studies, clopidogrel received a Food and Drug Administration (FDA) indication for the reduction of atherothrombotic events in patients with acute coronary syndrome and myocardial infarction, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions.[7,8,10-12]

Clinical trials have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized studies that compared ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin.[48,49] When compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis following coronary stenting.[65] Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[28] When ticlopidine was compared to cilostazol in stent patients, the rate of stenosis was similar between agents.[64] However, the rate of subacute thrombosis was notably greater with cilostazol. Cilostazol has limited indications and is only recommended for patients with disabling intermittent claudication.

Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo but has not been shown to be more effective than aspirin.[38,39] Dipyridamole with aspirin significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with

dipyridamole.[38] There was no significant difference in all-cause mortality among the active treatment groups. Dipyridamole plus aspirin significantly reduced the composite of death, nonfatal stroke or MI, and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache.[41] There are no studies that have compared the safety and efficacy of administration of the fixed-dose combination product to administration of the individual ingredients.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use. Clopidogrel (Plavix®) and the fixed-dose combination product containing aspirin and extended-release dipyridamole (Aggrenox®) should be available as first-line therapy for patients who have experienced an ischemic stroke or TIA through the medical justification portion of the prior-authorization (PA) process. Clopidogrel should also be available as first-line therapy in combination with aspirin for patients experiencing acute coronary syndrome and/or acute myocardial infarction and/or undergoing percutaneous coronary interventions through the medical justification portion of the PA process.

XI. Recommendations

No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiarrhythmic Agents
AHFS Class 240404
May 14, 2008

I. Overview

Cardiac contractions are regulated by electrical activity in the heart originating in the sinoatrial node and propagated through ion channels, chiefly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels. Arrhythmias, or disorders of heart rhythm, are caused by abnormalities in formation and transmission of impulses[1] and are classified based on their origin: supraventricular (atrial or atrioventricular [AV] junction) or ventricular.

Atrial fibrillation (AF) is the most common cardiac arrhythmia that is clinically significant and the prevalence ranges among ages. According to the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, the overall prevalence of AF in the United States is 2.3 million adults (0.95%), and ranges from 0.1% in adults less than 55 years of age to 9% in those greater than age 80. Also, the ATRIA study demonstrated a higher prevalence of AF in men compared to woman and in whites compared to African Americans.[2]

Research in recent years has provided extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs exert their action; however, the general approach to antiarrhythmic therapy remains largely empirical.[3] The antiarrhythmic agents are generally grouped into specific categories or classes based on their predominant mechanisms: (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade.[1] E. M. Vaughan Williams proposed the first antiarrhythmic classification system in 1970 and it is now the most widely used scheme. The Vaughan Williams classification system divides the antiarrhythmic agents into the following classes: Class I: fast sodium channel blockers, Class II: β-blockers, Class III: repolarization potassium current blockers, Class IV: calcium channel antagonists.[4] Due to the complexity of the mechanisms of the various antiarrhythmic agents, some do not fit into one single Vaughan Williams classification.[3] While additional limitations of the Vaughan Williams system have been explored by other researchers, it continues to be the most commonly used scheme. The antiarrhythmic agents exert their pharmacologic properties through a wide range of mechanisms and they are used to treat various atrial and ventricular arrhythmias. They also differ in their pharmacokinetic, drug interaction and side effect profiles.

Table 1 lists the antiarrhythmic agents included in this review and their respective Vaughan Williams Classifications. All of the antiarrhythmic agents with the exception of dofetilide, moricizine, and extended-release propafenone are available generically. This review encompasses all dosage forms and strengths. Of note, moricizine (Ethmozine®) will no longer be available from the manufacturer as of December 31, 2007. Also, as of November 2007, production of procainamide sustained-release tablets (Procanbid®) has been discontinued by the manufacturer.

Table 1. Antiarrhythmic Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Vaughan Williams Classification	Current PDL Agent(s)
amiodarone	injection, tablet	Cordarone®*, Pacerone®*	III	amiodarone
disopyramide	capsule, sustained-release capsule	Norpace®*, Norpace CR®*	Ia	disopyramide, Norpace®*, Norpace CR®*
dofetilide	capsule	Tikosyn®	III	none
flecainide	tablet	Tambocor®*	Ic	flecainide

Generic Name	Formulation(s)	Example Brand Name(s)	Vaughan Williams Classification	Current PDL Agent(s)
mexiletine	capsule	Mexitil®*†	Ib	mexiletine
moricizine	tablet	Ethmozine®‡	I	none
procainamide	capsule, injection, sustained-release tablet	Procanbid®§	Ia	procainamide
propafenone	sustained-release capsule, tablet	Rythmol®*, Rythmol SR®	Ic	propafenone
quinidine gluconate	injection, sustained-release tablet	Quinaglute®*†	Ia	quinidine gluconate
quinidine sulfate	sustained-release tablet, tablet	Quinidex®*†	Ia	quinidine sulfate

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
‡According to Shire Pharmaceuticals, manufacturing of Ethmozine® has been discontinued and patients should be transferred to alternative agents before December 31, 2007. Ethmozine® will be available by special shipment before that date (Shire Pharmaceuticals, "Dear Prescriber" letter, 2007 Sept).
§Manufacturing of Procanbid® was discontinued in November 2007, although it will remain available through pharmacies and wholesalers until current supplies are depleted (King Pharmaceuticals, "Dear Prescriber" letter, 2007 Nov 2).

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines using antiarrhythmics are listed in Table 2. There are several guidelines for the treatment of ventricular arrhythmias and sudden cardiac death that have been published since 2000. The American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) recently created a guideline[6] for the management of atrial arrhythmias that combines the recommendations provided by previously published guidelines to allow all the current recommendations to be available in one document.

Table 2. Treatment Guidelines Using Antiarrhythmics

Clinical Guideline	Recommendation (s)
North American Society of Pacing and Electrophysiology/Heart Rhythm Society (HRS) Practice Guidelines Subcommittee: **A Practical Guide for Clinicians Who Treat Patients With Amiodarone (2007)**[5]	<u>Ventricular Arrhythmias</u> • Oral amiodarone is the recommended agent of choice for use in combination with additional appropriate therapies, including β-blockers, in patients with sustained ventricular tachyarrhythmias associated with structural heart disease, especially those with left ventricular dysfunction (LVD), and who are not candidates for an implantable cardioverter-defibrillator (ICD). • It is recommended that amiodarone therapy be reserved for symptomatic patients with non-sustained ventricular tachyarrhythmias that are refractory to β-blocker therapy and concerning enough to require treatment. <u>Atrial Fibrillation (AF)</u> • This guideline refers to the recommendations provided by the ACC/AHA/ESC 2006 guidelines that recommend oral amiodarone be used for treatment of AF in particular subsets of patients including: 1) patients post-myocardial infarction (MI) who are not candidates for sotalol or dofetilide; 2) those with congestive heart failure (CHF)and LVD who are not candidates for dofetilide; 3) patients with significant left ventricular (LV) hypertrophy, and 4) those symptomatic patients who are refractory to antiarrhythmic treatments and an alternative to catheter ablation is preferred. • Amiodarone therapy should only be considered in those patients with AF who need ventricular rate control and have failed or are unable to use other appropriate agents including digoxin, β-blockers, or calcium channel blockers. • If prophylactic amiodarone therapy is to be used prior to aortocoronary bypass surgery, it is recommended to only consider this therapy in those patients that are high-risk (prior history

Clinical Guideline	Recommendation (s)
	of AF, valve replacement surgery) and therapy with β-blocker monotherapy will most likely still be associated with a high post-operative AF occurrence rate. <u>Pregnant Patients</u> • Due to some unfavorable characteristics possessed by amiodarone, including end-organ toxicity, therapy with it in pregnant patients is not recommended unless there are no other treatment options available. <u>Pediatric Patients</u> • There is a lack of data studying intravenous (IV) amiodarone in pediatric patients, however, in some lethal tachyarrhythmias, amiodarone is often used in these situations. • It is recommended that children receiving amiodarone therapy be supervised by a pediatric electrophysiologist. <u>Patient Follow-Up</u> • Patient follow-up is recommended for patient's receiving amiodarone therapy for either atrial or ventricular arrhythmias. • Follow-up recommendations include continued assessment of drug therapy, efficacy and toxicities. • It is recommended that follow-up evaluations with patients on amiodarone take place with personnel who are experienced with the agent. • It is recommended that initial assessments occur every 3-6 months to ensure efficacy and safety of the medication and arrhythmia stability. Following the initial period, follow-up assessments may occur every 6 months. <u>Pulmonary Toxicity</u> • Pulmonary toxicity is a well-known adverse event associated with amiodarone therapy. It is recommended that a pulmonologist be consulted when: 1) there is an abnormal chest radiography at baseline or follow-up; 2) there is an abnormal pulmonary function test value (particularly forced vital capacity and [D_LCO]) at baseline or follow-up evaluation; and/or 3) a new cough and/or dyspnea, especially if otherwise unexplained or unexpected. • It is recommended that all patients who are referred to a pulmonologist undergo full pulmonary function testing and high-resolution computed tomography (CT) scanning of the chest. <u>Effects on Thyroid Function</u> • Amiodarone is known to have adverse effects on thyroid function, either by causing hypo- or hyperthyroidism. It is recommended that an endocrinologist be consulted: 1) any time hyperthyroidism is suspected, even if suppression of thyroid-stimulating hormone (TSH) is mild and subclinical disease is possible; 2) an acutely ill patient where interpretation of thyroid function tests will be complicated by euthyroid sick syndrome; and/or 3) when considering treating subclinical hypothyroidism. • It is recommended to discontinue amiodarone therapy, if possible, in those patients who have underlying thyroid disease and treat them with high-doses of antithyroid drugs. The decision to discontinue amiodarone therapy should be based on the patient's cardiac needs. <u>Follow-Up Visits</u> • A history of complaints from the patient should be noted. In patients with ICDs, amiodarone therapy should not be altered without the involvement of an electrophysiologist or a cardiologist in charge of device follow-up. • A physical examination with documentation should be performed. If visual changes are reported, an examination by an ophthalmologist is required. • The following are recommended baseline tests that should be performed: liver function tests, thyroid function tests, chest x-ray, ophthalmologic evaluation, pulmonary function

Clinical Guideline	Recommendation (s)
	tests, high-resolution CT scan, and an electrocardiogram. The follow-up evaluation should include, at minimum, a yearly electrocardiogram and chest x-ray and semiannual thyroid tests and liver enzymes. Amiodarone levels may be obtained after dose adjustments or to help determine if the dose may be decreased. When to Refer to an Electrophysiologist • Refer when worsening arrhythmia symptoms. • Refer when evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation. Until the arrhythmia problem stabilizes, the patient may require intensive monitoring, electrophysiologic testing, ablative therapy, or pacemaker or ICD implantation. • Repeat defibrillation threshold testing is recommended for patients with an ICD due to the drugs effect of increasing this threshold. • Assess amiodarone-induced slowing of ventricular tachyarrhythmias rate in patients with an ICD such that ventricular tachyarrhythmias would not be detected by the device and therapy not delivered. • Refer for pregnant patients who require amiodarone. • Refer for pediatric patients who require amiodarone.
American College of Cardiology (ACC)/ American Heart Association (AHA)/European Society of Cardiology (ESC) Committee for Practice Guidelines: **Guidelines for the Management of Patients With Atrial Fibrillation (2006)**[6]	Pharmacological Rate Control During Atrial Fibrillation • When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a β-blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control heart rate. • IV procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway. Cardioversion of Atrial Fibrillation • Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. • Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF. • A single oral bolus dose of propafenone or flecainide may be used to terminate persistent AF outside the hospital once treatment has proven safe in hospital for selected patients without sinus or atrioventricular (AV) node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a β-blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. • Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary. • Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. • Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended. • Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm. • Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent AF. • For patients with persistent AF, administration of β-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain. • Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF.

Clinical Guideline	Recommendation (s)
	• Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient. <u>Maintenance of Sinus Rhythm</u> • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. • Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. • Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. • In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. • Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with class III drug–related proarrhythmia are not present. • Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well defined risk factors for proarrhythmia with that agent. <u>Special Considerations</u> • Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF. • It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide in patients who develop postoperative AF as advised for nonsurgical patients. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF. • Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. • Administration of quinidine or procainamide may be considered to achieve pharmacological cardioversion in hemodynamically stable patients who develop AF during pregnancy. • Antiarrhythmic medications can be useful to prevent recurrent AF in patients with hypertrophic cardiomyopathy. Available data is insufficient to recommend one agent over another in this situation, but disopyramide combined with a β-blocker or nondihydropyridine calcium channel antagonist or amiodarone alone is generally preferred. • In those patients with AF and concurrent obstructive lung disease, therapy with β-blockers, sotalol, propafenone, and adenosine are not recommended.
American College of Cardiology (ACC) /American Heart Association (AHA) /European Society of Cardiology (ESC) Committee for Practice Guidelines: **Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2006)**[7]	<u>Drug Therapy for Ventricular Arrhythmias</u> • β-blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness. • Other than β-blockers, alternative antiarrhythmic agents currently available have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death (SCD). • For patients that are arrhythmia-prone, antiarrhythmic agents may be effective as adjunctive therapy in particular situations. • Caution should be used when any antiarrhythmic agent is used for therapy, as there are many side effects associated with these agents. • β-blockers, or alternatively, amiodarone or sotalol, may be used in patients with ventricular tachycardia (VT) who do not meet criteria for an ICD.

Clinical Guideline	Recommendation (s)
	• Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with ICDs who have recurrent VT/ ventricular fibrillation (VF) with frequent appropriate ICD firing. <u>Ventricular Arrhythmia and Sudden Cardiac Death Related to Specific Pathology</u> LVD Due to Prior MI: • Amiodarone, often in combination with β-blockers, can be useful for patients with LVD due to prior MI and symptoms due to VT unresponsive to β-blocking agents. • Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LVD due to prior MI unresponsive to β-blocking agents. • Alternative therapies to the ICD to improve symptoms due to frequent episodes of sustained VT or VF in patients with LVD due to prior MI include agents such as amiodarone or sotalol. • To reduce symptoms in patients due to recurrent hemodynamically stable VT with LVD due to prior MI and who cannot or refuse to have an ICD implanted, amiodarone may be used as an alternative therapy. • To improve symptoms in patients with LVD due to prior MI and recurrent hemodynamically stable VT whose left ventricular ejection fraction (LVEF) is greater than 40% and an ICD is not appropriate, amiodarone may be considered an alternative treatment option. • In patients with LVD due to prior MI where an ICD is indicated but is not appropriate or desired by the patient, amiodarone may be considered an alternative treatment option. • Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. • Class Ic antiarrhythmic agents are not recommended in patients with a past history of MI. <u>Congenital Heart Disease</u> • Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated premature ventricular contractions (PVCs). <u>Metabolic and Inflammatory Conditions</u> • Antiarrhythmic therapy can be useful in patients with symptomatic non-sustained VT or sustained VT during the acute phase of myocarditis. <u>Pericardial Disease</u> • Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension or other pulmonary conditions. <u>Ventricular Arrhythmias Associated With Cardiomyopathies</u> Dilated Cardiomyopathy (DCM) (Nonischemic): • Amiodarone may be considered for sustained VT or VF in patients with nonischemic DCM. <u>Hypertrophic Cardiomyopathy (HCM)</u> • Amiodarone therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when ICD is not feasible. • Amiodarone may be considered for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor for SCD, if ICD implantation is not feasible. <u>Arrhythmogenic Right Ventricular (RV) Cardiomyopathy</u> • Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with arrhythmogenic RV cardiomyopathy when ICD implantation is not feasible.

Clinical Guideline	Recommendation (s)
	Heart Failure(HF) • Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with HF. • Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. • Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible. Genetic Arrhythmia Syndromes Long QT Syndrome (LQTS): • β-blockers are recommended for patients with an LQTS clinical diagnosis (ie, in the presence of prolonged QT interval). • Implantation of an ICD along with use of β-blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. • β-blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. • Implantation of an ICD with continued use of β-blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving β-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. Short QT Syndrome and Brugada Syndrome: • Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. Catecholaminergic Polymorphic Ventricular Tachycardia: • β-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic VT on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. • β-blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic VT is established during childhood based on genetic analysis. • β-blockers may be considered for patients with catecholaminergic polymorphic VT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. Arrhythmias in Structurally Normal Hearts Idiopathic Ventricular Tachycardia: • Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic VT arising from the right ventricle. Ventricular Arrhythmias and Sudden Cardiac Death Related to Specific Populations Pregnancy: • In pregnant women with the LQTS who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. Elderly: • The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.

Clinical Guideline	Recommendation (s)
	Pediatrics: • Digoxin or verapamil should not be used for treatment of sustained tachycardia in infants when VT has not been excluded as a potential diagnosis.
American College of Chest Physicians (ACCP): **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery (2005)**[8]	• β-blockers and nondihydropyridine calcium channel blockers are recommended as first and second-line agents to control ventricular response rate in AF after cardiac surgery. • Agents with proarrhythmic properties and those that are contraindicated in patients with coronary artery disease have not been shown to be effective in controlling the ventricular response rate in AF after cardiac surgery. • Amiodarone is the recommended first-line agent for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with depressed LV function who do not need urgent electrical cardioversion. • Sotalol and Class Ia antiarrythmics are the recommended first-line agents for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with coronary artery disease without CHF. • When prophylaxis to prevent postoperative AF is indicated, β-blockers are the recommended agents. • Sotalol may be an alternative therapy to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option. • Amiodarone may also be considered as an alternative therapy to β-blockers to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option.
American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation (2003)**[9]	• The recommendations provided in this guideline do not apply to the following patients: those with postoperative or post–MI AF, those with class IVHF, those already taking antiarrhythmic drugs, or those with valvular disease. • For the treatment of AF, rate control (with chronic anticoagulation) is the recommended first-line treatment strategy in the majority of patients. Due to the lack of efficacy shown in clinical trials in reducing morbidity and mortality, rhythm control should be reserved for occasions when necessary, such as patient symptoms, exercise tolerance, and patient preference. • Atenolol, metoprolol, diltiazem and verapamil are the recommended agents of choice for the treatment of AF who require rate control at rest and during exercise. • Digoxin may be used as a second-line agent for those patients with AF who require rate control at rest. • Pharmacological cardioversion is an appropriate treatment option for patients who elect to undergo acute cardioversion to achieve sinus rhythm. • Agents that have been shown to be effective during pharmacological cardioversion of AF include ibutilide, flecainide, dofetilide, propafenone, and amiodarone. Quinidine also has some moderate evidence to support its use for pharmacological cardioversion of AF. Due to the lack of safety data, the AAFP/ACP have not made recommendations regarding the setting of cardioversion. • Due to the risks associated with rhythm maintenance therapy, it is not recommended to convert a majority of AF patients to sinus rhythm. Rhythm maintenance therapy may be appropriate during certain circumstances, including in those patients whose quality of life is affected by AF. The agents that are recommended for rhythm maintenance include amiodarone, disopyramide, propafenone, and sotalol. The agent should be chosen based on patient specific characteristics. • For patients with congestive systolic HF and LV hypertrophy, amiodarone is considered one of the safer agents recommended. • In patients with coronary artery disease, sotalol and amiodarone are considered to be the safest recommended agents.
Institute for Clinical Symptoms Improvement (ICSI): **Healthcare Guideline: Atrial Fibrillation (2007)**[10]	• Sotalol and dofetilide are the recommended first-line agents for the treatment of patients with coronary artery disease without HF. • The main goals of therapy with antiarrhythmic agents are to reduce symptoms, prevent recurrent AF and avoid toxicity and proarrhythmia.

Clinical Guideline	Recommendation (s)
	• The use of antiarrhythmics should be individualized based on the patient's comorbidites, cardiac history and potential risk for side effects. • Propafenone and flecainide are first-line agents, followed by amiodarone and dofetilide as second-line agents, for the treatment of patients with AF without structural or organic heart disease. • Sotalol and dofetilide are first-line agents, followed by amiodarone as a second-line agent, for the treatment of patients with AF with structural heart disease but without HF. • Amiodarone and dofetilide are first-line agents for the treatment of patients with AF with structural heart disease and HF. • Sotalol and amiodarone are first-line agents for the treatment of patients with hypertension and evidence of significant LV hypertrophy. • Although amiodarone is commonly used, it is recommended to be reserved for those patients with structural heart disease/coronary artery disease with HF, moderate to severe systolic dysfunction and hypertension with significant LV hypertrophy due to the potential of serious side effects. • Due to the potential of serious side effects associated with antiarrhythmic agents, patients should be monitored closely while on therapy with these agents. • Due to the potential of antiarrhythmics to accelerate ventricular rate, rate control must be established before antiarrhythmic agents are initiated, especially in torsades de pointes.
National Institute for Health and Clinical Excellence (NICE): **Atrial Fibrillation (2006)**[11]	• Class Ic drugs are the agents of choice for the pharmacological cardioversion of patients with persistent AF and no structural heart disease. • Amiodarone is the drug of choice for pharmacological cardioversion of patients with persistent AF and structural heart disease. • It is recommended that therapy with amiodarone or sotalol be initiated at least 4 weeks prior to cardioversion in those AF patients who may not be successful at restoring sinus rhythm, such as those who have failed on previous attempts. • The use of antiarrhythmics should be individualized based on the patient's comorbidites, cardiac history and potential risk for side effects. • Appropriate antithrombotic therapy should be used in patients with persistent AF, regardless if they are to receive rhythm control or rate control therapy. • Rhythm control is the recommended initial therapy for patients with AF and the following conditions: symptomatic, young, first presentation of AF, AF due to secondary causes, and/or CHF. • As long as there are no risk factors for recurrence are present, therapy with an antiarrhythmic agent is not necessary for sinus rhythm maintenance in those patients who had persistent AF from a secondary cause that has been corrected. • β-blockers are the recommended first-line agents, followed by amiodarone as a second-line agent, for the maintenance of sinus rhythm in those patients with persistent AF and structural heart disease. • β-blockers are the recommended first-line agents, followed by a Class Ic agent or sotalol as the second-line agents and amiodarone as the third line agent, for the maintenance of sinus rhythm in those patients with persistent AF without structural heart disease. • β-blockers or rate-limiting calcium antagonists are the recommended first-line agents for rate control in those patients with permanent AF. Digoxin is only recommended to be used in patients that are predominately sedentary. • In patients who have permanent AF and need therapy to control heart rate during normal activities in addition to the β-blockers or rate-limiting calcium antagonists, digoxin may be added. • In patients who have permanent AF and need therapy to control heart rate during normal activities and exercise, in addition to the β-blockers or rate-limiting calcium antagonists, digoxin may be added. • β-blockers are the recommended first-line treatment options, followed by a Class Ic antiarrhythmic agent or sotalol as a second-line agents, followed by amiodarone as a third

Clinical Guideline	Recommendation (s)
	line agent, for the treatment of symptomatic paroxysms and no structural heart disease. • β-blockers are the recommended first-line treatment option, followed sotalol as a second-line agent, followed by amiodarone as a third line agent, for the treatment of paroxysmal AF and coronary artery disease. • β-blockers are the recommended first-line treatment option, followed by amiodarone as a second-line agent, for the treatment of paroxysmal AF and poor LVEF. • Patients who are receiving medication management for the treatment of their paroxysmal AF should be closely monitored for side effects of therapy. • IV amiodarone should be used in patients with new onset of AF and non life-threatening hemodynamic instability where electrical cardioversion is delayed. • Flecainide may be used to cardiovert patients with Wolff–Parkinson–White syndrome and non life-threatening hemodynamic instability. It is recommended not to use diltiazem, verapamil, or digoxin to cardiovert these patients. • In those patients who have poorly controlled ventricular rates causing hemodynamic instability, it is recommended to use a pharmacological rate-control strategy for treatment. • IV β-blockers or rate-limiting calcium antagonists are the recommended first-line agents, followed by amiodarone as a second-line agent for urgent rate control. • Amiodarone, β-blockers, sotalol, or rate-limiting calcium channel antagonists are recommended agents to prevent postoperative AF in those patients undergoing cardiothoracic surgery. Digoxin is not recommended in this specific situation. • Patients receiving β-blocker therapy prior to cardiothoracic surgery should continue their therapy unless indicated otherwise. • Rhythm control is the recommend initial therapy regimen for patients following cardiothoracic unless contraindications are present. • Patients should have a follow-up visit with their health care practitioner at 1 month and 6 months post successful cardioversion to assess maintenance of sinus rhythm.

III. Indications

Food and Drug Administration (FDA)-approved indications for antiarrhythmic agents are listed in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antiarrhythmic Agents[12-35]

Generic Name	Atrial Fibrillation/ Atrial Flutter	Cardioversion of Atrial Fibrillation/ Atrial Flutter	Paroxysmal Atrial Fibrillation/Atrial Flutter	Paroxysmal Supraventricular Tachycardia (PSVT)	Ventricular Arrhythmias
Amiodarone					✔
Disopyramide					✔
Dofetilide	✔	✔			
Flecainide			✔	✔	✔
Mexiletine					✔
Moricizine					✔
Procainamide					✔
Propafenone			✔	✔	✔
Quinidine gluconate	✔	✔			✔
Quinidine sulfate	✔	✔			✔

IV. Pharmacokinetics

The pharmacokinetic parameters for the antiarrhythmic agents are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Antiarrhythmic Agents [12-35]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Half-Life	Therapeutic Range (µg/mL)
Amiodarone	35-65	96	Hepatic	15-142 days	0.5-2.5
Disopyramide	60-83	20-65	Hepatic	4-10 hours	AA: 2.8-6 VA: 3.3-7.5
Dofetilide	>90	60-70	Hepatic	10 hours	-
Flecainide	85-95	40-50	Hepatic	7-27 hours	0.2-1
Mexiletine	90	50-70	Hepatic	10-14 hours	0.5-2
Moricizine	38	95	Hepatic	1.5-4 hours	-
Procainamide	75-95	15-20	Hepatic	2.5-4.7 hours	PRO:4-10 NAPA*:15-25 Combined: 10-30
Propafenone	3.4-10.6	>95	Hepatic	2-32 hours	-
Quinidine gluconate	70	80-90	Hepatic	6-8 hours	2-5
Quinidine sulfate	45-100	80-88	Hepatic	6-8 hours	2-5

AA=atrial arrhythmias, NAPA= N-acetylprocainamide, PRO=procainamide, VA=ventricular arrhythmias
*NAPA is the active metabolite of procainamide during metabolism in the liver

V. Drug Interactions

Significant drug interactions with the antiarrhythmic agents are listed in Table 5. Drug interactions are very common among this class of agents and may be both class specific and/or agent specific. Some of these interactions are very severe and potentially life threatening due to the effects that they may cause, including life-threatening cardiac arrhythmias.

Table 5. Significant Drug-Drug Interactions with the Antiarrhythmic Agents[35]

Drug(s)	Significance Level	Interaction	Mechanism
Antiarrhythmic agents	1	Cisapride	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia and Class III antiarrhythmic agents	1	Macrolide and related antibiotics	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia and Class III antiarrhythmic agents	1	Phenothiazines	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia and Class III antiarrhythmic agents	1	Quinolone antibiotics	Mechanism of interaction is unknown. Concurrent use may lead to an increased risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia and Class III antiarrhythmic agents	1	Ziprasidone	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia, Class III antiarrhythmics and	1	Ranolazine	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of

Drug(s)	Significance Level	Interaction	Mechanism
moricizine			life-threatening cardiac arrhythmias, including torsades de pointes.
Class Ia, Class III antiarrhythmics and moricizine	1	Vardenafil	Mechanism of interaction is unknown. Concurrent use may lead to an increased risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone	1	Digoxin	Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved. Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin.
Amiodarone	1	Fentanyl	Mechanism of interaction is unknown. Concurrent use of agents may lead to profound bradycardia, sinus arrest, and hypotension.
Amiodarone	1	HMG-CoA reductase inhibitors	Amiodarone may inhibit the metabolism of HMG-CoA reductase inhibitors (CYP3A4) thereby increasing plasma concentrations and increasing the risk of toxicity (eg, myositis, rhabdomyolysis).
Amiodarone	1	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of amiodarone thereby increasing amiodarone concentrations and increasing the risk of amiodarone toxicity.
Amiodarone	1	Quinidine*	Mechanism of interaction is unknown. Concurrent therapy may lead to an increase in quinidine concentrations and produce potentially fatal cardiac dysrhythmias.
Amiodarone	1	Warfarin	Amiodarone inhibits the metabolism (CYP1A2 and CYP2C9) of the R- and S-enantiomers of warfarin; therefore the hypoprothrombinemic effects may be augmented.
Dofetilide	1	Azole antifungals	Ketoconazole may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Also, itraconazole and ketoconazole may inhibit metabolism (CYP3A4) of dofetilide. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Cimetidine	Cimetidine may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Megestrol	Megestrol may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Thiazide diuretics	Thiazide diuretics may increase potassium excretion causing hypokalemia which may increase the risk of torsades de pointes.
Dofetilide	1	Trimethoprim	Trimethoprim may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Verapamil	Verapamil may increase the rate of dofetilide absorption by increasing portal blood flow thereby increasing dofetilide plasma concentrations which may increase the risk of ventricular arrhythmias, including torsades de pointes.
Flecainide	1	Ritonavir	Ritonavir may inhibit the metabolism (CYP2D6) of flecainide.

Drug(s)	Significance Level	Interaction	Mechanism
			Large increases in serum flecainide concentrations may occur, increasing the risk of flecainide toxicity.
Propafenone	1	Digoxin	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Propafenone	1	Ritonavir	Ritonavir may inhibit the metabolism (CYP2D6) of propafenone which may lead to an increase in serum concentrations and increase the risk of propafenone toxicity.
Quinidine*	1	Amiloride	Concurrent use of these agents may lead to a synergistic increase in myocardial sodium channel blockade which may contribute to proarrhythmia and reversal of the antiarrhythmic effects of quinidine.
Quinidine*	1	Azole antifungals	Certain azole antifungal agents may inhibit the metabolism (CYP3A4) and active renal secretion of quinidine. Plasma quinidine concentrations may be elevated, increasing the risk of serious cardiovascular events.
Quinidine*	1	Digoxin	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Quinidine*	1	Protease inhibitors	Ritonavir may inhibit the metabolism (CYP3A4) of quinidine. Large increases in serum quinidine concentrations may occur, increasing the risk of quinidine toxicity.
Quinidine*	1	Verapamil	Verapamil may decrease the clearance of quinidine and prolong its half-life which may lead to hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Quinidine*	1	Warfarin	Quinine derivatives also may inhibit the hepatically synthesized clotting factors. Anticoagulation may be potentiated by quinine derivatives and hemorrhage may occur.
Amiodarone	2	Cyclosporine	Mechanism of the interaction is unknown. Amiodarone may inhibit the metabolism of cyclosporine which may lead to an increase in cyclosporine blood concentrations, possibly increasing the risk of nephrotoxicity.
Amiodarone	2	Flecainide	Amiodarone may decrease the metabolism of flecainide and plasma levels may be increased.
Amiodarone	2	Hydantoins	Concurrent use of these agents may lead to a decrease in the metabolism of hydantoins and an increase in the metabolism of amiodarone. Increased serum hydantoin concentration may lead to symptoms of toxicity.
Amiodarone	2	Procainamide	Mechanism of interaction is unknown. Amiodarone may increase procainamide serum concentrations.
Disopyramide	2	Hydantoins	Phenytoin may increase the hepatic metabolism of disopyramide via stimulation of microsomal enzymes thereby decreasing the serum levels, t½, and bioavailability of disopyramide; while increasing the metabolite mono-N-dealkyldisopyramide.
Disopyramide	2	Rifampin	Rifampin may increase the hepatic metabolism of disopyramide thereby decreasing the serum levels. However, since the levels of an active metabolite may increase, it is difficult to predict if a decreased therapeutic response would occur.
Mexiletine	2	Propafenone	Propafenone may inhibit the metabolism (CYP2D6) of mexiletine. Mexiletine plasma concentrations may be elevated in extensive metabolizers, increasing the risk of side effects.

Drug(s)	Significance Level	Interaction	Mechanism
Mexiletine	2	Theophyllines	Mexiletine may inhibit the hepatic metabolism of theophyllines via the cytochrome CYP450 oxidase system thereby increasing serum theophylline levels which may result in an increase in the pharmacologic and toxic effects.
Moricizine	2	Cimetidine	Cimetidine may increase the serum concentrations of moricizine by inhibiting the hepatic enzymes responsible for metabolism. The pharmacologic and toxic effects of moricizine may be increased.
Moricizine	2	Diltiazem	Diltiazem may elevate moricizine concentrations, increasing the pharmacologic and adverse reactions, while moricizine may reduce diltiazem concentrations, decreasing the pharmacologic effects.
Procainamide	2	Cimetidine	Cimetidine may reduce the renal clearance of procainamide thereby an increase in serum concentrations may occur.
Procainamide	2	Ciprofloxacin, levofloxacin, ofloxacin	Ciprofloxacin and similar agents may decrease the active renal tubular secretion of procainamide thereby increasing procainamide plasma concentrations.
Procainamide	2	Trimethoprim	Concurrent use of these agents may lead to a competition for renal tubular cationic secretion thereby leading to elevated procainamide and N-acetylprocainamide serum levels which may increase the pharmacologic effects of procainamide.
Propafenone	2	β-blockers	Propafenone may decrease the clearance and increase the β-blocker plasma concentration by decreasing first-pass metabolism thereby potentially increasing the pharmacological effects. Both drugs are oxidized by the hepatic CYP450 system.
Propafenone	2	Quinidine*	Quinidine may inhibit the hepatic hydroxylation metabolic pathway of propafenone. Propafenone is metabolized by CYP2D6 and quinidine is a specific and potent inhibitor of that enzyme. Serum propafenone levels may be increased in rapid, extensive metabolizers of the drug (≈90% of the patients), increasing the pharmacologic effects of propafenone.
Propafenone	2	Rifamycins	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing propafenone. Increased propafenone clearance may lead to a decrease in plasma levels and a possible loss of therapeutic effects.
Propafenone	2	Serotonin reuptake inhibitors (SRIs)	Certain SRIs may inhibit the metabolism (CYP2D6) of propafenone. Plasma propafenone levels may be elevated, increasing the pharmacologic effects and adverse reactions.
Quinidine*	2	Antacids	Antacids may decrease the urinary excretion of quinidine by affecting the pH thereby increasing quinidine concentrations which may result in toxicity.
Quinidine*	2	Aripiprazole	Quinidine may inhibit the hepatic metabolism (CYP2D6) of aripiprazole thereby increasing plasma concentrations and potentiating the pharmacologic effects and adverse reactions.
Quinidine*	2	Barbiturates	Barbiturates may increase the metabolic clearance of quinidine thereby decreasing quinidine serum concentrations and elimination half-life.
Quinidine*	2	β-blockers	Quinidine may inhibit the oxidative metabolism of certain β-blockers. The effects of certain β-blockers may be increased in "extensive metabolizers."
Quinidine*	2	Cimetidine	It is unclear if this interaction is due to increased quinidine absorption, decreased quinidine metabolism or a combination thereof. An increase in the pharmacologic and toxicologic

Drug(s)	Significance Level	Interaction	Mechanism
			effects of quinidine may occur secondary to increased quinidine concentrations. The quinidine concentrations appear to return to pretreatment values approximately 48 hours after cimetidine is discontinued.
Quinidine*	2	Codeine	Quinidine may interfere with the metabolism of codeine to morphine and the analgesic effects of codeine may be decreased.
Quinidine*	2	Diltiazem	Diltiazem may inhibit the hepatic metabolism of quinidine by competition for the same isozyme thereby increasing the therapeutic and adverse effects of quinidine.
Quinidine*	2	Ketoconazole	Ketoconazole inhibits quinine derivative metabolism (CYP3A4) therefore quinine serum levels may increase which may potentiate therapeutic and toxic effects.
Quinidine*	2	Non-depolarizing muscle relaxants	Concurrent use of these agents may cause synergistic pharmacologic effects. Non-depolarizing muscle relaxants effects may be enhanced by quinine and quinine derivatives.
Quinidine*	2	Phenytoin	Phenytoin may cause an increase in quinidine metabolism by stimulating the hepatic microsomal enzyme system responsible for quinidine metabolism which may decrease the therapeutic effect.
Quinidine*	2	Rifamycins	Rifamycins increase the hepatic metabolism of quinine derivatives therefore the therapeutic effects of quinine derivatives may be decreased.
Quinidine*	2	Succinylcholine	Quinidine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. The neuromuscular blockade produced by succinylcholine may be prolonged.

Significance Level 1=major severity
Significance Level 2=moderate severity
*Indicates both quinidine gluconate and quinidine sulfate

VI. Adverse Drug Events

Significant adverse drug events with the antiarrhythmic agents are listed in Table 6. Also, the FDA black box warnings for the individual agents are listed in Tables 7–15. The antiarrhythmic agents have a very impressive side effect profile which causes their use to be limited. Many patients cannot tolerate these agents or simply cannot use them due to concurrent medical conditions.

Table 6. Adverse Drug Events (%) Reported with the Antiarrhythmic Agents[12-35]

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Cardiovascular									
Alters pacing threshold	-	-	-	<1	-	-	-	-	-
Angina	-	-	-	<1	2	-	-	2-5	6
Arrhythmia	(1-10)	-	-	-	-	-	<1	-	(1-10)
Asystole	(1-10)	-	-	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	-	-	1	-
AV block	5	<1	0.4-1.5	<1	<1	-	-	1-3	-
AV dissociation	-	-	-	-	-	-	-	<1	-
Bradycardia	3-5	-	-	<1	-	-	-	1-2	<1
Bundle branch block	-	-	<2	-	-	-	-	0-1	-
Cardiac arrest	(1-10)	-	<2	-	-	-	-	<1	-
Cardiac death	-	-	-	-	-	(1-10)	-	-	-
Cardiogenic shock	(1-10)	-	-	-	<1	-	-	-	-
Chest pain	-	(1-10)	10	5	3-8	<1	-	1-2	-
Conduction abnormalities	(1-10)	(1-10)	-	-	-	-	-	0-1	-
Congestive heart failure	3	(1-10)	-	<1	<1	(1-10)	-	1-4	-
Edema	(1-10)	(1-10)	-	3.5	-	-	-	0-1	-
Electrocardiogram abnormalities	-	-	-	-	-	(1-10)	-	-	-
Electromechanical dissociation	(1-10)	-	-	-	-	-	-	-	-
Heart block	-	-	<2	<1	-	-	<1	-	<1
Hypertension	-	-	-	-	-	<1	-	0-1	-
Hypotension	<1	(1-10)	-	-	<1	<1	✔	-	✔
Myocardial contractility decreased	-	-	-	-	-	-	<1	-	-
Myocardial infarction	-	-	<2	-	-	<1	-	-	-
Myocarditis	-	-	-	-	-	-	<1	-	-
Palpitations	-	-	-	6	4-8	(1-10)	-	1-3	7
Pericarditis	-	-	-	-	-	-	<1	-	-

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Premature ventricular contractions	-	-	-	-	1-2	-	-	1-2	-
Proarrhythmia	<1	<1	-	4-12	10-15	(1-10)	<1	2-10	-
P-R increased	-	-	-	<1	-	-	-	-	-
QRS duration	-	-	-	<1	-	-	-	1-2	-
QT interval increased	<1	-	-	-	-	-	<1	-	>10
SA node dysfunction	1-3	-	-	-	-	-	-	-	-
Sinus arrest	<1	-	-	-	<1	-	-	-	-
Sinus node dysfunction	-	-	-	1.2	-	-	-	<1	-
Stroke	-	-	<2	-	-	-	-	-	-
Tachycardia	-	-	-	1-3	-	-	-	-	<1
Torsades de pointes	<1	-	0.9-10.5	-	<1	-	<1	-	<1
Ventricular arrhythmia	-	-	-	<1	-	<1	<1	-	-
Ventricular fibrillation	<1	-	0-0.4	-	-	-	-	-	<1
Ventricular rate increase in atrial fibrillation/atrial flutter	-	-	-	<1	-	-	<1	-	<1
Ventricular tachycardia	(1-10)	-	2.6-3.7	-	-	<1	-	1-3	<1
Central Nervous System									
Abnormal gait/ataxia	(3-40)	-	-	-	-	-	-	-	-
Amnesia	-	-	-	<1	-	-	-	<1	-
Anxiety	-	-	-	1-3	-	-	-	1-2	-
Ataxia	-	-	-	1-3	10-20	-	-	0-2	-
Cerebral hypoperfusion	-	-	-	-	-	-	-	-	<1
Coma	-	-	-	-	-	-	-	<1	-
Confusion	<1	-	-	-	(1-10)	-	-	<1	<1
Delirium	-	-	-	-	-	-	-	-	<1
Depersonalization	-	-	-	<1	-	-	-	-	-
Depression	-	<1	-	1-3	2	-	<1	<1	<1
Disorientation	<1	-	-	-	-	-	<1	-	-
Dizziness	(3-40)	(1-10)	8	19-30	20-25	>10	-	4-15	-
Drowsiness	-	-	-	-	-	-	-	1	-
Encephalopathy	<1	-	-	-	-	-	-	-	-
Euphoria	-	-	-	<1	-	-	-	-	-
Fatigue	(3-40)	(1-10)	-	8	-	(1-10)	-	2-6	7
Fever	-	-	-	1-3	-	-	-	-	<1
Flushing	-	-	-	-	-	-	-	-	<1
Hallucinations	<1	-	-	-	<1	-	<1	-	<1

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Headache	(3-40)	(1-10)	11	4-10	(1-10)	(1-10)	-	2-5	7
Impaired memory	(3-40)	-	-	-	-	-	-	-	-
Insomnia	(3-40)	<1	4	1-3	5-7	(1-10)	-	0-2	-
Involuntary movement	(3-40)	-	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	11-25	-	-	-	15
Malaise	(3-40)	(1-10)	-	1-3	-	-	-	-	-
Mania	-	-	-	-	-	-	<1	-	-
Memory loss	-	-	-	-	-	-	-	<1	-
Nervousness	-	(1-10)	-	5	5-10	-	-	-	2
Paresis	-	-	-	1-3	-	-	-	-	-
Peripheral neuropathy	(3-40)	-	-	-	-	-	-	-	-
Poor coordination	(3-40)	-	-	-	10	-	-	-	1
Psychotic reaction/psychosis	-	<1	-	-	<1	-	<1	<1	<1
Seizure	-	-	-	-	<1	-	-	0.3	-
Sleep disturbances	(3-40)	-	-	-	-	-	-	-	3
Somnolence	-	-	-	1-3	-	-	-	-	-
Syncope	-	(1-10)	<2	(1-10)	<1	<1	-	1-2	1-8
Tardive dyskinesia	-	-	-	<1	-	-	-	-	-
Vertigo	-	-	-	1-3	-	-	-	<1	<1
Visual disturbances	<10	-	-	16	-	-	-	-	<1
Dermatological									
Abnormal pigmentation	-	-	-	-	-	-	-	-	<1
Alopecia	<1	-	-	<1	<1	-	-	<1	-
Eczematous dermatitis	-	-	-	-	-	-	-	-	<1
Epididymitis	<1	-	-	-	-	-	-	-	-
Erythema multiforme	<1	-	-	-	-	-	-	-	-
Exfoliative dermatitis	<1	-	-	<1	<1	-	-	-	<1
Flushing	(1-10)	-	-	-	-	-	-	-	-
Generalized dermatoses	-	(1-10)	-	-	-	-	-	-	-
Leukocytoclastic vasculitis	<1	-	-	-	-	-	-	-	-
Lichen planus	-	-	-	-	-	-	-	-	<1
Livedo reticularis	-	-	-	-	-	-	-	-	<1
Melanin pigmentation of hard palate	-	-	-	-	-	-	-	-	<1
Phlebitis	(1-10)	-	-	-	-	-	-	-	-
Photophobia	<1	-	-	<1	-	-	-	-	-

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Photosensitivity	10-75	-	-	-	-	-	-	-	<1
Pruritus	<1	(1-10)	-	<1	-	-	<1	<1	<1
Psoriaform rash	-	-	-	-	-	-	-	-	<1
Purpura	-	-	-	-	-	-	-	<1	-
Rash	<1	(1-10)	3	1-3	4	-	>1	1-3	5
Slate blue skin discoloration	<10	-	-	-	-	-	-	-	-
Spontaneous ecchymosis	<1	-	-	-	-	-	-	-	-
Stevens-Johnson syndrome	<1	-	-	-	<1	-	-	-	-
Toxic cutaneous blisters	-	<1	-	-	-	-	-	-	-
Toxic epidermal necrolysis	<1	-	-	-	-	-	-	-	-
Urticaria	-	-	-	<1	<1	-	<1	-	<1
Vasculitis	<1	-	-	-	-	-	<1	-	-
Endocrine and Metabolic									
Decreased libido	(1-10)	-	-	-	-	(1-10)	-	-	-
Erectile dysfunction	<1	-	-	-	-	-	-	-	-
Gynecomastia	-	<1	-	-	-	-	-	-	-
Hypercholesterolemia	-	(1-10)	-	-	-	-	-	-	-
Hyperglycemia	<1	-	-	-	-	-	-	<1	-
Hyperthyroidism	3-10	-	-	-	-	-	-	-	-
Hypertriglyceridemia	<1	(1-10)	-	-	-	-	-	-	-
Hypoglycemia	-	<1	-	-	-	-	-	-	-
Hypokalemia	-	(1-10)	-	-	-	-	-	-	-
Hypothyroidism	1-22	-	-	-	-	-	-	-	-
Impotence	<1	1-3	-	-	<1	-	-	<1	-
Gastrointestinal									
Abdominal bloating	-	(1-10)	-	-	-	-	-	-	-
Abdominal distention	-	(1-10)	-	-	-	-	-	-	-
Abdominal pain	(1-10)	-	3	3	1	-	-	1-2	-
Abnormal salivation	(1-10)	-	-	-	-	-	-	-	-
Abnormal taste	(1-10)	-	-	<1	-	-	>1	3-23	>10
Angioedema	<1	-	<2	-	-	-	-	-	<1
Anorexia	(10-33)	(1-10)	-	1-3	-	-	-	1-2	>10
Cholestasis	-	-	-	-	-	-	<1	0.1	-
Constipation	(10-33)	11	-	1	4-5	-	-	2-7	-
Diarrhea	-	(1-10)	3	0.7-3	4-5	(1-10)	3-4	1-3	35

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Dry throat	-	(1-10)	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	-	-	-	1-3	-
Dysphagia	-	-	-	-	<1	-	-	-	-
Esophagitis	-	-	-	-	-	-	-	-	<1
Flatulence	-	(1-10)	-	-	-	-	-	0-1	-
Gastrointestinal distress	-	-	-	-	41	-	3-4	-	>10
Ileus	-	-	-	-	-	(1-10)	-	-	-
Nausea	(10-33)	(1-10)	5	9	40	(1-10)	>1	2-11	>10
Stomach cramping	-	-	-	-	-	-	-	-	22
Swollen lips/tongue/mouth	-	-	-	<1	-	-	-	-	-
Upper gastrointestinal bleeding	-	-	-	-	<1	-	-	-	-
Vomiting	(10-33)	(1-10)	-	-	40	-	>1	2-11	>10
Weight gain	-	(1-10)	-	-	-	-	-	-	-
Xerostomia	-	32	-	-	3	-	-	1-2	-
Genitourinary									
Dysuria	-	<1	-	-	-	-	-	-	-
Urinary frequency	-	(1-10)	-	-	-	-	-	-	-
Urinary hesitancy	-	14-23	-	-	-	-	-	-	-
Urinary retention	-	(1-10)	-	<1	<1	-	-	-	-
Urinary urgency	-	(1-10)	-	-	-	-	-	-	-
Hematological									
Agranulocytosis	<1	<1	-	-	<1	-	<1	<1	-
Aplastic anemia	<1	-	-	-	-	-	<1	-	-
Coagulation abnormalities	(1-10)	-	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	<1	-	-	-	<1	-
Hemolytic anemia	<1	-	-	-	-	-	<1	-	<1
Hemoptysis	<1	-	-	-	-	-	-	-	-
Hypoplastic anemia	-	-	-	-	-	-	<1	-	-
Leukopenia	-	-	-	<1	<1	-	<1	<1	-
Neutropenia	<1	-	-	-	-	-	<1	-	-
Pancytopenia	<1	-	-	-	-	-	<1	-	<1
Thrombocytopenia	<1	<1	-	<1	<1	-	0.5	<1	<1
Hepatic									
AST or ALT level >2x normal	15-50	<1	-	-	-	-	-	-	-

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Cirrhosis	<3	-	-	-	-	-	-	-	-
Hepatic failure	-	-	-	-	-	-	<1	-	-
Hepatic necrosis	-	-	-	-	<1	-	-	-	-
Hepatitis	<3	-	-	-	<1	-	<1	0.03	<1
Hepatotoxicity	-	<1	<2	-	-	-	-	-	<1
Neuromuscular and Skeletal									
Arthralgia	-	-	-	-	1	-	-	0-1	<1
Back pain	-	-	3	-	-	-	-	-	-
Facial paralysis	-	-	<2	-	-	-	-	-	-
Flaccid paralysis	-	-	<1	-	-	-	-	-	-
Lupus	-	<1	-	-	<1	-	-	<1	-
Lupus-like syndrome	-	-	-	-	-	-	<1	-	<1
Muscle pain (myalgia)	-	(1-10)	-	-	-	-	-	-	<1
Myasthenia gravis	-	-	-	-	-	-	<1	-	-
Myopathy	<1	-	-	-	-	-	<1	-	-
Neuromuscular blockade	-	-	-	-	-	-	<1	-	-
Neuropathy	-	<1	-	<1	2-4	-	<1	<1	-
Paralysis	-	-	<2	-	-	-	-	-	-
Paresthesia	-	<1	<2	1	2	-	-	<1	-
Parkinsonian symptoms	<1	-	-	-	-	-	-	-	-
Rhabdomyolysis	<1	-	-	-	-	-	-	-	-
Trembling	-	-	-	-	>10	-	-	-	-
Tremor	(3-40)	-	-	5	13	-	<1	0-1	2
Unsteady gait	-	-	-	-	>10	-	-	-	-
Weakness	<1	(1-10)	-	5	5	-	-	1-2	5
Ocular									
Blurred vision	-	(1-10)	-	(1-10)	5-7	(1-10)	-	1-6	(1-10)
Corneal microdeposits	>90	-	-	<1	-	-	-	-	-
Diplopia	-	-	-	1-3	-	-	-	-	-
Dry eyes	-	(1-10)	-	-	-	-	-	-	-
Halo vision	<5	-	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	-	-	-	-	<1
Nystagmus	-	-	-	-	6	-	-	-	-
Optic neuritis	1	-	-	-	-	-	-	-	<1
Optic neuropathy	<1	-	-	-	-	-	-	-	-
Periorbital edema	-	-	-	-	-	(1-10)	-	-	-
Uveitis	-	-	-	-	-	-	-	-	<1

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
Visual disturbances	2-9	-	-	-	-	-	-	-	-
Renal									
Acute renal failure	<1	-	-	-	-	-	-	<1	-
Increased creatinine	-	<1	-	-	-	-	-	-	-
Nephropathy	-	-	-	-	-	-	-	-	<1
Nephrotic syndrome	-	-	-	-	-	-	-	<1	-
Respiratory									
Acute respiratory distress syndrome	2	-	-	-	-	-	-	-	-
Alveolar pneumonitis	✔	-	-	-	-	-	-	-	-
Apnea	-	-	-	-	-	<1	-	<1	-
Bronchiolitis oblitetans organizing pneumonia	<1	-	-	-	-	-	-	-	-
Bronchospasm	<1	-	-	<1	-	-	-	-	<1
Dyspnea	<1	(1-10)	6	~10	3	(1-10)	-	2-5	-
Hypersensitivity pneumonitis	✔	-	-	-	-	-	-	-	-
Pleural effusion	-	-	-	-	-	-	<1	-	-
Pleuritis	<1	-	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	<1	-	-	-	-	<1
Pulmonary alveolar hemorrhage	<1	-	-	-	-	-	-	-	-
Pulmonary edema	<1	-	-	-	-	-	-	-	-
Pulmonary embolism	-	-	-	-	-	-	<1	-	-
Pulmonary fibrosis	✔	-	-	-	<1	-	-	-	-
Pulmonary inflammation	✔	-	-	-	-	-	-	-	-
Pulmonary mass	<1	-	-	-	-	-	-	-	-
Pulmonary toxicity	2-17	-	-	-	-	-	-	-	-
Respiratory failure	<1	<1	-	-	-	-	<1	-	<1
Respiratory tract infection	-	-	7	-	-	-	-	-	-
Wheezing	<1	-	-	-	-	-	-	-	(1-10)
Other									
Abnormal smell	(1-10)	-	-	-	-	-	-	-	-
Anaphylactic shock	<1	-	-	-	-	-	-	-	-
Angioneurotic edema	-	-	-	-	-	-	<1	-	-
Blood urea nitrogen	-	<1	-	-	-	-	-	-	-

Adverse Event	Amiodarone	Disopyramide	Dofetilide	Flecainide	Mexiletine	Moricizine	Procainamide	Propafenone	Quinidine*
increased									
Bone marrow granuloma	<1	-	-	-	-	-	-	-	-
Bone marrow suppression	-	-	-	-	-	-	<1	-	-
Cerebellar ataxia	-	-	-	-	-	-	<1	-	-
Cholestatic jaundice	-	<1	-	-	-	-	-	-	-
Cinchonism	-	-	-	-	-	-	-	-	<1
Demyelinating polyradiculoneuropathy	-	-	-	-	-	-	<1	-	-
Diaphoresis	-	-	-	-	-	-	-	1	-
Flu syndrome	-	-	4	-	-	-	-	-	-
Hearing impairment	-	-	-	-	-	-	-	-	<1
Hypoxia	<1	-	-	-	-	-	-	-	-
Increased bleeding time	-	-	-	-	-	-	-	<1	-
Increased creatine phosphokinase	-	-	-	-	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	-	<1
Myelofibrosis	-	-	-	-	<1	-	-	-	-
Pancreatitis	<1	-	-	-	<1	-	<1	-	-
Positive Antinuclear Antibody test	-	-	-	-	-	-	<1	-	-
Positive Coomb's test	-	-	-	-	-	-	<1	-	-
Pseudo-obstruction	-	-	-	-	-	-	<1	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-	-
Sicca syndrome	-	-	-	-	-	-	-	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	<1	-	-	-	-	-	-	<1	-
Thyroid cancer/nodules	<1	-	-	-	-	-	-	-	-
Thyrotoxicosis	<1	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	1-3	2-3	-	-	<1	(1-10)
Vascular collapse	-	-	-	-	-	-	-	-	<1
Vasculitis	-	-	-	-	-	-	-	-	<1

ALT= Alanine aminotransferase, AST= Aspartate aminotransferase, AV=atrioventricular, SA=sinatrial
✓ Percent not specified
-Event not reported or incidence <1%
*Incorporates both quinidine gluconate and quinidine sulfate
(#)=range given, but exact percent not specified

Table 7. Black Box Warning for Amiodarone[12,22,23,34,35]

WARNING
Life-threatening arrhythmias: Amiodarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. **Potentially fatal toxicities:** Amiodarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10% to 17% in some series of patients with ventricular arrhythmias given doses of approximately 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal approximately 10% of the time. Liver injury is common with amiodarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, amiodarone can exacerbate the arrhythmia (eg, by making the arrhythmia less well tolerated or more difficult to reverse). This has occurred in 2% to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2% to 5%. In most cases, all of these events should be manageable in the proper clinical setting. Although the frequency of such proarrhythmic events does not appear greater with amiodarone than with many other agents used in this population, the effects are prolonged when they occur. **High-risk patients:** Even in patients at high risk of arrhythmic death in whom the toxicity of amiodarone is an acceptable risk, amiodarone poses major management problems that could be life-threatening in a population at risk of sudden death; therefore, make every effort to utilize alternative agents first. The difficulty of using amiodarone effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least 1 week, usually 2 weeks or more. Because absorption and elimination are variable, maintenance dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 patients required dose reduction and 18 required at least temporary discontinuation because of adverse reactions, and several series have reported 15% to 20% overall frequencies of discontinuation because of adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Table 8. Black Box Warning for Disopyramide[13,24,34,35]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (eg, those without recent MI) is uncertain. Considering the known proarrhythmic properties of disopyramide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of disopyramide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Table 9. Black Box Warning for Dofetilide[14,25,34,35]

WARNING
To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see Administration and Dosage. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Table 10. Black Box Warning for Flecainide[15,26,34,35]

WARNING
Mortality: Flecainide was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group. This rate was 5.1% for flecainide and 2.3% for the matched placebo. The average duration of treatment with flecainide in this study was 10 months. The applicability of the CAST results to other populations (eg, those without recent MI) is uncertain, but at present, it is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. **Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter:** A review of the world literature revealed reports of 568 patients treated with oral flecainide for paroxysmal atrial fibrillation/flutter (PAF). Ventricular tachycardia was experienced in 0.4% of these patients. Of 19 patients in the literature with chronic atrial fibrillation (CAF), 10.5% experienced ventricular tachycardia (VT) or ventricular fibrillation (VF). Flecainide is not recommended for use in patients with CAF. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased premature ventricular contractions (PVCs), VT, VF, and death. As with other Class I agents, patients treated with flecainide for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such as digoxin or β-blockers may lower the risk of this complication.

Table 11. Black Box Warning for Mexiletine[16,27,34,35]

WARNING
Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of Mexiletine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of Mexiletine as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmia. **Acute Liver Injury:** In postmarketing experience abnormal liver function tests have been reported, some in the first few weeks of therapy with Mexiletine hydrochloride. Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to Mexiletine hydrochloride has not been established.

Table 12. Black Box Warning for Moricizine[17,28,34,35]

WARNING
Mortality: Moricizine was 1 of 3 antiarrhythmic drugs included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST I), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a MI more than 6 days, but less than 2 years, previously. An excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with both of the Class IC agents included in the trial, which led to

WARNING
discontinuation of those 2 arms of the trial. Average duration of treatment was 10 months. The moricizine and placebo arms of the trial were continued in the NHLBI-sponsored CAST II. In this randomized, double-blind trial, patients with asymptomatic non-life-threatening arrhythmias who had an MI within 4 to 90 days and left ventricular ejection fraction 0.4 or less prior to enrollment were evaluated. The average duration of treatment with moricizine in this study was 18 months. The study was discontinued because there was no possibility of demonstrating a benefit toward improved survival with moricizine and because of an evolving adverse trend after long-term treatment, although there was no statistical significance vs placebo. The applicability of the CAST results to other populations (eg, those without recent MI) is uncertain. Considering the known proarrhythmic properties of moricizine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, it is prudent to reserve the use of moricizine for patients with life-threatening ventricular arrhythmias.

Table 13. Black Box Warning for Procainamide[18,29,34,35]

WARNING
The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test, with or without symptoms of a lupus erythematous-like syndrome. If a positive ANA titer develops, the benefits versus risks of continued procainamide therapy should be assessed. **Mortality:** In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had myocardial infarction more than 6 days but less than 2 years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to matched placebo-treated group (3%). The average duration of treatment with onoalnide or flecainide in this study was 10 months. The applicability of the cast results to other populations (eg, those without recent myocardial infarctions) is uncertain. Considering the known proarrhythmic properties of procainamide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of procainamide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias. **Blood dyscrasias:** Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia and thrombocytopenia in patients receiving procainamide have been reported at a rate of approximately 0.5%. Most of these patients received procainamide within the recommended dosage range. Fatalities have occurred (with approximately 20% to 25% mortality in reported cases of agranulocytosis). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts including white cell, differential and platelet counts be performed at weekly intervals for the first 3 months of therapy, and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat or stomatitis), bruising or bleeding. If any of those hematologic disorders are identified, procainamide therapy should be discontinued. Blood counts usually return to normal within 1 month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type.

Table 14. Black Box Warning for Propafenone[19,30,31,34,35]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (eg, those without recent MI) or other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart

WARNING
disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with non life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening symptoms or signs.

Table 15. Black Box Warning for Quinidine*[20,21,32-35]

WARNING
Many trials of antiarrhythmic therapy for non-life threatening arrhythmias, has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease. In the case of quinidine used to prevent or defer recurrence of atrial flutter/fibrillation, meta-analysis data has shown that the mortality associated with the use of quinidine was more than three times greater than placebo. Another meta-analysis showed that in patients with various non-life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

*Refers to both quinidine gluconate and quinidine sulfate

VII. Dosing and Administration

The usual dosing regimens for the antiarrhythmic agents are summarized in Table 16. Dosing with these agents differs based on the indication that is being treated, as well as the dosage form that is being used. Some agents, such as disopyramide, have specific dosing instructions for when a patient is being converted from another antiarrhythmic agent. Also, a majority of these agents are not FDA approved for use in the pediatric population, with the exception of flecainide.

Table 16. Dosing and Administration for the Antiarrhythmic Agents[12-35]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiodarone	Ventricular Arrhythmias: Tablet: Initial: 800–1,600 mg daily for 1–3 weeks, then titrate down to 600–800 mg daily for one month (for total daily doses of 1,000 mg or more or when gastrointestinal intolerance occurs, give in divided doses with meals). Maintenance: 400 mg daily, up to 600 mg daily, given as a single dose or divided twice daily. Intravenous (IV): Initial: 15 mg/min for 10 min (150 mg), then 1 mg/min IV for 6 hours (360 mg), then 0.5 mg/min IV for 18 hours (540 mg). Maintenance: 0.5 mg/min IV after the first 24 hours (720 mg/24 hours) with a concentration of 1-6 mg/mL. Breakthrough: breakthrough ventricular fibrillation (VF)/ventricular tachycardia (VT), 150 mg IV over 10 min. When converting from IV to oral: <1 week: IV to oral 800–1,600 mg daily; 1 to 3 week: IV to oral 600–800 mg daily; >3 week: IV to oral 400 to mg daily	Safety and efficacy in pediatrics have not been established.	Tablet: 100 mg 200 mg 300 mg 400 mg Intravenous: 50 mg/mL Disposable syringe: 150 mg/3mL
Disopyramide	Ventricular Arrhythmias: Capsule: Rapid Control (immediate release):	Safety and efficacy in pediatrics have not been established.	Capsule: 100 mg 150 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Patients >50 kg: 300 mg followed by appropriate maintenance dose Patients <50 kg: 200 mg followed by appropriate maintenance dose Sustained-release formulation is not recommended for initial therapy. Maintenance: Patients >50 kg: 400–800 mg daily (divided every 6 hours for immediate-release or every 12 hours for sustained-release formulation). Patients <50 kg: 400 mg daily in divided doses Maximum dose: 1,200–1,600 mg daily When converting a patient from procainamide or quinine sulfate, disopyramide should be started using the regular maintenance schedule without a loading dose 6-12 hours after the last dose of quinidine sulfate or 3-6 hours after the last dose of procainamide.		Capsule, sustained release (SR): 100 mg 150 mg
Dofetilide	Atrial fibrillation/Atrial Flutter: Normal renal function and QTc ≤440 msec: Initial: 500 µg twice daily; at 2–3 hours after first dose, if QTc increases >15% or >500 msec, reduce dose to 250 µg twice daily When converting a patient from a Class I or Class III antiarrhythmic agent to dofetilide, the previous antiarrhythmic agent should be discontinued for at least 3 half-lives prior to the initiation of dofetilide. When switching from amiodarone, amiodarone plasma levels should be less than 0.3 µg/mL prior to initiation of dofetilide therapy.	Safety and efficacy in pediatrics have not been established.	Capsule: 0.125 mg 0.25 mg 0.5 mg
Flecainide	Paroxysmal Atrial Fibrillation/Atrial Flutter: Initial: 50 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 300 mg daily Paroxysmal Supraventricular Tachycardia: Initial: 50 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 300 mg daily Ventricular Arrhythmias: Initial: 100 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 400 mg daily When converting a patient from another antiarrhythmic agent, the previous antiarrhythmic agent should be discontinued at least 2-4 plasma half-lives prior to the initiation of flecainide therapy. When giving flecainide concurrently with amiodarone, the flecainide dose should be dropped by 50% and	Paroxysmal Atrial Fibrillation/Atrial Flutter: <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily >6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily Paroxysmal Supraventricular Tachycardia: <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily	Tablet: 50 mg 100 mg 150 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	patient should be monitored closely for any adverse effects.	>6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily <u>Ventricular Arrhythmia:</u> <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily >6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily	
Mexiletine	<u>Ventricular Arrhythmias:</u> Capsule: Rapid Control: loading dose of 400 mg, then 200 mg in 8 hours Initial: 200 mg every 8 hours Titration: increase by 50–100 mg every 2-3 days or longer Maintenance: 200–300 mg every 8 hours Maximum dose: 1,200 mg daily IV: Initial: 150–250 mg bolus over 10 mins, then 250 mg infusion over 30–60 mins, then 250 mg infusion over 2.5 hours, then 500 mg infusion over 8 hours Maintenance: 250–500 mg infusion every 12 hours When converting a patient from a Class I antiarrhythmic agent to mexiletine, the following titration schedule is recommended: initiated mexiletine with a 200 mg dose, and titrate to response 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, 6-12 hours after the last dose of disopyramide or 8-12 hours after the last dose of tocainide. When switching therapy from lidocaine, the lidocaine infusion should be stopped when the first oral dose of mexiletine is administered.	Safety and efficacy in pediatrics have not been established.	Capsule: 150 mg 200 mg 250 mg
Moricizine	<u>Ventricular Arrhythmias:</u> Maintenance: 600–900 mg daily in divided doses every 8 hours Titration: increase by 150 mg daily every 3 days When converting a patient from another antiarrhythmic agent to moricizine, the previous antiarrhythmic agent should be discontinued at least 1-2 plasma half-lives prior to the initiation of moricizine therapy.	Safety and efficacy in pediatrics have not been established.	Tablets: 200 mg 250 mg 300 mg
Procainamide	<u>Ventricular Arrhythmias:</u> Tablets and capsules:	Safety and efficacy in pediatrics have not been established.	Capsule: 250 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial: 40–50 kg: 2 g daily in divided doses* 60–70 kg: 3 g daily in divided doses* 80–90 kg: 4 g daily in divided doses* >100 kg: 5 g daily in divided doses* Maximum dose: 50 mg/kg daily IV: Initial: Maximum rate of 50 mg/min to a maximum dose of 1 g Maintenance: infusion of 2–6 mg/min Intramuscular (IM): Initial: 50 mg/kg/ daily in divided doses of one-eighth to one-quarter every 3-6 hours		375 mg 500 mg Tablet, sustained release: 500 mg 750 mg 1,000 mg IV solution: 100 mg/mL 500 mg/mL
Propafenone	<u>Atrial Fibrillation/Atrial Flutter:</u> Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours Capsule, sustained release: Initial: 225 mg every 12 hours Titration: increase every 5 days to 325–425 mg every 12 hours <u>Paroxysmal Supraventricular Tachycardia:</u> Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours <u>Ventricular Arrhythmias:</u> Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours	Safety and efficacy in pediatrics have not been established.	Tablet: 150 mg 225 mg 300 mg Capsule, sustained release: 225 mg 325 mg 425 mg
Quinidine gluconate	<u>Atrial Fibrillation/Atrial Flutter:</u> Tablet, sustained release: 324 mg every 8–12 hours, may increase dose with caution if necessary <u>Atrial Fibrillation/Atrial Flutter-Cardioversion:</u> Tablet, sustained release: Option 1: 1,648 mg every 8 hours; if no cardioversion after 3–4 doses, may increase dose with caution if necessary Option 2: 2,324 mg every 8 hours for 2 days, then 648 mg every 12 hours for 2 days, then 648 mg every 8 hours for up to 4 days IV: Infusion of 0.25 mg/kg/min until sinus rhythm restored Maximum dose: 10 mg/kg	Safety and efficacy in pediatrics have not been established.	Tablet, sustained release: 324 mg IV: 80 mg/mL

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Ventricular Arrhythmia: Tablet, sustained release: 324 mg every 8–12 hours, may increase dose with caution if necessary IV: Infusion of 0.25 mg/kg/min until sinus rhythm restored Maximum dose: 10 mg/kg		
Quinidine sulfate	Atrial Fibrillation/Atrial Flutter: Tablet: 200 mg every 6 hours; may increase dose with caution if necessary Tablet, sustained release: 300 mg every 8–12 hours Atrial Fibrillation/Atrial Flutter-Cardioversion: Tablet: 400 mg every 6 hours; if no cardioversion after 4–5 doses, may increase dose with caution Tablet, sustained release: 300 mg every 8–12 hours; may increase dose with caution if necessary Ventricular Arrhythmia: Tablet: 200 mg every 6 hours; may increase dose with caution if necessary Tablet, sustained release: 300 mg every 8–12 hours	Safety and efficacy in pediatrics have not been established.	Tablet: 200 mg 300 mg Tablet, sustained release: 300 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antiarrhythmic agents are summarized in Table 17.

Table 17. Comparative Clinical Trials Using the Antiarrhythmic Agents

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cairns et al[36] Amiodarone loading dose of 10 mg/kg in two divided doses daily for 2 weeks, followed by 300–400 mg daily for 3–5 months, then 200–300 mg daily for 4 months, and finally 200 mg daily for 5–7 days per week for 16 months vs placebo Dose was reduced if suppression of arrhythmia was detected by ECG. If not detected, dose was not reduced.	DB, MC, PC, RCT Patients greater than 19 years who had an acute MI within the previous 6–45 days, and the development of new 40 ms Q-waves in ≥2 adjacent ECG leads or the development of a dominant R-wave in V1, 24 hour ambulatory ECG monitoring that recorded a mean of ≥10 VDPs per hour (≥18 hours of monitoring required), or at ≥1 run of VT (≥3 beats at a rate of 100–120 per min, or 3–10 beats at a rate of >120 per min)	N=1,202 2 years	Primary: RVF or AD Secondary: AD, cardiac death and all-cause mortality	Primary: Twenty five patients receiving amiodarone compared to 39 patients receiving placebo experienced an RVF or AD (RR reduction, 38.2; 95% CI, –2.1 to 62.6; *P*=0.029). Secondary: Twenty four patients receiving amiodarone compared to 33 patients receiving placebo experienced an AD (RR reduction, 29.3; 95% CI, –19.6 to 58.2; *P*=0.097). Cardiac mortality was not statistically significant between amiodarone and the placebo groups (44 vs 55 patients respectively; RR reduction 22.0; 95% CI, –15.9 to 47.6; *P*=0.108). All cause mortality was not statistically significant between the amiodarone and placebo groups (57 vs 68 patients respectively; RR reduction, 18.3; 95% CI, –16.1 to 42.6; *P*=0.129).
Julian et al[37] Amiodarone 800 mg daily for 2 weeks, followed by 400 mg daily for 14 weeks, then 200 mg daily until the end of the study vs	DB, MC, PC, RCT Patients between the ages of 18–75 years who survived ≥5 days post documentation of an MI, LVEF of ≤40% on MUGA done 5–21 days after admission to the coronary-care unit	N=1,486 2 years	Primary: All-cause mortality Secondary: Cardiac mortality, AD and AD plus resuscitated cardiac arrest	Primary: There was not a statistically significant difference in all-cause mortality between the amiodarone and placebo groups (102 vs 103 patients in group; risk ratio, 0.99; 95% CI, 0.76 to 1.31; *P*=0.96). Secondary: There was not a statistically significant difference in total cardiac mortality between the amiodarone and placebo groups (89 vs 85 patients; risk ratio, 0.94; 95% CI, 0.70 to 1.26; *P*=0.67).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				The amiodarone group had a lower number of patients who experienced an AD compared to the patients in the placebo group (50 vs 33 patients; risk ratio, 0.65; 95% CI, 0.42 to 1.00; *P*=0.05). The amiodarone group had a lower number of patients who experienced an AD and resuscitated cardiac arrest compared to the patients in the placebo group (61 vs 42 patients; risk ratio, 0.68; 95% CI, 0.46 to 1.00; *P*=0.05).
Deedwania et al [38] Amiodarone 800 mg QD for 2 weeks, then 400 mg QD for 50 weeks, then 300 mg QD vs placebo	DB, MC, PC Patients with history of HF (≥ 3 months), NYHA class II, III, or IV, LVEF ≤40%, evidence of dilated cardiomyopathy, dyspnea on exertion or history of paroxysmal nocturnal dyspnea, and frequent ventricular premature beats (≥10 per hour averaged over a 24-hour period) on 24-hour Holter monitoring	N=667 4.5 years	Primary: Rate control vs conversion to sinus rhythm in AF patients Secondary: Occurrence of new AF in patients who were in sinus rhythm at baseline and a comparison of survival rates in those patients with AF who converted to sinus rhythm to those who remained in AF during the remainder of the study	Primary: From time points at 2 weeks and beyond, the ventricular rates of those patients in the amiodarone treatment group were significantly lower than those in the placebo group (*P*=0.001 at week 2, and *P*=0.006 at months 6 and 12). Of the patients that had AF at baseline, 16 patients in the amiodarone group compared to 4 patients in the placebo group, spontaneously converted to sinus rhythm (*P*=0.002). Secondary: Eleven patients in the amiodarone group compared 22 patients in the placebo group experienced new-onset AF (*P*=0.005). Patients in the amiodarone group who spontaneously converted to sinus rhythm and maintained it during the follow-up period had significantly lower mortality compared with those who remained in AF (*P*=0.04).
Torp-Pederson et al[39] Dofetilide 250 µg QD–500 µg BID depending on creatinine clearance vs placebo	DB, MC, PC, RCT Patients ≥18 years hospitalized with new or worsening CHF and who within the preceding month had had ≥1 episode of shortness of breath on minimal	N=1,518 1 year	Primary: Death from any cause Secondary: Death from cardiac causes, death from arrhythmia, death from cardiac causes	Primary: Death did not differ significantly between dofetilide treatment group and placebo (311 [41%] vs 317 [42%] respectively; HR, 0.95; 95% CI, 0.81 to 1.11; *P*=0.54). Secondary: There was not a significant difference in death from cardiac causes between dofetilide treatment group and placebo (255 [33%] vs 251 [33%] patients respectively; *P* value was not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Initially, 500 µg bid for patients without AF and 250 µg BID for patients with AF. After the first 288 patients, initial dosing was changed and was based on creatinine clearance: 40–59 mL/min received 250 µg BID and <40 mL/min received 250 µg QD.	exertion or at rest or paroxysmal nocturnal dyspnea, were postmenopausal or were using a reliable means of contraception, and provided written informed consent		or successful resuscitation after cardiac arrest, arrhythmias requiring treatment, worsening CHF and MI, and in patients with baseline AF, incidence of conversion to and maintenance of sinus rhythm	There was not a significant difference in death from arrhythmias between dofetilide treatment group and placebo (156 [20%] vs 151 [20%] patients respectively; *P* value was not reported). Fewer hospitalizations due to worsening heart failure were experienced in the dofetilide group compared to placebo (30% vs 38% respectively; *P* value was not reported). There was a statistically significant greater number of patients with AF at baseline who converted to sinus rhythm in the dofetilide compared to those patients with AF at baseline in the placebo group. At 1 month: 12% vs 2% respectively ($P<0.001$) and at 12 months: 44% vs 13% respectively ($P<0.001$). After cardioversion, more patients with baseline AF in the dofetilide group maintained sinus rhythm compared to those patients in the placebo group (HR, 0.35; 95% CI, 0.22 to 0.57; $P<0.001$).
Kochiadakis GE et al[40] Amiodarone 15 mg/kg QD for 7 days, followed by 10 mg/kg QD for 7 days, then tapered dose over 7–12 days to maintenance levels over 7-12 days to a maintenance dose of 200 mg QD vs Propafenone 150-300 mg followed by a maintenance dose of 150 mg TID	RCT, SB Patients greater than 18 years of age, ECG documentation of AF, symptoms such as light-headedness, palpitation, chest pain, and dyspnea in association with AF; successful chemical or electrical cardioversion to sinus rhythm in the patients with persistent AF	N=146 3 years	Primary: Time to adverse events (relapse to AF or intolerable side effects) whichever occurred first Secondary: Maintenance of AF free time	Primary: There was not a significant difference between the amiodarone and propafenone groups for the suppression of recurrent symptomatic AF or in side effects ($P=0.44$). Secondary: Amiodarone and propafenone were equally effective in maintaining sinus rhythm without side effects included ($P=0.058$).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cast Investigators[41-43] CAST I trial: Encainide 35–50 mg TID, flecainide 100–150 mg BID or moricizine 200–250 mg TID vs placebo Doses not specified, but lowest dose was tried first and titration was open labeled.	MC, OL, PC, RCT Patients 6 days to 2 years post documented MI who had ≥6 VDPs per hour during an ambulatory ECG recording, and a LVEF of ≤55% if recorded 6–90 days after MI, or ≤40% if recorded 90 days-2 years post-MI	N=2,371 1 year	Primary: Overall survival and free of cardiac arrest or AD Secondary: Not reported	Primary: After 1 year of therapy 90% of patients in the active treatment group survived compared to 95% of patients in the placebo group (*P*=0.0006). A higher total mortality rate was seen in the encainide and flecainide groups: 56 patients (7.7%) taking encainide or flecainide compared to 22 patients (3.0%) taking placebo (RR, 2.5; 95% CI, 1.6 to 4.5; *P* value was not reported). After 1 year of therapy, 93% of patients in the active treatment group were free of cardiac arrest or AD compared to 96% of patients in the placebo group (*P*=0.003). Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests: 33 patients (4.5%) taking encainide or flecainide compared to 9 patients (1.2%) taking placebo (RR, 3.6; 95% CI, 1.7 to 8.5; *P* value was not reported). After a mean follow up of 10 months, due to a significantly higher death rate in the active treatment group (63 patients) compared to the placebo group (26 patients; *P*=0.000), the flecainide and encainide arms of this trial were stopped early. Also, death or cardiac arrest due to arrhythmia was significantly higher in the active treatment group (43 patients) compared to the placebo group (16 patients; *P*=0.0004). Secondary: Not reported
Cast Investigators[41-43] CAST II trial: Moricizine 200 mg TID titrated up to 900 mg TID vs placebo	MC, PC, RCT Patients with LVEF greater than or equal to 40%, who were within 4-90 days of having an MI	N=1,178 2 years and 14 days	Primary: Sudden death Secondary: Not reported	Primary: During the initial 2-week trial, 17 patients (2.3%) died compared to 3 (0.3%) in the placebo group. The RR was 5.6 (95% CI, 1.7 to 19.1; *P* value not reported). There was found to be a less than 8% chance of finding a survival benefit if the study was completed. Due to the excess mortality in the moricizine arm, the trial was terminated early. Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
This was a continuation of the CAST I trial above.[41-43]				Not reported
Wyse et al[44] Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs Rate control therapy: β-blockers, calcium-channel blockers, digoxin, and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)	MC, RCT Patients 65 years and older who had AF that was likely recurrent, AF was likely to cause illness or death, long-term treatment for AF was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization	N=4,060 3.5 years	Primary: Overall mortality Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest	Primary: The difference in mortality between the two groups was not statistically significant (HR, 1.15; 95% CI, 0.99 to 1.34; *P*=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (*P*=0.33).
Van Gelder et al[45] Rhythm control therapy: electrical cardioversion, then sotalol 160-320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200-300 mg QD or propafenone 450-900 mg QD; if	MC, RCT Patients with recurrent persistent AF or atrial flutter, who have undergone one electrical cardioversion during the previous two years, with a maximum of two	N=522 2 years	Primary: Composite of death from cardiovascular causes, HF, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of –5.4; 90% CI, –11.0 to 0.4). Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, –3.4 to 3.9). HF occurred in 9 (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of –1.0; 90% CI, –3.8 to 1.8).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
recurrence again, electrical cardioversion repeated along with amiodarone 600 mg QD for 4 weeks then 200 mg QD vs Rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination			Secondary: Not reported	Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of –2.4; 90% CI, –6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in 9 (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, –1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in 2 (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of –3.7; 90% CI, –6.0 to –1.4). A pacemaker was implanted in 3 (1.2%) patients in rate-control group and in 8 (3.0%) patients in the rhythm-control group (absolute difference of –1.8; 90% CI, –3.9 to 0.2). Secondary: Not reported
Opolski et al[46] Rhythm control therapy: propafenone 450–600 mg QD, disopyramide 300–600 mg QD or sotalol 160–320 mg QD vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs. All patients underwent	MC, OL, RCT Patients between 50–75 years of age with AF known to be present continuously for between 7 days and 2 years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization,	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; $P>0.71$). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1 ± 8.6 beats/min) in 24 hour Holter monitoring compared to the patients in the rate control group (85.8 ± 7.5 beats/min; $P<0.003$). Four patients in the rhythm control group experienced proarrhythmic effects (*P* value not reported). Whether this lead to discontinuation of therapy was not mentioned. At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion (*P* values not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
electric cardioversion prior to the initiation of study medication. Drug given to patient was determined by their arrhythmia etiology, concomitant heart diseases and age. If patient had recurrent AF, cardioversion was repeated and an alternate antiarrhythmic agent was given in addition to amiodarone.			new or worsening CHF, or changes in exercise tolerance	There was not a statistical difference seen in bleeding complications between the rhythm control group (8 patients) and rate control group (5 patients; *P* value not reported). A significantly lower number of hospitalizations were seen in the rate control arm compared to the rhythm control arm (12% vs 74%, respectively; *P*<0.001). Both the rhythm control group and rate control group had significant improvements in CHF class at some point during follow-up compared to baseline (*P*<0.001 and *P*<0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow-up period (*P* value was not reported). At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (*P*<0.001 and *P*<0.001, respectively).

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: CI=confidance interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized control trial, SB=single-blinded
Miscellaneous abbreviations: AD=arrhythmic death, AF=atrial fibrillation, CAST=Cardiac Arrhythmia Suppression Trial, CHF=congestive heart failure, ECG= electrocardiographic, HF=heart failure, HR=hazard ratio, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MUGA= multiple-gated nuclear angiography, NYHA=New York Heart Association, OR=odd ratio, RR=relative risk, RVF=resuscitated ventricular fibrillation, VDPs=ventricular premature depolarizations, VT=ventricular tachycardia

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 18. Relative Cost of the Antiarrhythmic Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amiodarone	injection, tablet	Cordarone®*, Pacerone®*	$$-$$$$$	$$$
disopyramide	capsule, sustained-release capsule	Norpace®*, Norpace CR®*	$$$	$$$
dofetilide	capsule	Tikosyn®	$$$$	N/A
flecainide	tablet	Tambocor®*	$$$$$	$$$
mexiletine	capsule	Mexitil®*†	N/A	$$
moricizine	tablet	Ethmozine®	$$$$	N/A
procainamide	capsule, injection, sustained-release tablet	Procanbid®	$$$$-$$$$$	$$
propafenone	sustained-release capsule, tablet	Rythmol®*, Rythmol SR®	$$$$	$$$
quinidine gluconate	injection, sustained-release tablet	Quinaglute®*†	N/A	$$
quinidine sulfate	sustained-release tablet, tablet	Quinidex®*†	N/A	$$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=not available.

X. Conclusions

The antiarrhythmic agents are broken down into classifications based on their primary mechanism of action. The Vaughan Williams classification system is the most widely used scheme and breaks down the agents into four main classes: sodium channel blockers, β-blockers, potassium blockers, and calcium channel antagonists. The FDA approved indications differ between agents and may include atrial arrhythmias and/or ventricular arrhythmias. With the exceptions of dofetilide, moricizine and extended-release propafenone, all other antiarrhythmics reviewed are available in generic formulations. Two products, moricizine (Ethmozine®) and procainamide sustained-release tablets (Procanbid®) were discontinued by the manufacturer in 2007.

Adverse events and major drug interactions are common among the antiarrhythmic agents and these properties tend to limit their use in clinical practice. Several clinical trials have demonstrated these adverse events. One important trial, the Cardiac Arrhythmia Suppression Trial (CAST),[41,42] showed that some antiarrhythmic agents, in particular the class Ic agents, were associated with higher mortality rates when compared to placebo. Due to these results, the CAST trial was stopped prematurely and the FDA placed a black box warning on this class of agents recommending that they be reserved for patients with severe, life-threatening arrhythmias. Some adverse events are dose dependant, therefore manufacturers recommend using the lowest effective dose to prevent the occurrence of adverse reactions. Also, several of these agents have recommended therapeutic ranges to assist health care providers in effectively dosing these agents and avoiding potential adverse events or toxicities.[12-35]

Guidelines incorporating the use of antiarrhythmic agents for the treatment of both atrial and ventricular arrhythmias have recently been published.[5-11] The antiarrhythmics are generally not recommended as first-line agents for the treatment of ventricular arrhythmias. Amiodarone and sotalol may be used to treat ventricular tachycardias in patients with left ventricular dysfunction due to a prior myocardial infarction and who are not responding to β-blockade from other agents. In those patients with atrial fibrillation, rate control is the recommended treatment strategy but rhythm control may be appropriate in certain circumstances, particularly in patients whose quality of life is affected by atrial fibrillation. Some antiarrhythmic agents may be appropriate to use for rhythm control in patients with particular disease states, for instance sotalol and Class IA antiarrythmics may be used for postoperative atrial fibrillation or atrial flutter in patients with coronary artery disease without congestive heart failure.[5-11] There are many factors that should be addressed prior to the selection of an antiarrhythmic agent for a patient, including the type of arrhythmia, concurrent disease states, and potential risk to benefit ratio of therapy.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Pharmacotherapy Review of Cardiotonic Agents
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I. Overview

Digitalis was initially obtained from the foxglove plant, *Digitalis lanata*, and later found to possess positive inotropic effects on the heart.[1] The cardiotonic agent reviewed here, digoxin, is one of the cardiac glycosides and is extracted from the leaves of the *Digitalis lanata* plant.[2] The efficacy of digoxin in patients with heart failure and atrial fibrillation has been well established and widely accepted. Digoxin is a potent and selective inhibitor of the active transport of Na^+ and K^+ across the cell membrane.[1] In congestive heart failure, digoxin increases cardiac contractility by inhibiting the Na^+ and K^+ adenosine triphospate (ATPase) pump. In supraventricular arrhythmias, digoxin suppresses atrioventricular node conduction of electrical impulses thereby slowing ventricular rates.[3] Adverse effects and drug interactions are common with digoxin and its narrow therapeutic concentration range makes precise dosing extremely vital in order to limit toxicity.

Table 1 lists the cardiotonic agents included in this review. Digoxin is available generically in both oral and injectable formulations. This review encompasses all dosage forms and strengths.

Table 1. Cardiotonic Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
digoxin	capsule, elixir, injection, tablet	Lanoxicaps®, Lanoxin®*, Lanoxin Pediatric®	digoxin, Lanoxicaps®

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

The role of digoxin in therapy has changed over the last decade. McNamara and colleagues[4] published a background review summarizing the evidence of the efficacy of medications to treat atrial fibrillation (AF) which supports the recommendations provided by the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) guideline.[5] Also, many guidelines that have been published by particular organizations are endorsed by other organizations, for example, the American College of Chest Physicians (ACCP) endorses the American College of Cardiology (ACC)/American Heart Association (AHA) guideline update for the diagnosis and management of chronic heart failure (HF).[6] Guidelines that incorporate digoxin in the treatment of AF as well as heart failure are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiotonic Agents

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Health Care Guideline for Atrial Fibrillation (2007)**[7]	• β-blockers and calcium channel blockers (CCBs) are recommended first and second line agents and digoxin is a third line agent for rate control. It is not recommended to give digoxin to patients with wide QRS/WPW/preexcitation, hypokalemia, hypomagnesemia, and renal impairment. • Digoxin can be utilized for patients with significant systolic congestive heart failure (CHF), but is not as effective for exercise rate as the other agents. • Agents such as diltiazem, verapamil and digoxin are ineffective in controlling ventricular response. Such agents may increase a patient's risk of ventricular fibrillation by facilitating conduction through the accessory pathways.
American College of Cardiology (ACC)/ American Heart Association (AHA)/ European Society of	• Oral digoxin may effectively control the heart rate at rest in patients with AF and is indicated for patients with HF, left ventricular (LV) dysfunction, or for sedentary individuals. • Digoxin is no longer considered first-line therapy for rapid management of AF, except in

Clinical Guideline	Recommendation(s)
Cardiology (ESC) Committee for Practice Guidelines: **Guidelines for the Management of Patients with Atrial Fibrillation (2006)**[8]	patients with HF or LV dysfunction, or perhaps in patients who are so sedentary as to obviate the need for rate control during activity because there are more effective agents that are now available. • To control heart rate, digoxin use concurrently with either a β-blocker or nondihydropyridine CCB is reasonable in patients with AF, both at rest and during exercise. The medication chosen should be individualized and bradycardia should be avoided by closely monitoring and changing digoxin therapy. • Concurrent use of digoxin and β-blockers appears to be more effective than the concurrent use of digoxin and a CCB. • It is not recommended to use digoxin for pharmacological cardioversion of AF as harm may be caused. • Digitalis glycosides have not been proven to be more efficacious than placebo for the conversion of recent-onset AF to sinus rhythm. Digoxin may actually prolong the duration of paroxysmal AF episodes in some patients. • Evidence does not support the use of digitalis to suppress recurrent AF in most patients. • Digoxin, a β-blocker, or a nondihydropyridine CCB are all options and are recommended in pregnancy to control ventricular response rate.
National Institute for Health and Clinical Excellence (NICE): **Atrial Fibrillation (2006)**[9]	• For patients who need rate control for chronic AF, β-blockers and calcium channel blockers are first line agents. Digoxin should only be used as first line in sedentary patients or in those who cannot tolerate β-blockers or CCBs. • For patients who are prescribed digoxin alone for rate control, a diagnosis should be written on the prescription. • Combination therapies such as digoxin/β-blocker or digoxin/CCB may be considered once a patient has failed monotherapy. • Digoxin has been proven to be infective in pharmacological cardioversion and therefore is determined to be an inappropriate therapy for this indication. • Digoxin should not be used in AF patients who are hemodynamically unstable due to its slow onset of action. • The use of digoxin in patients with Wolff-Parkinson-White (WPW) syndrome is contraindicated due to the potential of exacerbating a rapid AF. • Digoxin has not been clinically proven to be effective in preventing postoperative AF therefore should not be used in this indication.
American College of Chest Physicians (ACCP): **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery (2005)**[10]	• β-Blockers and nondihydropyridine CCBs are recommended as first- and second line agents to control ventricular response rate in AF after cardiac surgery. Digoxin has shown little efficacy in this patient population. • Current medical evidence does not support the use of digitalis for the prevention of postoperative AF. • No recommendation can be made regarding the use of digoxin for rhythm control of postoperative AF or atrial flutter.
American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation (2003)**[5]	• For patients with AF, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil. Digoxin is only effective for rate control at rest and therefore should only be used as a second-line agent for rate control in AF. • Combinations of digoxin plus diltiazem, atenolol, or betaxolol have also been shown to be effective at rest and with exercise, but these may be better reserved for occasions when single agent therapy has failed.
Heart Failure Society of America (HFSA): **Comprehensive Heart Failure Guideline (2006)**[11]	• Digoxin should be considered for patients with LV systolic dysfunction (left ventricular ejection fraction [LVEF] <40%) who have signs or symptoms of HF while receiving standard therapy, including angiotensin converting enzyme inhibitors (ACEI) and β-blockers: New York Heart Association (NYHA) class II-III and IV. • It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of

Clinical Guideline	Recommendation(s)
	patients and the serum digoxin level should be <1.0 ng/mL. • Doses greater than 0.25 mg daily for rate control are not recommended. • It is recommended that patients taking amiodarone and digoxin concurrently, that the maintenance dose of digoxin be reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended.
American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines: **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)[6]**	• The safety and efficacy of digoxin does not compare favorably with that of other agents such as aldosterone blockers. • Digoxin may be added to concurrent therapy with diuretics, an ACEI or angiotensin receptor blocker (ARB), and a β-blocker in those patients with persistent HF symptoms or in those patients who have not yet responded to this initial therapy. • Digoxin therapy may be delayed until the patient remains symptomatic despite therapy with the neurohormonal antagonists or delay digoxin therapy until the symptomatic patient has tried and did not respond or could not tolerate aldosterone antagonist as well. • Digoxin should be considered an adjunct therapy to β-blockers for rate control because β-blockers improve survival and may be effective at controlling rate alone. • In patients with an acute exacerbation of HF symptoms, patient should be initially treated with appropriate HF therapy, and once stable, digoxin may be initiated as part of a long-term treatment plan. • Digoxin should be avoided in patients with significant sinus or atrioventricular (AV) block (unless patient has pacemaker) and it should be used cautiously in patients who are on other agents that may suppress sinus or AV nodal function or affect digoxin levels.
European Society of Cardiology (ESC): **Guideline for the Diagnosis and Treatment of Chronic Heart Failure (2005)[12]**	• Cardiac glycosides are indicated in AF and symptomatic HF, regardless of LV dysfunction. • β-blockers and digoxin or a combination of these agents are treatment options for patients with asymptomatic AF. • Digoxin is the recommended first line agent in patients with symptomatic AF and systolic dysfunction. • A combination of digoxin and β-blocker appears more efficacious to either agent alone in patients with AF. • Digoxin has no effect on mortality but may reduce hospitalizations and, particularly, worsening HF hospitalizations, in the patients with HF caused by LV systolic dysfunction and sinus rhythm treated with ACEI, β-blockers, diuretics and in severe HF, spirinolactone. • Digoxin therapy should be initiated at lower doses in elderly patients so that there is a lower risk of adverse effects. This same principle should be applied to patients with elevated serum creatinine.
European Society of Cardiology (ESC): **Guideline on the Diagnosis and Treatment of Acute Heart Failure (2005)[13]**	• Patients who have had a myocardial infarction and acute HF, providing inotropic support with cardiac glycosides is not recommended due to the potential of proarrhythmias. • Cardiac glycosides may be used in patients with tachycardia-induced HF. • Cardiac glycosides are contraindicated in the following: bradycardia, second and third degree AV-block, sinus sick syndrome, carotid sinus syndrome, WPW syndrome, hypertrophic obstructive cardiomyopathy, hypokalemia, and hypercalcemia.
National Institute for Health and Clinical Excellence (NICE): **Management of Chronic Heart Failure in Adults in Primary and Secondary Care (2003)[14]**	• First line therapy for patients with heart failure is an ACEI or ARB (if ACEI is not tolerated). • Digoxin may be added to concurrent therapy with a diuretic, ACEI, ARB, or β-blocker if the patient remains symptomatic and is in sinus rhythm. • If a patient has symptomatic HF and AF, digoxin should be used as the first line agent. • Digoxin is recommended for patients with worsening or severe HF due to LV systolic dysfunction despite therapy with ACEI, β-blocker and diuretic therapy. • Digoxin is recommended in patients with AF and any degree of HF. • Serum potassium should be monitored when patients are on digoxin therapy.

Clinical Guideline	Recommendation(s)
	• It is not recommended to obtain serum digoxin levels on a routine basis. A digoxin level drawn between 8–12 hours after the last dose may supply useful information to determine toxicity or non-compliance. • Reminder that patient's may experience signs of toxicity even if there digoxin level is in the recommended therapeutic range.

III. Indications

Food and Drug Administration (FDA)-approved indications for the cardiotonic agents are listed in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cardiotonic Agents[2,14]

Indication	Digoxin
For the treatment of mild to moderate heart failure	✔
For the control of ventricular response rate in patients with chronic atrial fibrillation	✔

IV. Pharmacokinetics

The pharmacokinetic parameters for the cardiotonic agents are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiotonic Agents[2,15]

Digoxin Dosage Form	Bioavailability (%)	Protein Binding (%)	Metabolism	Elimination	Serum Half-Life*
Tablet	60-80	25	16% metabolized via hydrolysis, oxidation and conjugation	Renal	1.5-2 days†
Pediatric elixir	75-85				
Capsule	90-100				
Injection	100				

*Renal excretion of digoxin is proportional to glomerular filtration rate (GFR).
†In normal renal function. Half-life may range from 3.5-5 days in anuric patients.

V. Drug Interactions

Significant drug interactions with the cardiotonic agents are listed in Table 5. Any drug that may decrease renal function may decrease the excretion of digoxin, therefore caution should be exercised in patient's who are taking these agents concurrently with digoxin. The manufacturer lists several potential drug interactions that may be seen with concurrent therapy with digoxin. Agents such as alprazolam, amiodarone, indomethacin, itraconazole, propafenone, quinidine, rifampin, spirinolactone, and verapamil may reduce the clearance, and therefore may cause an increase in serum digoxin levels. Clarithromycin, erythromycin, and tetracycline may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, resulting in an increase in serum digoxin levels. Also, antacids, certain anticancer drugs, kaolinpectin, neomycin and sulfasalazine may interfere with the intestinal absorption of digoxin, which may lead to lower serum digoxin levels.[2]

Table 5. Significant Drug-Drug Interactions with the Cardiotonic Agents[15]

Drug(s)	Significance Level	Interaction	Mechanism
Digoxin	1	Amiodarone	Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved. Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin.

Drug(s)	Significance Level	Interaction	Mechanism
Digoxin	1	Propafenone	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Digoxin	1	Quinidine	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Digoxin	2	Cholestyramine	Cholestyramine may decrease the gastrointestinal absorption of digoxin by binding to it. Cholestyramine may also interrupt the enterohepatic recycling of digoxin.
Digoxin	2	Metoclopramide	Metoclopramide may decrease the absorption of digoxin by increasing gastrointestinal motility.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Significant adverse drug events with the cardiotonic agents are listed in Table 6. The adverse drug events reported with digoxin are dose dependant. Adverse events are less common when digoxin is used at recommended doses to achieve a therapeutic effect. It is also recommended that digoxin be used within the recommended therapeutic concentration range of 4.0-5.5 mmol/L and medications given concurrently be monitored closely to decrease the incidence of adverse drug events.[2]

Digoxin is contraindicated in patients with a known hypersensitivity to digoxin or any component of digoxin. Also, digoxin is contraindicated in those with a hypersensitivity to cardiac glycosides (another may be tried); a history of toxicity; ventricular tachycardia or fibrillation; idiopathic hypertrophic subaortic stenosis; constrictive pericarditis; amyloid disease; second- or third-degree heart block (except in patients with a functioning artificial pacemaker); Wolff-Parkinson-White syndrome and atrial fibrillation concurrently.[2]

Table 6. Adverse Drug Events (%) Reported with the Cardiotonic Agents[2,3,16]

Adverse Reaction	Digoxin
Cardiovascular	
Accelerated junctional rhythm	✔
Asystole	✔
Atrial tachycardia with block	✔
Atrioventricular dissociation	✔
Heart block (1st, 2nd, or 3rd degree)	✔
Palpitations	<1
PR prolongation	✔
ST segment depression	✔
Ventricular fibrillation	✔
Ventricular premature contractions, unifocal or multiform (especially bigeminy or trigeminy)	<1
Ventricular tachycardia	✔
Central Nervous System	
Anxiety	✔
Apathy	✔
Confusion	✔
Delirium	✔
Depression	✔
Dizziness	4.9
Fever	✔
Hallucinations	✔
Headache	3.2

Adverse Reaction	Digoxin
Mental disturbances	4.1
Visual disturbances (blurred or yellow vision)	✔
Dermatological	
Alopecia	✔
Edema (facial, angioneurotic, or laryngeal)	✔
Maculopapular rash	1.6
Pruritus	✔
Rash (bullous, erythematous, papular, scarlatiniform or vesicular)	✔
Shedding of fingernails or toenails	✔
Urticaria	✔
Endocrine and Metabolic	
Gynecomastia	<1
Plasma estrogen increased (men and postmenopausal women)	<1
Plasma testosterone decreased (men)	<1
Serum luteinizing hormone decreased (men and postmenopausal women)	<1
Sexual dysfunction	<1
Gastrointestinal	
Abdominal pain	✔
Anorexia	<1
Diarrhea	3.2
Nausea	3.2
Vomiting	1.6
Hematological	
Eosinophilia	<1
Thrombocytopenia	<1
Neuromuscular and skeletal	
Weakness	✔
Other	
Hemorrhagic necrosis of the intestines	<1
Intestinal ischemia	<1
Vaginal cornification	<1

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the cardiotonic agents are summarized in Table 7. Several factors must be taken into account when dosing digoxin including the patient's lean body weight, renal function, age, concomitant disease states, concurrent medications, or other factors that may alter the pharmacokinetic properties of digoxin. In addition, measuring serum digoxin concentrations may be useful for clinicians to determine the adequacy of digoxin therapy and avoid digoxin adverse events and/or toxicity.[14]

Table 7. Usual Dosing for the Cardiotonic Agents[2,3,16]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Digoxin	Heart Failure: Tablet: Rapid digitalization: 0.5-0.75 mg orally; monitor response; additional doses of 0.125-0.375 mg orally may be given cautiously at 6-8 hour intervals to achieve response Maintenance or gradual digitalization: give 0.125 to 0.5 mg once daily, titrate every 2 weeks	Heart Failure: IV and/or oral capsule: Rapid digitalization (give in divided doses): Premature: 15-25 µg/kg Full-term: 20-30 µg/kg 1-24 months: 30-50 µg/kg 2-5 years: 25-35 µg/kg 5-10 years: 15-30 µg/kg Over 10 years: 8-12 µg/kg	Capsule: 100 µg 200 µg Elixir: 50 µg/mL Injection: 100 µg/mL 250 µg/mL

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Intravenous (IV) injection or capsule: Rapid digitalization: 0.4-0.6 mg; additional doses of 0.1-0.3 mg may given cautiously at 6-8 hour intervals to achieve response Maintenance or gradual digitalization: give 0.1-0.4 mg once daily, titrate every 2 weeks Elixir: Maintenance: 3 µg/kg daily, adjust as necessary Without loading dose Tablet or elixir: Initial: 0.25 mg orally once daily Maintenance: 0.125-0.5 mg orally once daily; titrate dose every 2 weeks <u>Supraventricular Arrhythmia:</u> IV/Oral: Loading dose: 0.25 mg every 2 hours; maximum of 1.5 mg Maintenance dose: 0.125-0.375 mg orally daily OR 0.125-0.25 mg IV daily	Maintenance dose or gradual digitalization: (give in divided doses) Premature: 20%-30% of IV digitalizing dose All other pediatrics: 25%-35% of oral or IV digitalizing dose Elixir: Rapid digitalization (give in divided doses): Premature: 20-30 µg/kg Full-term: 25-35 µg/kg 1-24 months: 35-60 µg/kg 2-5 years: 30-40 µg/kg 5-10 years: 20-35 µg/kg Over 10 years: 10-15 µg/kg Maintenance doses or gradual digitalization (give in divided doses) Premature: give 20%-30% of oral digitalizing dose All other pediatrics: 25%-35% of oral digitalizing dose Tablet: Maintenance dose (give in divided doses): 2-5 years: 10-15 µg/kg 5-10 years: 7-10 µg/kg Over 10 years: 3-5 µg/kg <u>Supraventricular Arrhythmia:</u> Usual dose: 8-12 µg/kg Dose should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects.	Tablet: 125 µg 250 µg 500 µg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cardiotonic agents are found in Table 8.

Table 8. Outcomes Evidence for the Cardiotonic Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atrial Fibrillation				
Hallberg et al[17] AF group: Patients with AF on digoxin vs patients with AF not on digoxin CHF group: patients with CHF on digoxin vs patients with CHF not on digoxin AF and CHF group: Patients with AF and CHF on digoxin vs patients with AF and CHF not on digoxin	Cohort AF group: ECG finding of AF at admission, at discharge or had a discharge diagnosis of AF CHF group: History of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission AF and CHF group: ECG finding of AF on admission, ECG finding of AF at discharge or a discharge diagnosis of AF, and a medical history of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission	N=60,764 1 year	Primary: One year mortality Secondary: Effects on LVEF, s-creatinine and AMI	Primary: Patients with AF who received digoxin did significantly worse than those AF patients who did not receive digoxin therapy (RR of death was 1.42; 95% CI, 1.29 to 1.56; *P* value was not reported). Patients with CHF who received digoxin therapy did significantly worse than those CHF patients who did not receive digoxin therapy (RR of death was 1.11; 95% CI, 1.04 to 1.19; *P* value was not reported). In the group of patients with AF and CHF, there was no mortality difference between those that received digoxin therapy and those that did not receive digoxin therapy (RR of death was 1.00; 95% CI, 0.94 to 1.06; *P* value was not reported). Secondary: In patients with an LVEF of ≤30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.06; 95% CI, 0.86 to 1.31; *P* value was not reported). In patients with an LVEF of >30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.14; 95% CI, 0.98 to 1.32; *P* value was not reported). Regardless of level of s-creatinine (low, normal, high), there was not a significant difference in mortality between those who received digoxin therapy and those who did not: low s-creatinine (RR of death was 1.23; 95% CI, 0.91 to 1.66), normal s-creatinine (RR of death was 1.22; 95% CI, 0.94 to 1.58), high s-creatinine (RR of death was 0.98; 95% CI, 0.83 to 1.16) respectively; *P* values were not reported. In patients with an AMI, the RR for death was 1.17; 95% CI, 1.10 to 1.24

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				between those that received digoxin therapy and those that did not receive digoxin therapy; *P* value was not reported. In patients without an AMI, the RR for death was 1.10; 95% CI, 1.04 to 1.16 between those that received digoxin therapy and those that did not receive digoxin therapy; *P* values were not reported.
Khand et al[18] <u>Phase 1:</u> Digoxin with placebo vs digoxin with carvedilol <u>Phase 2:</u> digoxin vs carvedilol	DB, PC, PG, RCT Patients with persistent AF for >1 month and HF who were receiving digoxin and diuretics	N=47 Phase 1: 4 months Phase 2: 6 months	Primary: Assessment of LVEF, ventricular rate control, symptom improvement, exercise test Secondary: Not reported	Primary: Phase 1: The patients in the digoxin with carvedilol group experienced a reduction in mean ventricular rate compared to the patients in the digoxin with placebo group (65.2±15 vs 74.9±11.2 respectively; *P*<0.0001). The patients in the digoxin with carvedilol group experienced improved LVEF compared to the patients in the digoxin with placebo group (30±9.6 vs 26±12.4 respectively; *P*=0.048). The patients in the digoxin with carvedilol group experienced an improvement in symptom scores compared to the patients in the digoxin with placebo group (7 [3 to 12.5] vs 8 [3 to 15] respectively; *P*=0.039). The patients in the digoxin with carvedilol group experienced a reduced ventricular rate at rest and throughout steady-state exercise (peak ventricular rate 106 beats/min) compared to those patients in the digoxin with placebo group (peak ventricular rate 123 beats/min; *P*<0.05). Phase 2: There was no significant difference in ventricular rate control between the digoxin and the carvedilol treatment groups (88.8±18.7 vs 75.7±10.6 respectively; *P*=0.13). There was no significant difference in LVEF between the digoxin and the carvedilol treatment groups (21.6±11 vs 27.2±11.7 respectively; *P*=0.15). There was no significant difference in symptom scores between the digoxin and the carvedilol treatment groups (6 [2 to 17] vs 8 [5 to 15.5] respectively; *P*=0.08). There was no significant difference in ventricular rate at steady-state exercise between the digoxin and the carvedilol treatment groups (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). Secondary: Not reported
Koh, Song et al[19] Digoxin 0.125–0.5 mg QD plus diltiazem 90 mg BID vs digoxin 0.125–0.5 mg QD plus betaxolol QD	PRO, RCT, XO Patients with persistent AF for >1 month	N=37 7 months	Primary: Effects on ventricular rate, blood pressure, rate-pressure, maximal exercise tolerance Secondary: Safety	Primary: Patients in the digoxin plus betaxolol group experienced a significant reduction in ventricular rates both at rest and during exercise (67±3 and 135±5 beats/min, respectively) compared to the patients in the digoxin plus diltiazem group (80±7 and 154±5 beats/min, respectively; $P<0.05$). Patients in the digoxin plus betaxolol group experienced a significant reduction in systolic blood pressure during maximal exercise (164±4 mm Hg) but not at rest (127±3 mm Hg) compared to the patients in the digoxin plus diltiazem group (173±4 and 130±4 mm Hg, respectively; $P<0.05$, $P>0.05$, respectively). Patients in the digoxin plus betaxolol group experienced significantly less rate-pressure products at rest (85±4 x 10^2 mm Hg/min) and during exercise (213±12 x 10^2 mm Hg/min) compared to the patients in the in digoxin plus diltiazem group (105±6 and 269±12, respectively; $P<0.05$ for both). Both the digoxin plus betaxolol group and the digoxin plus diltiazem group experienced a significant improvement in exercise capacity compared to baseline ($P<0.05$), but the groups were not statistically significant from one another (9.3±0.5 vs 9.7±0.5 MET; $P>0.05$). There were no statistical differences between the treatment groups in any of the efficacy points measured between time points at weeks 4 and 7 months (*P* values were not reported). Secondary: No patients withdrew from the study in either treatment groups due to side effects. The digoxin plus betaxolol group experienced more side effects, which were considered minimal, compared to the digoxin plus diltiazem group (*P* values were not reported). The minimal side effects observed in the digoxin plus betaxolol group included dyspnea, gastric pain, fatigue and constipation.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hemels et al[20] Group 1: Digoxin 0.125-0.25 mg QD plus acute (within 24 hours) ECV vs digoxin 0.125-0.25 mg QD plus routine ECV Group 2: verapamil 120-360 mg QD with acute (within 24 hours) ECV vs verapamil 120-360 mg QD plus routine ECV Study medications were dosed to reach a target HR<100 beats/min and were administered for 4 weeks before ECV and continued during total follow-up. ECV was done one month after randomization and was only performed if anticoagulation therapy had been adequate (goal INR 2.5 to 3.5).	MC, PRO, RCT Patients with persistent AF, defined as non–self-terminating arrhythmia and requiring ECV to obtain SR), and no contraindications to anticoagulation therapy	N=144 18 months	Primary: Freedom from permanent AF Secondary: Quality of life	Primary: At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the acute and routine ECV groups (32%; 95% CI, 22 to 44 vs 31%; 95% CI, 21 to 44, respectively; *P*=0.85), despite more ECVs in the acute versus the routine group ([median 3 vs 2 ECVs; *P*<0.05] and [≥3 ECVs in 54% vs 33% of patients, respectively; *P*<0.01]). At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the verapamil and digoxin groups (28%; 95% CI, 19 to 40 vs 36%; 95% CI, 25 to 48, respectively; *P*=0.33), despite more ECVs in the digoxin group compared to the verapamil group ([median 3 vs 2 ECVs, respectively; *P*<0.001] and [≥3 ECVs in 60% vs 28% of patients, respectively; *P*<0.001]). Secondary: At the end of the 18 month follow-up period, there were no significant differences in quality of life between the acute and the routine cardioversion groups. Also, at the end of the 18 months, there were no significant differences in quality of life between the digoxin and verapamil groups (*P* values were not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heart Failure				
Koh, Kwon et al[21] Without digoxin, diltiazem, or betaxolol (Group I) vs digoxin 0.125–0.5 mg QD (Group II) vs digoxin 0.125–0.5 mg QD and diltiazem 90 mg BID (Group III) vs digoxin 0.125–0.5 mg QD and betaxolol 20 mg QD (Group IV)	PRO, RCT Patients with chronic HF for >1 month	N=45 4 weeks	Primary: HR, blood pressure, rate-pressure Secondary: Not reported	Primary: Resting ventricular rates were lower in all patients receiving active treatment (groups II, III, IV) compared those patients in group I who did not receive digoxin (*P*<0.01). Ventricular rates during exercise were lower in groups III and IV compared to groups I and II (*P*<0.01). No significant differences in ventricular rate were noted between groups III and IV, either at rest or during exercise (*P*<0.01). Systolic blood pressure was not significantly different between the four groups (*P*=0.09). Rate-pressure product at rest and during exercise was significantly lower in groups III and IV compared with groups I and II (*P*<0.01). Secondary: Not reported
DIG[22] Digoxin 0.125-0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACEI). Initial dosing of digoxin was based on patient's age, sex, weight and renal	DB, MC, PC, RCT Patients ≥21 years old with HF and LVEF of 0.45 or less and who were in normal sinus rhythm	N=6,800 37 months	Primary: Mortality Secondary: Mortality from cardiovascular causes, death from worsening HF, hospitalization for worsening HF, and hospitalization for other causes (specifically due to digoxin toxicity)	Primary: In the digoxin group, there were 1,181 (34.8%) deaths compared to 1,194 (35.1%) deaths in patients receiving placebo (95% CI, 0.91 to 1.07; *P*=0.80). Secondary: In the digoxin group, 1,016 (29.9%) patients died from cardiovascular compared to 1,004 (29.5%) patient deaths in the placebo group (95% CI, 0.93 to 1.10; *P*=0.78). There were 394 deaths in the digoxin group that were attributed to worsening HF compared to 449 deaths in the placebo (95% CI, 0.77 to 1.01; *P*=0.06). In the digoxin group, 910 patients were hospitalized for worsening HF compared to 1,180 patients in the placebo group (95% CI, 0.66 to 0.79; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
function.				Overall, the placebo group had a significantly higher number of patients hospitalized compared to the digoxin group, 2,184 vs 2,282 respectively (95% CI, 0.87 to 0.98; *P*<0.006). Other reasons for hospitalizations included cardiac events and respiratory infection. There was a statistically significantly higher number of patients in the digoxin group hospitalized for suspected digoxin toxicity compared to placebo, 67 vs 31 respectively (95% CI, 1.42 to 3.32; *P*<0.001).
Ahmed, Rich, Fleg et al[23] Digoxin 0.125-0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACEI). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	MC, PC, RCT Patients with diastolic HF (LVEF >45%) and normal SR at baseline This was an ancillary trial conducted in parallel with the main DIG trial.[22]	N=988 37 months	Primary: Combined end point of HF hospitalization or HF mortality Secondary: Not prespecified, however the following outcomes were studied: all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalizations, and the combined outcome of HF hospitalization and cardiovascular mortality	Primary: At the end of the study, there was not a statistically significant difference in the number of patients who experienced HF hospitalization or HF mortality between the digoxin group and the placebo group (102 [21%] vs 119 [24%], respectively; HR, 0.82; 95% CI, 0.63 to 1.07; *P*=0.136). Secondary: At the end of the study, there was not a statistically significant difference in the number of all-cause deaths between the digoxin group and the placebo group (115 [23%] vs 116 [23%], respectively; HR, 0.99; 95% CI, 0.76 to 1.28; *P*=0.925). Also, the difference in the number of cardiovascular deaths was not significantly different between the digoxin and the placebo group (81 patients in each group; HR, 1.00; 95% CI, 0.73 to 1.36; *P*=0.978). At the end of the study, there was not a statistically significant difference in the number of all-cause hospitalizations between the digoxin group and the placebo group (68% vs 67%, respectively; HR, 1.03; 95% CI, 0.89 to 1.20; *P*=0.683). Also, the difference in the number of cardiovascular hospitalizations was not significantly different between the digoxin and the placebo group (241 [49%] vs 225 [45%], respectively; HR, 1.10; 95% CI, 0.92 to 1.32; *P*=0.301). At the end of the study, there was not a statistically significant difference in the number of patients who experienced HF hospitalization or cardiovascular mortality between the digoxin group and the placebo group (142 [29%] vs 154 [31%], respectively; HR, 0.88; 95% CI, 0.70 to 1.11; *P*=0.269).
Ahmed, Rich, Love et al[24] Digoxin 0.125-0.5 mg QD vs	DB, MC, PC, RCT Patients with HF, regardless of ejection fraction, and who were	N=5,548 40 months	Primary: All-cause mortality Secondary:	Primary: At 40 months, all cause death rate was 33% in the placebo group, 29% in the group of patients with a SDC of 0.5 to 0.9 ng/mL, and 42% in the group of patients with the SDC of ≥1.0 ng/mL (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.77; 95% CI, 0.67 to 0.89; *P*<0.0001 and placebo vs SDC ≥1

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	in normal SR This was a post hoc analysis of a combination of the main DIG trial[22] and the ancillary DIG trial[23]		Mortality due to cardiovascular causes and HF, hospitalizations due to all causes, cardiovascular causes, and worsening HF	ng/mL; adjusted HR, 1.06; 95% CI, 0.93 to 1.20; *P*=0.406). Secondary: At 40 months, cardiovascular mortality rate was 26% in the placebo group, 24% in the SDC of 0.5 to 0.9 ng/mL group, and 33% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.83; 95% CI, 0.71 to 0.97; *P*=0.019 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.07; 95% CI, 0.93 to 1.24; *P*=0.339). At 40 months, mortality rate due to HF was 12% in the placebo group, 9% in the SDC of 0.5 to 0.9 ng/mL group, and 14% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.63; 95% CI, 0.49 to 0.82; *P*<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.87; 95% CI, 0.70 to 1.09; *P*=0.236). At 40 months, all cause hospitalization rates were 67% in the placebo group, 64% in the SDC of 0.5 to 0.9 ng/mL group, and 71% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.85; 95% CI, 0.78 to 0.92; *P*<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.95; 95% CI, 0.87 to 1.05; *P*=0.331). At 40 months, cardiovascular hospitalization rates were 53% in the placebo group, 48% in the SDC of 0.5 to 0.9 ng/mL group, and 55% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.79; 95% CI, 0.72 to 0.88; *P*<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.91; 95% CI, 0.82 to 1.01; *P*=0.086). At 40 months, hospitalization rates due to HF were 33% in the placebo group, 23% in the SDC of 0.5 to 0.9 ng/mL group, and 29% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5-0.9 ng/mL; adjusted HR, 0.62; 95% CI, 0.54 to 0.72; *P*<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.68; 95% CI, 0.59 to 0.79; *P*=0.086).
Uretsky et al[25] Digoxin 0.125, 0.25, 0.375, or 0.5 mg QD vs	DB, MC, PC, PG, RCT Patients ≥18 years old with NYHA Class II or III HF, normal SR, receiving digoxin and diuretics, LVEF ≤35%,	N=88 12 weeks	Primary: Treadmill time on maximal exercise testing, distance covered in a 6-minute walking test, incidence of	Primary: At 12 weeks, patients in the placebo group experienced a median decline of 96 seconds in maximal exercise testing compared to a 4.5 second increase in the digoxin group (*P*=0.003). Digoxin did not display a significantly different effect on distance covered in a 6-minute walking test (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo QD Digoxin was dosed to obtain a serum digoxin concentration of 0.9-2.0 ng/mL. Patients continued on background therapy of diuretics.	a LVED dimension of ≥60 mm or 34 mm/m^2		treatment failure, time to treatment failure Secondary: Change in signs and symptoms of HF, MLHF questionnaire, HF score, 7-point GEP, LVEF, vital signs and body weight	Patients in the placebo group experienced a 39% rate of treatment failures compared to 19% in the digoxin group (*P*=0.039). The patients in the placebo group also experienced a decreased time to treatment failure compared to the digoxin group (*P*=0.037). Treatment failures included hospital admissions, increase in drug therapy and death. Secondary: At the end of the 12-week study, there was not a statistically significant difference between the placebo and digoxin groups in changes in signs and symptoms of HF, MLHF questionnaire or HF score. At the end of 12 weeks, patients in the digoxin group experienced a mean increase in LVEF by 2%±2% compared to a mean decrease in LVEF of 3%±2% for the patients in the placebo group (*P*=0.016). Heart rate and body weight were significantly lower in the digoxin group compared to the patients in the placebo group (*P*=0.03 and *P*=0.044, respectively).
Packer et al[26] Digoxin QD vs placebo QD All patients started in an 8-week, single-blind run-in period during which the doses of background therapy for HF were adjusted to achieve optimal clinical benefits. After the run-in period, patients were randomized to either continue receiving digoxin therapy or receive placebo.	DB, MC, PC, RCT Patients ≥18 years old with NYHA Class II or III heart failure, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2, evidence of reduced exercise capacity, and normal SR, who were clinically stable while receiving digoxin, diuretics, and an ACEI	N=178 12 weeks	Primary: Rates of withdrawal from the study due to worsening HF, time to withdrawal, changes in exercise tolerance Secondary: Effects of discontinuing digoxin therapy on symptoms, quality of life, functional class, overall progress during the study and cardiac	Primary: Four patients who received digoxin, compared to 23 patients in the placebo group, withdrew from the study due to worsening of HF (*P*<0.001). The patients in the placebo group had a higher risk of worsening HF compared to the patients in the digoxin group over the 12-week study (RR, 5.9; 95% CI, 2.1 to 17.2; *P*<0.001). Exercise tolerance remained stable in patients receiving digoxin compared to deterioration in exercise tolerance in patients receiving placebo. The median difference in exercise duration between the 2 groups after 12 weeks was 42 seconds (*P*=0.006). Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo. The median difference in submaximal exercise endurance between the 2 groups after 10 weeks was 41 meters (*P*=0.01). Secondary: Of the patients in the placebo group, 38% experienced worsening dyspnea

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Digoxin was dosed to obtain a serum digoxin concentration of 0.9-2.0 ng/mL. Patients continued on background therapy of diuretics and an ACEI.			dimensions and function	and fatigue compared to 16% and 18% of patients in the digoxin group (*P*=0.14 and *P*=0.04, respectively). Thirty-three percent of patients in the placebo group experienced a less of an improved quality of life compared to 47% in the digoxin group (*P*=0.04). Also, 48% of patients in the placebo group experienced a more frequent decline in quality of life compared to 41% in the digoxin group (*P*=0.04). In the placebo group, 27% of patients were reported as having a deterioration in NYHA class compared to 10% of patients in the digoxin group (*P*=0.019). Thirty-one percent of patients in the placebo group reported that they felt moderately worse or much worse, compared to 9% of patients in the digoxin group (*P*=0.007).

Drug regimen abbreviations: BID=twice daily, QD=daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MC=multicenter, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Other abbreviations: ACEI=angiotensin-converting enzyme inhibitor, AF=Atrial Fibrillation, AMI=acute myocardial infarction, CHF=congestive heart failure, DIG=Digitalis Investigation Group, ECG=electrocardiogram, ECV=electrical cardioversions, GEP=global evaluation of progress, HF=heart failure, HR=heart rate, INR=international normalized ratio, LVED=left ventricular end-diastolic, LVEF= left ventricular ejection fraction, MET=mean exercise tolerance, MLHF=Minnesota Living with Heart Failure, NYHA=New York Heart Association, SDC=serum digoxin concentration, SR=sinus rhythm

Additional Evidence

Dose Simplification:
There are no differences in dosing regimens for the oral digoxin products. All of the agents reviewed in this class can be dosed once a day. An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Cardiotonic Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
digoxin	capsule, elixir, injection, tablet	Lanoxicaps®, Lanoxin®*, Lanoxin Pediatric®	$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Digoxin is a Class IV antiarrhythmic agent derived from a species of *Digitalis* or foxglove, plants whose medical use was described over two centuries ago.[1] It is FDA approved for the treatment of atrial fibrillation and heart failure. For the treatment of atrial fibrillation, digoxin applies its effects by increasing contractility via inhibition of the Na^+ and K^+ ATPase pump. The effects of digoxin in heart failure are mediated by its direct suppression of the AV node.[14] Although there are minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.

Currently, there are several guidelines that discuss the role of digoxin therapy for the treatment of atrial fibrillation and heart failure. According to the current treatment guidelines for atrial fibrillation, β blockers and calcium channel blockers are considered first-line agents and digoxin is recommended as a second- or third-line agent. Digoxin may be used in specific patient populations including those that are sedentary, those who have concurrent heart failure, or those who cannot tolerate or have failed single therapy with β blockers and calcium channel blockers.[17-20] In the current guidelines for the treatment of heart failure, it is recommended that digoxin may be added to standard therapy in those patients who continue to have symptoms of heart failure. In those patients with concurrent symptomatic heart failure and atrial fibrillation, digoxin should be used as the first-line agent.[21-26]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous Cardiac Drugs
AHFS Class 240492
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I. Overview

Ranolazine is currently the only agent classified as a miscellaneous cardiac drug via the American Hospital Formulary Service (AHFS).[1] It was Food and Drug Administration (FDA) approved on January 27, 2006 for the treatment of chronic angina in combination with amlodipine, β-adrenergic blocking agents (β-blockers), or nitrates, in patients who have not achieved an adequate response with other antianginal agents.[2] It does not abate an acute angina episode, but rather is designed to minimize or prevent recurrent episodes from occurring. The mechanism of action of ranolazine is unknown. It is suggested that ranolazine inhibits the slow sodium channel in the cardiac muscle, thereby reducing sodium/calcium exchange and preventing the accumulation of calcium and diastolic stiffness.[3] This in turn improves myocardial perfusion. Unlike other antianginal agents, ranolazine does not reduce heart rate or blood pressure. At maximal exercise, it does not increase the rate-pressure product, which is a measure of myocardial work.[4]

Angina occurs when the myocardial oxygen demand exceeds the oxygen supply, resulting in chest discomfort or pain. The currently available treatment options for chronic angina include nitrates, β-blockers, and calcium-channel blocking agents (CCBs). These agents either decrease oxygen demand and/or increase oxygen supply.[5] Nitrates, such as isosorbide dinitrate, isosorbide mononitrate, and transdermal nitroglycerin, reduce cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance and dilating coronary arteries. However, the use of nitrates as first-line agents has been limited because of tolerance that develops with chronic use. β-Blockers, such as atenolol and metoprolol, reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. β-Blockers are recommended as first-line agents in patients with stable angina since they have been shown to reduce mortality following myocardial infarction.[6] CCBs, such as amlodipine, diltiazem, and verapamil, increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction, and reducing contractility. CCBs also decrease cardiac oxygen demand by reducing systemic vascular resistance and arterial pressure.[5] CCBs are often used because they are presumed to have similar efficacy and fewer side effects when compared to β-blockers. However, short-acting CCBs have been shown to increase the risk of cardiac events in patients with hypertension and nifedipine has been shown to increase mortality following acute ischemic syndromes.[6] Differences in long-term rates of survival or myocardial infarction between classes of antianginal agents have not been studied.

Ranolazine is not indicated for use as initial therapy. It can prolong the QT interval and therefore can increase the risk of arrhythmias. Ranolazine should not be used with medications including diltiazem and verapamil that prolong the QT interval or increase ranolazine plasma concentrations.

Table 1 lists all the miscellaneous cardiac drugs included in this review. This review encompasses all dosage forms and strengths.

Table 1. Miscellaneous Cardiac Drugs Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
ranolazine	sustained-release tablet	Ranexa®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the miscellaneous cardiac drugs are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Cardiac Drugs

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: **2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[7]	• Sublingual nitroglycerin (NTG) 0.4 mg may be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. Doses can be repeated every 5 minutes if needed for 3 total doses. If pain persists after 3 doses, immediate medical attention should be sought. <u>Early Hospital Care</u> • Oral β-adrenergic blocking agents (β-blockers) should be initiated within the first 24 hours unless contraindicated (ie, patient has 1 or more of the following: signs of heart failure, evidence of a low-output state, increased risk of cardiogenic shock, or other relative contraindications to β-blockade). • A nondihydropyridine calcium-channel blocker (CCB) (diltiazem or verapamil) should be given as first-line treatment to patients who do not have a contraindication to either of these agents and have a contraindication to a β-blocker. These agents may also be used after β-blockers and nitrates have been fully used. • Immediate-release dihydropyridine CCBs may be considered in patients with UA/NSTEMI with ongoing ischemia or hypertension in the presence of adequate β-blockade. • Angiotensin-converting enzyme inhibitors (ACEI) should be administered orally to patients who do not have a contraindication within the first 24 hours to patients with congestive heart failure, diabetes, hypertension and/or left ventricular systolic dysfunction (ejection fraction <0.40). If the patient is intolerant to an ACEI, an angiotensin receptor blocker should be administered. • At the time the patient presents with UA/NSTEMI nonsteroidal anti-inflammatory drugs, except for aspirin, should be discontinued, however β-blockers should be continued indefinitely unless contraindicated. • Ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve underlying disease. <u>Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care</u> • Aspirin should be used routinely in all patients, unless contraindicated. • Clopidogrel may be used when aspirin is contraindicated or not tolerated. • Combination of aspirin and clopidogrel can be used for 12 months following UA/NSTEMI. • Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are recommended. • Fibrates or niacin should be recommended if high-density lipoprotein (HDL) <40 mg/dL, or if triglycerides are elevated. • The use of ranolazine as a component of a postdischarge regimen was not addressed.
American College of Cardiology/American Heart Association (ACC/AHA): **2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[8]	• Individual recommendations in this focused update will be incorporated into future revisions and/or updates of the ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina (2002). • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • The use of ranolazine for the treatment of angina was not addressed.
American College of Cardiology/American Heart Association	• Aspirin 75-325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is contraindicated.

Clinical Guideline	Recommendations
(ACC/AHA): **2002 Guideline Update for the Management of Patients With Chronic Stable Angina (2002)**[9]	• β-Blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol (LDL-C). • ACEIs should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual NTG or NTG spray for immediate relief of angina. • Long-acting CCBs or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine CCB can increase adverse cardiac events and should not be used. • A long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States (2006).
European Society of Cardiology: **Management of Stable Angina Pectoris (2006)**[10]	• HMG-CoA reductase inhibitor therapy should be instituted in all patients with coronary artery disease. • Fibrates or nicotinic acid may be used as adjuncts to HMG-CoA reductase inhibitor therapy. • Aspirin should be administered at a dose of 75 mg daily, unless contraindicated. • Clopidogrel may be used in patients who can not take aspirin. • ACEI therapy is indicated in patients with hypertension, heart failure, left ventricular dysfunction with or without history of prior myocardial infarction, or diabetes. • β-blockers are indicated for most patients with more than mild angina, unless contraindicated. • Short-acting nitrates may be used for prompt relief or prevention of angina, and should be offered to all patients. • Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. • Ranolazine has not been approved for use in the European Union. It is mentioned in the guideline but no recommendations were issued concerning its use.
European Society of Cardiology: **Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-segment Elevation (2007)**[11]	• β-Blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia and are usually well tolerated. • Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes. • CCBs provide symptom relief in patients already receiving nitrates and β-blockers; they are useful in patients with contraindications to β-blockade and in the subgroup of patients with vasospastic angina. • Nifedipine, or other dihydropyridines, should not be used unless combined with β-blockers. • It is noted that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI) trial. • The use of ranolazine for the treatment of angina was not further addressed. Ranolazine has not been approved for use in the European Union.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery**	• Aspirin therapy (75-325 mg daily) should be used by all patients. • Clopidogrel may be used in patients when aspirin therapy is contraindicated. • Sublingual NTG tablets or spray may be used for anginal discomfort that has not relieved by discontinuation of activity or removal from a stressful event. Doses can be repeated every 5 minutes if needed for 3 total doses. If pain persists after 3 doses, immediate medical attention should be sought. • β-blockers should be strongly considered as initial therapy, unless contraindicated. • HMG-CoA reductase inhibitors therapy should be recommended even in mild-to-moderate elevations of LDL-C.

Clinical Guideline	Recommendations
Disease (2004)[12]	• ACEIs should be recommended for patients with symptomatic chronic stable angina to prevent myocardial infarction and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Sublingual NTG or NTG spray for immediate symptomatic relief of angina. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States (2006).

III. Indications

Food and Drug Administration (FDA)-approved indications for the miscellaneous cardiac drugs are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Cardiac Drugs[3]

Drug	Indication*
Ranolazine	Ranolazine is indicated for the treatment of chronic angina. It should be reserved for patients who have not achieved an adequate response with antianginal drugs due to its ability to prolong the QT interval. Ranolazine should be used in combination with amlodipine, β-blockers, or nitrates. The effect on angina rate or exercise tolerance appeared to be smaller in women than in men.

*Ranolazine is contraindicated in patients with pre-existing QT prolongation, with hepatic impairment, on QT prolonging drugs, and on potent and moderately potent cytochrome P450 3A (CYP3A) inhibitors, including diltiazem.

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous cardiac drugs are summarized in Table 4. Compared with normal subjects, ranolazine plasma concentrations increased about 50% in patients with renal impairment. The mean diastolic pressure was increased by 10-15 millimeters of mercury in patients with severe renal impairment.[3,13] The plasma concentration of ranolazine increased by a factor of 1.3 in patients with mild hepatic impairment and by a factor of 1.6 in patients with moderate hepatic impairment. In addition, the increases in the QT interval were larger in patients with hepatic impairment compared with normal subjects at the same plasma concentration of ranolazine.[3,14] Ranolazine is contraindicated in patients with hepatic impairment.[3]

Table 4. Pharmacokinetic Parameters of the Miscellaneous Cardiac Drugs[3,15]

Drug	Bioavailability (%)	Protein binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Ranolazine	Absorption is highly variable	62	Mainly CYP3A4 and to a lesser extent CYP2D6	Four most abundant metabolites have half-lives of 6 to 22 hours*	Fecal excretion: 25 Urinary excretion: 75	7

*Pharmacologic activity not well characterized

V. Drug Interactions

Ranolazine is almost completely metabolized by the cytochrome P450 isoenzyme system. Therefore the potential for numerous drug interactions does exist. As such, other potent or moderately potent CYP3A inhibitors should not be coadministered. Since ranolazine can prolong the QT interval, other QT-prolonging drugs should not be coadministered.[3,16-17] Significant drug interactions with the miscellaneous cardiac drugs are listed in Table 5.

Table 5. Significant Drug-Drug Interactions With the Miscellaneous Cardiac Drugs[3,16-17]

Drug	Significance Level	Interaction	Mechanism
Ranolazine	1	Antiarrhythmic agents (amiodarone, bretylium, disopyramide, dofetilide, ibutilide, moricizine, procainamide, quinidine, sotalol)	Concurrent administration of ranolazine and anti-arrhythmic agents can lead to additive effects of QT interval prolongation and therefore should be avoided. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Ranolazine	1	Azole antifungals (itraconazole, ketoconazole, voriconazole)	Azole antifungals are potent inhibitors of CYP3A and therefore may increase the steady-state plasma concen-tration of ranolazine, increasing the risk of dose-related prolongation in the QT interval, torsades de pointes–type arrhythmias, and sudden death.
Ranolazine	1	Diltiazem	Diltiazem inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Grapefruit juice	Grapefruit juice inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Macrolide and related antibiotics (azithromycin, clarithromycin, dirithromycin, erythromycin, telithromycin)	Macrolide antibiotics inhibit the metabolism of ranolazine by the CYP3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Phenothiazines (thioridazine)	There is a possible additive prolongation of the QT interval when ranolazine is administered with a phenothiazine (thioridazine). Concurrent administration may lead to additive effects on QT prolongation.
Ranolazine	1	Protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Verapamil	Verapamil inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Ziprasidone	There is a possible additive prolongation of the QT interval when ranolazine is administered with ziprasidone. Concurrent administration may lead to additive effects on QT prolongation.

Significance Level 1=major severity

VI. Adverse Drug Events

Ranolazine has been shown to prolong the QT interval in a dose-dependent manner.[3] The relationship between ranolazine and QT interval is linear with a slope of 2.6 microseconds per 1,000 ng/mL of ranolazine. With repeated dosing of ranolazine administered at 1,000 mg twice daily, the QT interval is prolonged by 6 microseconds. In 5% of the population the prolongation of QT is 15 microseconds. In patients with hepatic dysfunction, the QT-prolonging effect is increased approximately 3-fold. The full clinical significance of this QT prolongation effect is not known. Other drugs that have the potential to prolong the QT interval have been associated with torsades de pointes-type arrhythmias and sudden death.[3]

The most common adverse drug events reported with the miscellaneous cardiac drugs are noted in Table 6. It is important to note that in placebo controlled trials approximately 6% of patients taking ranolazine discontinued the study medication

compared to 3% taking placebo. Reasons for discontinuation varied but were related to the common adverse events associated with ranolazine.[3]

Table 6. Adverse Drug Events (%) Reported with the Miscellaneous Cardiac Drugs[3]

Adverse Event	Ranolazine
Cardiovascular	
Bradycardia	<0.5
Hypotension	≤0.5
Orthostatic hypotension	≤0.5
Palpitations	0.5-2.0
QT prolongation	✔
Syncope	0.7
Central Nervous System	
Dizziness	5.0-6.2
Headache	3.0-5.5
Vertigo	0.5-2.0
Endocrine and Metabolic	
Blood urea nitrogen elevations	✔
Serum creatinine elevations	✔
Gastrointestinal	
Abdominal pain	0.5-2.0
Constipation	4.5-8.0
Dry mouth	0.5-2.0
Nausea	4.0-4.4
Vomiting	0.5-2.0
Hematologic	
Hematuria	≤0.5
Respiratory	
Dyspnea	0.5-2.0
Syncope	0.7
Other	
Blurred vision	≤0.5
Hypoesthesia	≤0.5
Peripheral edema	0.5-2.0
Tinnitus	0.5-2.0
Tremor	≤0.5

✔ Percent not specified

VII. Dosing and Administration

Ranolazine is recommended to be given in combination with amlodipine, β-blockers, or nitrates. Doses of greater than 1,000 mg twice daily should not be used, as QT prolongation is dose-related.[3]

Ranolazine can be taken with or without meals. It is available as a sustained-release tablet which should be swallowed whole and not crushed, broken, or chewed. Electrocardiograms should be obtained at baseline and during follow-up to monitor for effects on QT interval.[3] The usual dosing regimens for the miscellaneous cardiac drugs are summarized in Table 7.

Table 7. Usual Dosing for the Miscellaneous Cardiac Drugs[3]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Ranolazine	Initial: 500 mg twice daily Maximum: 1,000 mg twice daily	Safety and efficacy in children have not been established.	Sustained-release tablet: 500 mg 1,000 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs are found in Table 8.

Table 8. Comparative Clinical Trials Using the Miscellaneous Cardiac Drugs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chaitman, Pepine, et al[18] CARISA Ranolazine 750 or 1,000 mg BID in combination with diltiazem 180 mg QD, atenolol 50 mg QD, or amlodipine 5 mg QD vs placebo BID in combination with diltiazem 180 mg QD, atenolol 50 mg QD, or amlodipine 5 mg QD	DB, MC, PC, PG, RCT Patients with symptomatic chronic angina despite treatment with diltiazem 180 mg QD, atenolol 50 mg QD, or amlodipine 5 mg QD	N=823 12 weeks followed by long-term open-label study of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, frequency of angina attacks, frequency of nitroglycerin use, survival	Primary: In the ranolazine group, exercise duration (*P*=0.01) was significantly increased compared to placebo. Secondary: Time to angina (no *P* value reported) and time to 1 mm ST-segment depression (no *P* value reported) were significantly increased compared with placebo. Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week for the 750 mg group; *P*=0.006; and 3.3 vs 2.1 attacks per week for the 1,000 mg group; *P*<0.001), and nitroglycerin use (no *P* value reported) compared with placebo. The most common adverse effects were constipation, dizziness, nausea, and asthenia (≤7.3% in the ranolazine group vs ≥0.7% in the placebo group; no *P* value reported). The survival rates for patients taking ranolazine were 98.4% (95% CI, 97.4% to 99.5%) at year one and 95.9% (95% CI, 94.0% to 97.7%) at year two.
Stone et al[19] ERICA Ranolazine 1,000 mg BID in combination with amlodipine 10 mg QD vs placebo in combination with amlodipine 10 mg	DB, PC, PG, RCT Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended dosage of amlodipine (10 mg/day)	N=565 6 weeks	Primary: Frequency of angina episodes per week Secondary: Average weekly nitroglycerin consumption rate, SAQ, safety as assessed by adverse events	Primary: Angina frequency at baseline averaged 5.63 ± 0.18 episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared with placebo (2.88 ± 0.19 vs 3.31± 0.22; *P*=0.028). Secondary: Nitroglycerin consumption use at baseline averaged 4.72 ± 0.21 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared with placebo (2.03 ± 0.20 vs 2.68 ± 0.22; *P*=0.014). The SAQ scores on angina frequency were significantly improved in the ranolazine arm compared with placebo arm (*P*=0.008). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD			and electrocardio-gram	anginal stability, disease perception, and treatment satisfaction. Ranolazine was well tolerated.
Chaitman, Skettino, et al[20] MARISA Ranolazine 500, 1,000, or 1,500 mg BID vs placebo BID	DB, PC, RCT, XO Patients with well-documented coronary artery disease and at least 3 month history of effort angina that responded to antianginal agents	N=191 4 weeks, with long-term follow-up of up to 36 months	Primary: Exercise duration Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, exercise duration at peak, long-term survival	Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration (P<0.001). Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina (P<0.001) and time to 1 mm ST-segment depression (P<0.001). No clinically significant changes in heart rate or blood pressure at rest or exercise were observed. The rates of adverse events were similar for the 500 mg and placebo group, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg; no P values reported). The survival rates were 96.3% (95% CI, 93.0% to 99.5%) at one year and 93.6% (95% CI, 89.3% to 98.0%) at two years.
Rousseau et al[21] Ranolazine immediate-release* 400 mg TID for 7-10 days, atenolol 100 mg QD for 7-10 days, and placebo QD for 7-10 days Trial design used all 6 possible treatment sequences and each treatment period lasted 7-10 days.	DB, MC, PC, XO Patients with well-documented coronary artery disease and chronic angina, who were on standard doses of atenolol	N=158 21-30 days	Primary: Time to onset of angina Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency, nitroglycerin use	Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-segment depression when compared with placebo (P<0.05 for all). Secondary: There was no significant difference between ranolazine and atenolol in the time to angina (P=0.18), time to 1 mm ST-segment depression (P=0.86), angina frequency (no P value reported), or nitroglycerin use (no P value reported). However, the increase in exercise duration was significantly greater in the ranolazine group than atenolol (mean difference of 21.1 seconds, 95% CI, 6.2 to 36.0; P=0.006).
Timmis et al[22] Ranolazine 750 or	Posthoc analysis of CARISA trial	N=823 12 weeks,	Primary: Exercise tolerance	Primary: In the CARISA trial, 23% of the subjects were diabetic and 77% were not diabetic.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,000 mg BID plus atenolol 50 mg QD, diltiazem 180 mg QD, or amlodipine 5 mg QD vs placebo plus atenolol 50 mg QD, diltiazem 180 mg QD, or amlodipine 5 mg QD	Patients with chronic angina and diabetes (insulin- and non-insulin-dependent) compared with nondiabetic patients	followed by open-label extension study	Secondary: Time to onset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin usage, and HbA_{1c} levels in diabetic patients only and lipid panel as posthoc analysis	The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration (*P*=0.89), time to onset of angina (*P*=0.54), or time to ≥1 mm ST-segment depression (*P*=0.44). There was also no difference in the diabetic patients compared with the nondiabetic patients in angina frequency (*P*=0.81) or nitroglycerin consumption (*P*=0.063). Secondary: Compared with placebo, there were significant reductions in the HbA_{1c} levels in the ranolazine 750 mg (*P*=0.008) and ranolazine 1,000 mg (*P*=0.0002) treatment groups. A subgroup analysis showed that there were significant reductions in the HbA_{1c} levels in insulin-dependent diabetics treated with ranolazine (*P*=0.016 in the 750 mg group and *P*=0.008 in the 1,000 mg group). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in HbA_{1c} with the 1,000 mg dose (*P*=0.007), but not with the 750 mg dose (*P*=0.087). Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile (no *P* values reported).
Cocco et al[23] Ranolazine 10 mg, 60 mg, 120 mg or 240 mg single dose in addition to their regular antianginal medication of a β-blocker or diltiazem vs placebo in addition to patient's regular β-blocker or diltiazem	DB, MC, PC, RCT, XO Patients with chronic stable angina who remained symptomatic despite treatment with β-blocker (atenolol, metoprolol, or propranolol) or diltiazem	N=104 4-9 days	Primary: Exercise duration, time to angina, time to 1 mm ST-segment depression Secondary: Heart rate, blood pressure	Primary: Exercise duration, time to angina, and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the β-blocker group and the groups combined (*P*<0.05 for both). There was no significant difference in exercise duration, time to angina, or time to 1 mm ST-segment depression with ranolazine treatment in patients that were on the diltiazem regimen (*P*>0.05 for all). Secondary: Treatment with ranolazine did not result in significant changes in heart rate or blood pressure compared with placebo (*P*>0.05).
Pepine et al[24] Ranolazine immediate-	DB, MC, PC, RCT, XO	N=312 5 weeks	Primary: Time to angina onset, exercise	Primary: At peak ranolazine concentrations, time to angina onset (*P*≤0.02), exercise duration (*P*=0.013), and time to 1 mm ST-segment depression (no *P* value reported) were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
release* 400 mg BID, 267 mg TID, or 400 mg TID vs placebo	Patients with chronic stable angina that responded to conventional antianginal therapy		duration, and time to 1 mm ST-segment depression at peak and trough concentrations Secondary: Safety	significantly improved with all dosing regimens. At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved (*P*=0.047). Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6% to 10.7% vs 3.2%; no *P* value reported).
Koren et al[25] Ranolazine titrated to an optimal dose between 500 and 1,000 mg BID	MC, OL Patients who had completed the MARISA or CARISA trial, who were willing to participate in an open-label extension	N=746 Duration varied with a mean follow-up of 2.82 years	Primary: Discontinuation, adverse events, electrocardio-gram findings, and mortality Secondary: Not reported	Primary: 571 patients (76.7%) remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing. There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; *P*<0.001). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; *P*=0.030). Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed (*P*<0.001). However there were no significant differences in PR or QRS intervals during this time (*P* value not reported.). A total of 64 deaths (all causes) occurred during the 2,102 patient-years (3.0% annual incidence) of the study. This translates to a 97.2% and 94.4%, 1- and 2-year survival from this incidence. Secondary: Not reported
Rich et al[26] Ranolazine 750 mg vs ranolazine 1,000 mg vs	MA Patients with symptomatic chronic angina despite treatment	N=1,387 6 weeks	Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina	Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing (*P*≤0.03). There was no difference in ranolazine's effect on exercise time in younger patients compared to older patients (*P*>0.8). Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Ranolazine and placebo were administered BID in combination with diltiazem 180 mg QD, atenolol 50 mg QD or amlodipine 5-10 mg QD.			frequency, and adverse events Secondary: Not reported	4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group). Adverse events were more commonly reported in the older patient population (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group). Secondary: Not reported
Morrow et al[27] MERLIN-TIMI 36 Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally twice a day until study completion vs matching placebo Study medication was administered in addition to standard therapy.	DB, MC, PC, RCT Patients 18 years of age or older with symptoms consistent with myocardial ischemia at rest, lasting more than 10 minutes and present within the previous 48 hours and had at least 1 of the following indicators of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable	N=6,560 Duration varied with a median follow-up of 348 days	Primary: Time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia Secondary: Rate of major cardiovascular events (cardiovascular death, myocardial infarction, or severe recurrent ischemia), rate of failure of therapy (cardiovascular death,	Primary: In 21.8% of the patients in the ranolazine group and 23.5% of patients in the placebo group, the primary end point occurred (HR, 0.92; 95% CI, 0.83 to 1.02; *P*=0.11). In 10.4% of the patients in the ranolazine group and 10.5% of patients in the placebo group a cardiovascular death or myocardial infarction occurred (HR, 0.99; 95% CI, 0.85 to 1.15; *P*=0.87). In 13.9% of the patients in the ranolazine group and 16.1% of patients in the placebo group recurrent ischemia was reduced (HR, 0.97; 95% CI, 0.76 to 0.99; *P*=0.03). Secondary: Failure of therapy occurred in 36.8% of patients in the ranolazine group compared to 38.3% in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; *P*=0.16). In 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group the secondary end point occurred (HR, 0.96; 95% CI, 0.86 to 1.08; *P*=0.50). There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; *P*=0.84). There was no difference in the total mortality in the ranolazine group compared to the placebo group (172 vs 175; HR, 0.99; 95% CI, 0.80 to 1.22; *P*=0.91).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	angina/non-ST-elevation myocardial infraction ≥3)		myocardial infarction, or severe recurrent ischemia), safety (death from any cause, symptomatic arrhythmias)	
Scirica et al[28] MERLIN-TIMI 36 Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally twice a day until study completion vs matching placebo Study medication was administered in addition to standard therapy.	RCT Patients hospitalized with a non-ST-elevation acute coronary syndrome	N=6,560 7 days	Primary: Incidence of clinically significant arrhythmias (as monitored by ECG or Holter recording performed for the first 7 days after randomization) Secondary: Not reported	Primary: Ventricular arrhythmias: Ventricular tachycardia ≥3 beats ≥100 bpm was significantly less in the ranolazine group (52.1%) compared to placebo (60.6%) (RR, 0.86; 95% CI, 0.82 to 0.90; *P*<0.001). Ventricular tachycardia ≥4 beats ≥100 bpm was significantly less in the ranolazine group (20.9%) compared to placebo (29.5%) (RR, 0.71; 95% CI, 0.6 to 0.78; *P*<0.001). Ventricular tachycardia ≥8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to placebo (8.3%) (RR, 0.63; 95% CI, 0.52 to 0.76; *P*<0.001). There was no significant difference in polymorphic ventricular tachycardia ≥8 beats in the ranolazine group (1.2%) compared to placebo (1.4%) (RR, 0.83; 95% CI, 0.54 to 1.28; *P*=0.40). There was no significant difference in sustained ventricular tachycardia (≥30 seconds) in the ranolazine group (0.44%) compared to placebo (0.44%) (RR, 1.01; 95% CI, 0.48 to 2.13; *P*=0.98). This includes monomorphic (0.13% vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; *P*=0.37) and polymorphic (0.32% vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; *P*=0.46). Supraventricular arrhythmias: There was no significant difference in new-onset atrial fibrillation in the ranolazine group (1.7%) compared to placebo (2.4%) (RR, 0.74; 95% CI, 0.52 to 1.05; *P*=0.08). Other supraventricular arrhythmias ≥120 bpm lasting at least 4 beats were significantly less in the ranolazine group (44.7%) compared to placebo (55.0%) (RR, 0.81; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.77 to 0.85; *P*<0.001). Secondary: Not reported

*The immediate-release and injectable formulations of ranolazine are not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: bpm=beats per minute, CARISA=Combination Assessment of Ranolazine in Stable Angina, ERICA=Efficacy of Ranolazine in Chronic Angina, HbA_{1c}=glycosylated hemoglobin A1c, MARISA=Monotherapy Assessment of Ranolazine in Stable Angina, MERLIN-TIMI=Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes, SAQ=Seattle Angina Questionnaire, TIMI=thrombolysis in myocardial infarction

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
In the MARISA trial, patients who had at least a 3-month history of effort angina responding to β-blockers, calcium channel blockers, and/or long-acting nitrates were switched to ranolazine or placebo.[20] Treatment with ranolazine resulted in statistically significant increases in exercise duration, time to angina, and time to 1 mm ST-segment depression compared to placebo. However, these treatment effects of ranolazine were not compared with those of the baseline antianginal agents.

Impact on Physician Visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Miscellaneous Cardiac Drugs

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
ranolazine	sustained-release tablet	Ranexa®	$$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

The only agent classified as a miscellaneous cardiac drug is ranolazine. This agent is an antianginal drug that has been shown to significantly improve exercise duration, time to onset of angina, and time to 1 mm ST-segment depression. It also reduces angina frequency and nitroglycerin usage.[19-21] Ranolazine is approved for use in combination with nitrates, β-blockers, or amlodipine.

Ranolazine has a different mechanism of action than currently available drugs to treat angina and does not cause hemodynamic changes such as reduction in blood pressure or heart rate.[3] The most common adverse effects were dizziness, nausea, asthenia, and constipation.[18-21] A significant concern with ranolazine is its potential for QT prolongation.[1] Therefore, ranolazine should be avoided in patients with pre-existing QT prolongation, who are taking QT-prolonging drugs or potent or moderately potent CYP3A inhibitors or patients with any type of hepatic

impairment or severe renal impairment. Due to the dose-dependent potential for QT prolongation, the manufacturer has recommended that ranolazine be reserved for patients that have shown inadequate response to other antianginal drugs.

Most current guidelines do not address the use of ranolazine, as it was approved after their publication dates or has not been approved in their host countries.[8-9,12] The ACC/AHA guideline on unstable angina and NSTEMI, states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease.[7] The European Society of Cardiology does mention ranolazine in their Management of Stable Angina Pectoris guideline but no recommendations were issued concerning its use.[10] The European Society of Cardiology notes in their Management of ACS in Patients Presenting Without Persistent ST-segment Elevation guideline that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in the MERLIN-TIMI trial.[11]

Currently there is limited data comparing ranolazine to other currently available antianginal agents such as β-blockers, calcium channel blockers, and long-acting nitrates. In one trial, Rousseau and colleagues demonstrated that the immediate-release formulation of ranolazine, when compared to atenolol, increased exercise duration. However, ranolazine proved similar to atenolol in its effect on other anginal symptoms such as time to angina, time to 1 mm ST-segment depression, angina frequency, and nitroglycerin use.[21]

Therefore, since ranolazine should be reserved for use in combination with other antianginal agents in those patients who have not achieved an adequate response with other antianginal drugs, it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

XI. Recommendations

No brand miscellaneous cardiac drug is recommended for preferred status, regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Bile Acid Sequestrants
AHFS Class 240604
May 14, 2008

I. Overview

Dyslipidemia is a complex of related conditions that affects many individuals. Multiple lipid-lowering agents, or antilipemic agents, are available and have been divided by the American Hospital Formulary Service (AHFS) into the following classes: bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), nicotinic acid (niacin), and omega-3 acid ethyl esters.[1] The bile acid sequestrant class consists of cholestyramine, colesevelam and colestipol of which cholestyramine and colestipol are available generically.[1] Bile acid sequestrants are primarily indicated to reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[2-5]

Cholesterol is a precursor to bile acid. The production and degradation of cholesterol by the liver involves many steps, pathways and biochemicals. Bile acid sequestrants interrupt one step in the cycle. These agents, as anion exchange resins, bind bile acid in the intestine and the complex is excreted in the feces, interrupting the enterohepatic circulation of bile acid.[6] The resultant decrease of bile acid in the liver stimulates the breakdown of cholesterol, lowering overall cholesterol levels. Bile acid sequestrants can lower LDL-C by 15%-30%, in addition to raising high-density lipoprotein cholesterol (HDL-C) by 3%-5%.[7]

The bile acid sequestrants that are included in this review are listed in Table 1. Colesevelam is available as oral tablets; cholestyramine is available as a powder for suspension and in packets containing powder for suspension; colestipol is available as oral tablets as well as granules for oral suspension. This review encompasses all dosage forms and strengths.

Table 1. Bile Acid Sequestrants Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
cholestyramine and aspartame	powder (bulk or packet)	Questran Light®*	cholestyramine
cholestyramine and sucrose	powder (bulk or packet)	Questran®*	cholestyramine
colesevelam	tablet	Welchol®	none
colestipol	tablet, granule (bulk or packet)	Colestid®*	colestipol

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the bile acid sequestrants are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

In January 2008, colesevelam received approval from the Food and Drug Administration (FDA) for the indication of type 2 diabetes, as an adjunctive treatment to diet and exercise to improve glycemic control. The most recent guidelines on the treatment of diabetes mellitus, from the American Diabetes Association, were released in the same month. They do not incorporate colesevelam, or any other bile acid sequestrants, into their treatment algorithm and therefore are not included in Table 2.

Table 2. Treatment Guidelines Using the Bile Acid Sequestrants

Clinical Guideline	Recommendation
National Heart, Lung, and Blood	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical

Clinical Guideline	Recommendation
Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[8]	management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). For the treatment of homozygous FH • Bile acid sequestrants are not effective. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[7]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Bile Acid Sequestrants • Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL-C, for younger persons with elevated LDL-C, for women

Clinical Guideline	Recommendation
	with elevated LDL-C who are considering pregnancy, and for persons needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in persons with very high LDL-C levels.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[9]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[10]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[11]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[12]	• Statins are considered first-line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid-lowering alternatives. • Bile acid sequestrants tend to increase triglycerides (TG); should only be used when TG are <~180 mg/dL or given in conjunction with TG-lowering agents. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Association of the Study of Liver Disease (AASLD): **Management of Primary Biliary Cirrhosis (2000)**[13]	• There is no evidence that topical treatments are effective in treating pruritus associated with primary biliary cirrhosis (PBC). • Ursodeoxycholic acid therapy is currently supported by the most data and is recommended for use in appropriately selected patients with PBC, who have abnormal liver chemistry. • Pruritus is a complication of PBC and cholestyramine is the drug of choice for the treatment of this complication. • Rifampin is a second-line treatment option for pruritus to those who fail or are intolerant to cholestyramine. • Opioid antagonists and liver transplant are third- and fourth-line options.

III. Indications

Food and Drug Administration (FDA)-approved indications for the bile acid sequestrants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Bile Acid Sequestrants [2-5]

Drug	Cholestyramine	Colesevelam	Colestipol
For the reduction of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia (Fredrickson Type IIa, elevated LDL-C)*	✔	✔	✔
In combination with an HMG-CoA reductase inhibitor, for the reduction of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia (Fredrickson Type IIa), as adjunct to diet and exercise		✔	
For the relief of pruritus associated with partial biliary obstruction	✔		
To improve glycemic control in adults with type 2 diabetes mellitus†		✔	

*As adjunctive therapy to diet, for patients who do not respond adequately to diet
†As adjunctive therapy to diet and exercise

IV. Pharmacokinetics

The pharmacokinetic parameters for the bile acid sequestrants are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Bile Acid Sequestrants[2-5,14,15]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Cholestyramine	0	0	None	None	0	Feces 100%	Not reported
Colesevelam	0	0	None	None	0.05	Feces near 100%	Not reported
Colestipol	0	0	None	None	<0.05	Feces 100%	Not reported

V. Drug Interactions

Significant drug interactions observed with the bile acid sequestrants are identified in Table 5. The bile acid sequestrants have the potential to bind to other drugs, which may delay or reduce the absorption of concomitant oral medications.[15] To minimize this interaction, other drugs should be taken at least 1 hour before, or 4-6 hours after the bile acid sequestrants.[3,4] The manufacturer recommends that drugs that interact with colesevelam or those that have not been tested, be taken 4 hours before colesevelam.[5] Monitoring is recommended for drugs that have a narrow therapeutic index or safety range, and are taken with bile acid sequestrants.[2-5] It is worth noting that the NCEP ATP III states that colesevelam does not need to be administered separately from other drugs, because it does not effectively decrease the absorption of drugs given in conjunction with it.[8]

Table 5. Significant Drug-Drug Interactions for the Bile Acid Sequestrants[5,15]

Drugs	Significance Level	Interaction	Mechanism
Bile acid sequestrants (cholestyramine, colestipol)	2	Corticosteroids (hydrocortisone)	Bile acid sequestrants may decrease the gastrointestinal (GI) absorption of hydrocortisone, resulting in lower systemic levels of corticosteroids.
Bile acid sequestrants (cholestyramine,	2	Digoxin	Cholestyramine and colestipol may decrease GI absorption of digoxin, as well as alter the enterohepatic recycling of digoxin. This may result in lower systemic levels of digoxin. In addition,

Drugs	Significance Level	Interaction	Mechanism
colestipol)			administering colestipol with digoxin may result in a shorter half-life of digoxin, potentially decreasing the effectiveness of digoxin.
Bile acid sequestrants (cholestyramine, colestipol)	2	Loop diuretics (furosemide)	Cholestyramine and colestipol may decrease the GI absorption of furosemide, due to binding by the anion exchange resins, resulting in lower systemic effects of furosemide. Cholestyramine and furosemide administration should be separated by as much time as possible (at least 2 hours). Colestipol should be taken as long as possible (at least 2 hours) after furosemide.
Cholestyramine	2	Anticoagulants (dicumarol, warfarin)	Cholestyramine may decrease the GI absorption of oral anticoagulants, resulting in lower systemic levels of anticoagulants, and potentially decreasing the effectiveness of the anticoagulant.
Cholestyramine	2	Thyroid hormones (levothyroxine, liothyronine, liotrix, thyroid)	Cholestyramine may decrease the GI absorption of thyroid hormones by binding to them, resulting in lower systemic levels of thyroid hormones.
Cholestyramine	2	Valproic acid (divalproex sodium, valproic acid)	Cholestyramine may decrease the GI absorption of valproic acid, resulting in lower systemic levels of valproic acid.
Colesevelam	2	Glyburide	Colesevelam may decrease systemic levels of glyburide, decreasing the effect of glyburide.
Colesevelam	2	Levothyroxine	Colesevelam may decrease systemic levels of levothyroxine, decreasing the effect of levothyroxine.
Colesevelam	2	Oral contraceptives containing ethinyl estradiol and norethindrone	Colesevelam may decrease systemic levels of ethinyl estradiol and norethindrone, leading to lower systemic levels of hormone and potentially decreasing efficacy.

Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse reactions reported with the bile acid sequestrants are noted in Table 6. The adverse effect profiles of the bile acid sequestrants are similar; gastrointestinal side effects are the primary complaint for all agents.[7] Constipation and flatulence are also reported frequently.[3-5] These symptoms may diminish over time or may be relieved by increasing dietary fiber. All the bile acid sequestrants can cause an increase in triglyceride levels, and therefore should not be utilized in patients with triglyceride levels >400 mg/dL.[2] Cholestyramine and colestipol can decrease plasma folate levels, so supplementation should be considered in younger women and children.[2-4] In addition, bile acid sequestrants can decrease the absorption of vitamins A, D, E, K.[2-5]

Table 6. Adverse Drug Events (%) Reported with the Bile Acid Sequestrants [2-5]

Adverse Event(s)	Cholestyramine	Colesevelam	Colestipol
Body as a Whole			
Accidental injury	-	4	-
Asthenia/weakness	-	4	✔
Back pain	-	3	✔
Fatigue	-	-	✔
Flu syndrome	-	3	-
Infection	-	10	-
Pain	-	5	-
Rash	✔	-	✔
Swelling of hands and feet	-	-	✔

Adverse Event(s)	Cholestyramine	Colesevelam	Colestipol
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Cardiovascular			
Angina	-	-	✔
Chest pain	-	-	✔
Tachycardia	-	-	✔
Central Nervous System			
Dizziness/light-headedness	✔	-	✔
Headache	✔	6	✔
Insomnia	-	-	✔
Migraine	-	-	✔
Sinus headache	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	5	✔
Anorexia	✔	-	✔
Constipation	✔	11	✔
Diarrhea	✔	5	✔
Dyspepsia	-	8	✔
Eructation	✔	-	-
Flatulence	✔	12	✔
Nausea	✔	4	✔
Steatorrhea	✔	-	-
Vomiting	✔	-	-
Hematological			
Hypoprothrombinemia associated with vitamin K deficiency	✔	-	-
Musculoskeletal			
Myalgia	-	2	✔
Osteoporosis	✔	-	-
Respiratory			
Cough increased	-	2	-
Pharyngitis	-	3	-
Rhinitis	-	3	-
Shortness of breath	-	-	✔
Sinusitis	-	2	-
Laboratory Test Abnormalities			
Abnormal liver function tests (AST, ALT, Alk Phos)	✔	-	✔
Changes in triglyceride levels	✔	✔	✔

Alk Phos=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase
- Event not reported or incidence <1%
✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the bile acid sequestrants are summarized in Table 7.

Table 7. Dosing and Administration for the Bile Acid Sequestrants[2-5]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Cholestyramine	Primary Hyperlipidemia: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily	Although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose	Powder bulk: Regular (with sucrose), 4 g Light (with aspartame), 4 g Powder packets:

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pruritus Associated With Partial Biliary Obstruction: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily	of 240 mg/kg/day in 2-3 divided doses, normally not to exceed 8 g/day.[4] The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients are unknown.	Regular (with sucrose), 4 g Light (with aspartame), 4 g
Colesevelam	Primary Hyperlipidemia: Maintenance: 3 tablets twice per day with meals or 6 tablets once daily with a meal and liquid Type 2 Diabetes Mellitus: Maintenance: 3 tablets twice per day with meals or 6 tablets once daily with a meal and liquid	Safety and efficacy in children have not been established.	Tablet: 625 mg
Colestipol	Primary Hyperlipidemia: Tablets: Initial, 2 g once or twice daily Maintenance, 2-16 g/day once or in divided doses Granules: Initial, 5 g (1 packet or level teaspoon) once or twice daily Maintenance, 5-30 g (1-6 packets or level scoopfuls) given once or in divided doses	Safety and efficacy in children have not been established.	Granules for solution bulk: 5 g Granules for solution packet: 5 g 7.5 g Tablet: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the bile acid sequestrants are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Bile Acid Sequestrants

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al[16] Colesevelam 1.5-3.75 g/day vs placebo	DB, MC, PC, RCT Hypercholesterolemia patients, LDL-C >160 mg/dL, average age of 56 years old	N=137 6 weeks	Primary: LDL particle size and LDL particle number Secondary: Not reported	Primary: Mean LDL particle size increased significantly in the group receiving colesevelam 3.75 g/day (*P*=0.01). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.75 g/day by 13.7% (*P*=0.0002). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.0 g/day by 6.8% (*P*=0.03). Secondary: Not reported
Bays et al[17] Colesevelam 3.75 g/day vs placebo	MA of 3 trials (each DB, MC, PC, PG, RCT) Patients were 18 years old or older and had an LDL-C ≥100 mg/dL and ≤250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy, either atorvastatin, pravastatin or simvastatin for ≥4 weeks	N=204 6 weeks	Primary: Mean percent change in LDL-C level from baseline to end point Secondary: HsCRP, absolute and percent change in HDL-C, TC, apo AI, apo B, TG, and absolute change in hsCRP; safety (measured by incidence of treatment-emergent adverse events)	Primary: Patients receiving colesevelam with a statin had significantly greater reductions in LDL-C than those receiving placebo plus a statin at the end of the study (*P*<0.01 for absolute difference; *P*≤0.001 for % treatment difference). Secondary: HsCRP levels decreased significantly as compared to placebo when colesevelam was combined with simvastatin or pravastatin (*P*=0.0154 and *P*=0.0279, respectively). Patients receiving colesevelam with a statin did not have a significant increase in HDL-C as compared to those receiving placebo plus a statin at the end of the study (*P*>0.05). Patients receiving colesevelam with a statin had significantly greater reductions in TC than those receiving placebo plus a statin at the end of the study (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Apo B levels were not significantly different (*P* value not reported). No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher in the groups receiving colesevelam with a statin (13% to 26%) than placebo with a statin (0% to 13%; *P* value not reported).
The Lipid Research Clinics Coronary Primary Prevention Trial[18,19] Cholestyramine vs placebo	DB, MC, RCT Asymptomatic males with primary hypercholesterolemia, following a moderate cholesterol-lowering diet	N=3,806 7.4 years average	Primary: CHD death and/or nonfatal MI Secondary: TC and LDL-C changes, incidence rates of: positive stress tests, angina, coronary bypass surgery	Primary: The cholestyramine group had a 19% reduction in risk of CHD death or nonfatal MI ($P<0.05$). Secondary The cholestyramine group had a reduction in TC of 13.4% and a reduction in LDL-C of 20.3%. The placebo group had a TC reduction of 4.9% and a LDL reduction of 7.7% (*P* values not reported). Incidence rates of positive stress tests, angina and coronary bypass surgery were decreased in the cholestyramine group by 25%, 20%, and 21%, respectively (*P* values not reported).
Ballantyne et al[20] Rosuvastatin 80 mg vs rosuvastatin 80 mg and cholestyramine 16 g	MC, OL, PG, RCT Adults, 18 years and older, with severe hypercholesterolemia (LDL-C 190-400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks (6 weeks of 40 mg rosuvastatin, followed by 6 weeks of rosuvastatin 80 mg with or without cholestryramine)	Primary: Percent change in LDL-C from baseline to end of treatment Secondary Percent change from baseline in LDL-C after 6 weeks of 40 mg rosuvastatin; percent change from baseline at 6 and 12 weeks of rosuvastatin treatment for: TC, HDL-C, TG, apo	Primary: At 12 weeks, no significant difference between the groups was seen: the rosuvastatin group had an LDL-C reduction of 56.4% and rosuvastatin with cholestyramine group had an LDL-C reduction of 60.5% ($P<0.08$). Secondary: LDL-C reductions were 52.2% after treatment with 40 mg rosuvastatin. Other measurements, TC, HDL-C, TG, apo B, apo AI and lipid ratios were not significantly different between the groups (P=0.20, 0.71, 0.47, 0.75, 0.53, 0.17, respectively). Decreases in CRP were 29% after 6 weeks, 42% after rosuvastatin 80 mg and 48% after rosuvastatin 80 mg with cholestryramine (*P* value not reported). 49% of patients in the cholestyramine group were not compliant with the cholestyramine treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			AI, apo B, lipid ratios (LDL:HDL) and inflammatory markers (CRP, IL6); compliance	
Eriksson et al[21] Cholestyramine 16 g vs cholestyramine 8 g and pravastatin 20 mg vs pravastatin 20 mg vs pravastatin 40 mg	MC, RCT Men and women, aged 30-65 years old	N=2,036 12 months	Primary: Reduction in LDL-C Secondary: Compliance	Primary: Percent change (CI) in LDL-C from baseline to end point within each group: Cholestyramine: –26% (–23% to –29%) Cholestyramine and pravastatin: –36% (–33% to –39%) Pravastatin 20 mg: –27% (–25% to –29%) Pravastatin 40 mg: –32% (–30% to –34%) Secondary: Compliance rates: Cholestyramine: 44% Cholestyramine and pravastatin: 53% Pravastatin 20 mg: 76% Pravastatin 40 mg: 78% Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common in the cholestyramine group and the cholestyramine with pravastatin group.
Insull et al[22] Colesevelam 2.3 g vs colesevelam 3.0 g vs colesevelam 3.8 g vs	DB, MC, PC, RCT Patients with primary hypercholesterolemia, LDL-C levels between 130-220 mg/dL	N=467 32 weeks (8 weeks diet lead in and 24 weeks treatment)	Primary: Mean absolute change in LDL-C from baseline to the end of 24-week treatment Secondary: Mean percent change in LDL-C, mean absolute and percent change in TC, apo B, apo AI, and median	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (*P*<0.001 for all). Absolute change decreases and percent decreases in LDL-C for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 14 mg/dL (9%), 19 mg/dL (12%), 24 mg/dL (15%) and 28 mg/dL (18%). Secondary: All doses of colesevelam resulted in significant reductions of TC (*P*<0.001). Absolute change decreases and percent decreases in TC for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 10 mg/dL (4%), 15 mg/dL (6%), 18 mg/dL (7%) and 24 mg/dL (10%). All doses of colesevelam resulted in significant increases in HDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
colesevelam 4.5 g vs placebo			absolute change and percent change in HDL-C and TG	(*P*<0.001). Absolute changes (increases) and percent increases in TC for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 2 mg/dL (3%), 2 mg/dL (4%), 2 mg/dL (3%) and 2 mg/dL (3%). All doses of colesevelam resulted in significant reductions in apo B relative to baseline (*P*<0.001). Changes in apo AI and lipoprotein did not result in significant changes relative to baseline, except the 2.3 g and 3.0 g doses resulted in significant changes in apo AI (*P*=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo, however increases, 5% to 10%, were seen within groups from baseline to end point (*P*<0.05).
Hunninghake et al[23] Colesevelam 3.8 g vs atorvastatin 10 mg vs colesevelam 3.8 g and atorvastatin 10 mg vs atorvastatin 80 mg vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change in LDL-C Secondary: Change in TC, HDL-C, TG, apo B, apo AI and lipoprotein(a) from baseline	Primary: All treatment groups resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions were –12% in the colesevelam 3.8 g group, –38% in the atorvastatin 10 mg group, –48% in the colesevelam 3.8 g and atorvastatin 10 mg group and –53% for the atorvastatin 80 mg group (*P*<0.05, *P*<0.0001, *P*<0.0001, and *P*<0.0001, respectively, for change from baseline to end point). Secondary: Colesevelam 3.8 g/day reduced TC –6% (*P*<0.05), increased HDL-C 3% (*P*<0.05), and increased TG 10% (*P* value not reported). Atorvastatin 10 mg reduced TC –27% (*P*<0.0001), increased HDL-C 8% (*P*<0.05), and reduced TG –24% (*P*<0.05). Colesevelam 3.8 g and atorvastatin 10 mg reduced TC –31% (*P*<0.0001), increased HDL-C 11% (*P*<0.05), and reduced TG –1% (*P* value not reported). Atorvastatin 80 mg reduced TC –39% (*P*<0.0001), increased HDL-C 5% (*P*<0.05), and reduced TG –33% (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam 3.8 g with atorvastatin 10 mg. No significant differences in HDL-C were found between the groups (*P* value not reported). Apo B levels decreased significantly for all groups relative to baseline (*P*<0.01). No significant changes in Apo AI and lipoprotein were reported.
Knapp et al[24] Colesevelam 3.8 g vs simvastatin 10 mg vs colesevelam 3.8 g with simvastatin 10 mg vs colesevelam 2.3 g vs simvastatin 20 mg vs colesevelam 2.3 g with simvastatin 20 mg vs	DB, MC, PC, RCT Men and women, age 18 years and older, with elevated LDL-C levels, ≥160 mg/dL and TG ≤300 mg/dL and not taking cholesterol-lowering medication	N=258 6 weeks	Primary: Change in serum LDL-C from baseline to end point Secondary: Percent change in LDL-C, mean and percent change in TC, HDL-C, TG, apo B and apo AI from baseline	Primary: LDL-C serum changes were –7 mg/dL in the placebo group, –31 mg/dL in the colesevelam 3.8 g group, –48 mg/dL in the simvastatin 10 mg group –80 mg/dL in the colesevelam 3.8 g and simvastatin 10 mg group, –17 mg/dL in the colesevelam 2.3 g group, –61 mg/dL in the simvastatin 20 mg group and –80 mg/dL for the colesevelam 2.3 g and simvastatin 20 mg group (*P*<0.05, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, and *P*<0.0001, respectively, for change from baseline to end point). Secondary: LDL-C percent changes were –4% in the placebo group, –16% in the colesevelam 3.8 g group, –26% in the simvastatin 10 mg group, –42% in the colesevelam 3.8 g and simvastatin 10 mg group , –8% in the colesevelam 2.3 g group, –34% in the simvastatin 20 mg group and –42% for the colesevelam 2.3 g and simvastatin 20 mg group (*P*<0.05, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, and *P*<0.0001, respectively, for change from baseline to end point). Significant changes from baseline were found for all treatment groups in mean and percent change in TC (*P*<0.0001 for all except colesevelam 2.3 g for which *P*<0.05). Significant changes from baseline were found for mean and percent change in HDL-C for simvastatin 10 mg (*P*<0.05), colesevelam 3.8 g with simvastatin 10 mg (*P*<0.0001), colesevelam 2.3 g (*P*<0.05), simvastatin 20 mg (*P*<0.05), and colesevelam 2.3 g with simvastatin 20 mg (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Significant changes from baseline were found for mean and percent change in TG for colesevelam 3.8 g (*P*<0.05), simvastatin 10 mg (*P*<0.05), simvastatin 20 mg (*P*<0.05), and colesevelam 2.3 g with simvastatin 20 mg (*P*<0.05). Significant reductions from baseline for apo B were found for all groups. Reductions were significant (*P*<0.05) compared to placebo for all treatment groups except colesevelam 2.3 g. Significant increases in apo AI were seen in all treatment groups except simvastatin 10 mg (*P*<0.05).
Davidson et al [25] Colesevelam 2.3 g vs lovastatin 10 mg vs colesevelam 2.3 g and lovastatin 10 mg taken together vs colesevelam 2.3 g and lovastatin 10 mg taken apart vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels	N=135 4 week	Primary: Percent change in LDL-C Secondary: Changes in TC, HDL-C, TG, apo B	Primary: Colesevelam 2.3 g and lovastatin 10 mg together significantly reduced LDL-C 34% (-60 mg/dL; *P*<0.0001). Colesevelam 2.3 g and lovastatin 10 mg apart significantly reduced LDL-C 32% (-53 mg/dL; *P*<0.0001). Lovastatin 10 mg reduced LDL-C 22% (-39 mg/dL; *P* value not reported). Colesevelam 2.3 g reduced LDL-C 7% (-13 mg/dL; *P* value not reported). Both combination treatments were more effective than either treatment alone (*P*<0.05). Secondary: Both combination treatments resulted in reductions in TC by 21% and apo B by 24% (*P*<0.0001 for each). No significant effect on HDL-C or TG was found for the combination treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Type 2 Diabetes Mellitus				
Zieve et al[26] GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients diagnosed with type 2 diabetes, an HbA_{1c} 7.0%-10.0%, and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in fructosamine levels, FPG levels, postprandial glucose level, meal glucose response (difference between pre and postprandial glucose levels) % change in lipids: LDL, TC, TG, apo AI and B	Primary: The change in HbA_{1c} from baseline to 12 weeks for the colesevelam group was –0.3% and for placebo +0.2%, for a treatment difference of 0.5% (*P*=0.007). For patients with a baseline HbA_{1c} ≥8.0, there was a greater difference in HbA_{1c}, –1.0%, after 12 weeks of treatment (*P*=0.002). The reduction in HbA_{1c} in the treatment groups did not differ based on oral antidiabetic treatment (*P* value not reported). Secondary: Significantly lower FPG was seen in the colesevelam group at weeks 4 and 8, (*P*=0.016, *P*=0.011), but not at week 12. Significantly lower fructosamine levels were seen in the colesevelam group at week 12 (*P*=0.011). Significantly lower postprandial glucose levels were seen in the colesevelam group at week 12 (*P*=0.026). No significant difference was seen in meal glucose response (*P*=0.195). Significantly lower lipid parameters, including LDL, TC, apo B and LDL particle concentration, were seen in the colesevelam group as compared to placebo (*P*=0.007, *P*=0.019, *P*=0.003, and *P*=0.037, respectively).

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial

Miscellaneous abbreviations: apo=apolipoprotein, CHD=coronary heart disease, CRP=C-reactive protein, FPG=fasting plasma glucose, GLOWS=Glucose-Lowering Effect Of WelChol; HbA_{1c}=glycosylated hemoglobin, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IL6=interleukin 6, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, TC=total cholesterol, TG=triglycerides

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Bile Acid Sequestrants

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
cholestyramine and aspartame	powder (packet)	Questran Light®*	$-$$$$$	$-$$$$
cholestyramine and sucrose	powder (packet)	Questran®*	$-$$$$$	$
colesevelam	tablet	Welchol®	$$$$	N/A
colestipol	tablet, granule (packet or bulk)	Colestid®*	$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

Included in the bile acid sequestrant class are cholestyramine, colesevelam and colestipol. The bile acid sequestrants are primarily indicated for the reduction of total cholesterol and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[2-5] These agents reduce cholesterol levels by binding to, and removing bile acid from circulation. The resultant lower levels of bile acid lead to increased breakdown of cholesterol into bile acid, lowering the overall total cholesterol levels.[6] The bile acid sequestrants are effective at reducing LDL-C, while slightly increasing high-density lipoprotein cholesterol.[7]

There is a lack of head-to-head trials comparing agents within the bile acid sequestrant class to each other and current treatment guidelines do not give preference to one agent over another.[7-10,12] Although colesevelam may offer a more favorable drug-interaction profile, potential drug interactions with bile acid sequestrants may be minimized by adjusting the timing of the doses. Cholestyramine and colestipol are available generically. Colesevelam and colestipol are available in tablet formulation. Colestipol is also available as granules for suspension. Cholestyramine is only available in a powder form for suspension.

Treatment guidelines recommend statin therapy as first-line treatment for dyslipidemia.[7-10,12] The guidelines recommend the use of bile acid sequestrants as an alternative for patients who have a contraindication or intolerance to a statin, or as additional treatment for patients who can not achieve goal cholesterol levels with monotherapy alone. All the bile acid sequestrants can be used in conjunction with a statin, or as monotherapy. Colesevelam recently received an FDA indication for the adjunctive treatment of type 2 diabetes; its use for improving glycemic control is not addressed in the current American Diabetes Association treatment guidelines.[5]

Clinical trials demonstrate efficacy of each agent in reducing low-density lipoprotein, non–high-density lipoprotein, total cholesterol and other markers of dyslipidemia.[16-26] The bile acid sequestrants are an effective alternative option to first-line treatment or as adjunctive treatment for decreasing cholesterol.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
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Pharmacotherapy Review of Cholesterol Absorption Inhibitors
AHFS Class 240605
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I. Overview

At the time of this review, ezetimibe is the only antilipemic agent that is classified as a cholesterol absorption inhibitor via the American Hospital Formulary Service (AHFS).[1-2] Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds. Ezetimibe reduces blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol by the small intestine resulting in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately to lower systemic cholesterol levels.[1,3]

Table 1 lists all the cholesterol absorption inhibitors included in this review. This review encompasses all dosage forms and strengths.

Table 1. Cholesterol Absorption Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
ezetimibe	tablet	Zetia®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the cholesterol absorption inhibitors are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Cholesterol Absorption Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[4]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia.

Clinical Guideline	Recommendation
	Polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[5]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Cholesterol Absorption Inhibitors • Cholesterol absorption inhibitors (eg, ezetimibe) are not mentioned in this guideline.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[6]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[7]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[8]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age.

Clinical Guideline	Recommendation
	• Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[9]	• Statins are considered first-line drugs for lowering LDL-C. • As monotherapy, cholesterol absorption inhibitors have mild LDL-lowering effects and can be used for patients with active liver disease, having adverse effects on statins or when statins, fibrates and nicotinic acid are contraindicated. • Their primary role in therapy is in combination with statins. • Cholesterol absorption inhibitors have not been shown in clinical trials to reduce myocardial infarction and coronary death. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the cholesterol absorption inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cholesterol Absorption Inhibitors[3]

Indication(s)*	Ezetimibe
When administered alone, as adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia	✔
When administered in combination with a hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, and apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia	✔
When administered in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-high-density lipoprotein cholesterol (non–HDL-C) in patients with mixed hyperlipidemia	✔
When administered in combination with atorvastatin or simvastatin, for the reduction of elevated TC and LDL-C levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein apheresis) or if such treatments are unavailable	✔
When administered alone, as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia	✔

*Prior to initiating therapy with ezetimibe, secondary causes for dyslipidemia (ie, diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C) should be excluded or, if appropriate treated.[3]

IV. Pharmacokinetics

The pharmacokinetic parameters for the cholesterol absorption inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Cholesterol Absorption Inhibitors[3,10]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Ezetimibe	35-60	>90	Glucuronide conjugation with minimal oxidation	ezetimibe-glucuronide	Feces: 78 Urine: 11	22 for both drug and active metabolite

V. Drug Interactions

Significant drug interactions with the cholesterol absorption inhibitors are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with Cholesterol Absorption Inhibitors[3,10,11]

Drug	Significance Level	Interaction	Mechanism
Ezetimibe	2	Cyclosporine	Although the mechanism is unknown, when cyclosporine and ezetimibe are administered concomitantly exposure to both drugs may be increased, potentially increasing the pharmacologic effects and adverse reactions. Monitor cyclosporine concentrations when ezetimibe is coadministered and adjust the cyclosporine dose as needed. In addition, monitor patients for cyclosporine or ezetimibe adverse reactions.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Common side effects of ezetimibe include abdominal pain, diarrhea, arthralgia, back pain, myalgia, headache, cough, sinusitis and fatigue. More serious side effects include hepatitis, drug-induced myopathy and rhabdomyolysis. The most common adverse drug events reported with the cholesterol absorption inhibitors are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with Cholesterol Absorption Inhibitors[3,10]

Adverse Event	Ezetimibe
Cardiovascular	
Chest pain	1.8-3.4
Central Nervous System	
Depression	✔
Dizziness	1.8-2.7
Fatigue	1.9-2.8
Headache	6.3-8
Dermatologic	
Rash	✔
Urticaria	✔
Endocrine and Metabolic	
Cholecystitis	✔
Cholelithiasis	✔
Elevated creatine phosphokinase	✔
Elevations in liver transaminase	2.7
Hepatitis	✔
Pancreatitis	✔
Gastrointestinal	
Abdominal pain	2.7-3.5
Diarrhea	2.8-3.7
Nausea	✔
Hematologic	
Thrombocytopenia	✔
Musculoskeletal	
Arthralgia	3.4-3.8
Back pain	3.4-4.3
Myalgia	4.5-5.0
Myopathy	Very rarely
Rhabdomyolysis	Very rarely

Adverse Event	Ezetimibe
Respiratory	
Angioedema	✔
Coughing	2.3
Pharyngitis	2.3-3.1
Sinusitis	3.5-4.6
Upper respiratory tract infection	11.8-13
Other	
Anaphylaxis	✔
Cholecystectomy	1.7
Hypersensitivity reactions	✔
Infection viral	2.2

✔ Percent not specified

VII. Dosing and Administration

No dosage adjustment of ezetimibe is necessary in patients with mild hepatic insufficiency or renal insufficiency. There is limited experience with ezetimibe in the pediatric population and it is not recommended to be used in children less than 10 years of age. The usual dosing regimens for the cholesterol absorption inhibitors are summarized in Table 7.

Table 7. Usual Dosing for the Cholesterol Absorption Inhibitors[3,10]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	10 mg once daily	Safety and efficacy in children (<10 years of age) have not been established.	Tablet: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cholesterol absorption inhibitors are found in Table 8.

Table 8. Comparative Clinical Trials Using Cholesterol Absorption Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dujovne et al[12] Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=892 12 weeks	Primary: Percent change from baseline to end point in plasma concentration of direct LDL-C Secondary: Changes and percent changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, and HDL-C at end point, changes from baseline HDL_2-C and HDL_3-C, apo AI, apo B, Lp(a) at end point, adverse events	Primary: The ezetimibe group achieved a mean percent reduction from baseline to end point in the plasma concentration of LDL-C of 16.9% compared to 0.4% in the placebo group (*P*<0.01). Secondary: There was a –17.68% compared to a 1.11% change in the calculated LDL-C from baseline in the ezetimibe and placebo groups, respectively (*P*<0.01). Ezetimibe also significantly decreased the apo B, TC, and TG as well as significantly increased HDL-C and HDL_3-C from baseline (*P*<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (*P*=0.76 and *P*=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients taking ezetimibe and 63% of patients taking placebo. The most commonly reported adverse event in both treatment groups were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups (*P* value not reported).
Knopp, Gitter et al[13] Ezetimibe 10 mg QD vs	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130	N=827 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of direct LDL-C	Primary: The mean plasma concentration of direct LDL-C from baseline to end point was 17.7% in the ezetimibe group compared to 0.8% in the placebo group (*P*<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a) and significantly increased HDL-C and HDL_2-C (*P*≤0.01 for all). However, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	to 250 mg/dL and TG ≤350 mg/dL)		Secondary: Changes and percentage changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, HDL-C at end point, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	change in HDL_3-C, apo AI, and TG from baseline did not result in significant differences between treatment groups (*P*=0.49, *P*=0.27, *P*=0.09). The percentage of patients reporting treatment-emergent adverse events was 61% in the ezetimibe group and 65% in the placebo group. No individual adverse event was prevalent in either group and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between both treatment groups (*P* value not reported).
Knopp, Dujovne et al[14] Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Pooled data of men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout) Includes the 827 patients from Knopp, Gitter, et al (above) plus 892 patients from a second study.	N=1,719 (2 trials) 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline in the ezetimibe group compared to an increase of 0.9% in the placebo group (*P*<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a), and TG and increased HDL-C compared to placebo (*P*<0.01). However, there were no statistically significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (*P*=0.08, *P*=0.06, and *P*=0.26). The overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 62% of patients in the ezetimibe group and 62% of patients in the placebo group reported adverse events. Also, there were no significant between-group differences in the laboratory or clinical safety parameters or gastrointestinal, liver, or muscle side effects.
Wierzbicki et al[15] Ezetimibe 10 mg QD	PRO Patients with refractory familial hyperlipidemia	N=200 Not reported	Primary: LDL-C, TG, HDL-C, CRP, ALT	Primary: Ezetimibe was associated with 7% reductions in LDL-C and 11% reductions in apo B. The proportion of patients achieving LDL-C <3 mmol/L increased from 6% to 18%. There were no significant differences in TG, HDL-C, CRP, or ALT.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo QD	or intolerance to statin therapy		Secondary: Not reported	Secondary: Not reported
Kalogirou et al[16] Ezetimibe 10 mg QD vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD, average 54 years of age, average BMI of 26.9 kg/m^2	N=50 16 weeks	Primary: Effect of monotherapy ezetimibe on lipoprotein subfractions Secondary: Not reported	Primary: A significant median reduction in serum HDL-C concentration from 1.5 mmol/L (1.1 to 2.6) at baseline to 1.4 mmol/L (0.9 to 2.6) posttreatment was observed with ezetimibe treatment. The median change in HDL-C was –6.6% (*P*<0.001). A significant median reduction in TC from 7.1 mmol/L (4.9 to 11.1) at baseline to 5.8 mmol/L (4.3 to 8.9) posttreatment was observed with ezetimibe treatment. The median change in TC was –15.5% (–34.5% to 4.2%) with ezetimibe treatment (*P*<0.001 vs placebo). Mean serum TG decreased from 1.5 mmol/L (0.6 to 4.28) at baseline to 1.4 mmol/L (0.6 to 3.2) posttreatment; a median percent change of 9.3% (–32.4% to 15.7%; *P*<0.05). Mean serum LDL-C levels significantly decreased from 3.8 mmol/L (2.5 to 7.3) at baseline to 3.2 mmol/L (1.8 to 5.4) posttreatment; a median percent change of –20.1% (–51.1% to 23.1%; *P*<0.001). Secondary: Not reported
Gonzalez-Ortiz et al[17] Ezetimibe 10 mg QD vs placebo QD	DB, PC, RCT Obese, dyslipidemic patients 18-45 years old	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL	Primary: Ezetimibe-treated patients compared with placebo-treated patients had decreased TC (6.0 vs 4.2 mmol/L; *P*=0.011) and LDL-C (4.0 vs 2.2 mmol/L; *P*=0.003) without affecting insulin sensitivity. Secondary: There were no differences in HDL-C, TG, and VLDL (*P*=not significant).
Gagné, Bays et al[18] Ezetimibe 10 mg QD plus a statin	DB, MC, PC, RCT Adults aged ≥18 years, currently on a stable daily dose of a statin	N=769 8 weeks	Primary: Mean percentage change in LDL-C from baseline to end point	Primary: There was an additional LDL-C reduction of 25.1% in patients receiving ezetimibe therapy compared to a reduction of 3.7% in patients receiving placebo (*P*<0.001 for between-group differences).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo plus a statin	for ≥6 weeks, must have been previously instructed on a cholesterol-lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors, ≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)		Secondary: Percentage of patients who achieved NCEP ATP II target levels for LDL-C, HDL-C, TC, TG, adverse events	Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of patients taking ezetimibe plus statin achieved the prespecified NCEP ATP II target LDL-C levels at end point compared to 27.3% of patients taking placebo plus statin (OR, 19.6; *P*<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5% vs 18.9% of patients taking ezetimibe and placebo, respectively, achieved target LDL-C goals. HDL-C was increased by 2.7% compared with an increase of 1.0% in patients taking ezetimibe and placebo, respectively (*P*<0.05). TG decreased by 14.0% and 2.9%, respectively (*P*<0.001). TC was also improved significantly with coadministration of ezetimibe compared to placebo (*P*<0.001). The overall incidence of treatment-related adverse events was similar between both groups (21% ezetimibe vs 17% placebo; *P* value not reported).
Pearson, Francis et al[19] Ezetimibe 10 mg QD Patients either received ezetimibe as monotherapy, in combination with a low-dose statin (20 mg/day or less of atorvastatin or its equivalent), or in combination with a high-dose statin (20 mg/day or more of	RETRO Cohort Men and women ≥18 years old who took ezetimibe for a minimum of two weeks	N=84 2-6 weeks	Primary: Change in fasting lipid profile at baseline to 2-6 weeks of ezetimibe therapy, clinical effectiveness results stratified by primary versus secondary prevention Secondary: Percentage of patients able to achieve their LDL-C target levels in	Primary: The mean reductions from baseline to 2-6 weeks of ezetimibe therapy were: TC 1.11mmol/L (16.5%), LDL-C level 1.01 mmol/L (22.3%), and ratio of TC:HDL 0.68 mmol/L (12.8%) (all *P*<0.001). The HDL-C level increased by 0.06 mmol/L (4.6%) from baseline to 2-6 weeks of ezetimibe therapy (*P*<0.001). Results were similar when stratified by primary (N=28) versus secondary (N=56) prevention. Among the primary prevention group, only the TC levels, LDL-C levels and TC:HDL ratio reductions were statistically significant (*P*<0.001). In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC:HDL ratio all achieved statistical significance (*P*<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were –1.03 mmol/L (–20.5%) for ezetimibe monotherapy, –1.19 mmol/L (–30.1%) for ezetimibe and a low-dose statin, and –0.95 mmol/L (–22.5%) for ezetimibe plus a high-dose statin (*P*<0.001 for ezetimibe monotherapy and ezetimibe plus a high-dose statin; *P*=0.0017 for ezetimibe plus a low-dose statin).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin or its equivalent).			accordance with their calculated Framingham risk category and defined Canadian guidelines and safety and tolerability	Secondary: There were 7 patients out of 34 (20.6%) in the ezetimibe monotherapy group, 5 out of 12 (41.6%) in the ezetimibe plus low-dose statin group and 18 out of 38 (47.4%) in the ezetimibe plus high-dose statin group who achieved previously unattainable target LDL-C levels. There were 4 patients who discontinued therapy due to treatment-related adverse event.
Bissonnette et al[20] Ezetimibe 10 mg QD coadministered with current statin therapy	MC, OL, PRO Men and women ≥18 years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels of ≥2.5 mmol/L for patients at high 10-year CAD risk, ≥3.5 mmol/L for patients at moderate 10-year CAD risk and ≥4.5 mmol/L for patients at low 10-year CAD risk category, on a stable diet and statin regimen for at least 4 weeks before study entry	N=953 6 weeks	Primary: Percentage of change in LDL-C during the 6-week treatment period Secondary: Percentage of patients who had achieved the recommended target LDL-C levels at the end of the 6-week treatment period and the percentage of change in TC, TG, HDL-C , apo B and the TC:HDL-C ratio and safety and tolerability	Primary: After 6 weeks of treatment with ezetimibe, a statistically significant mean reduction was observed in LDL-C (30.5%; *P*<0.001). Secondary: At 6 weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After 6 weeks of treatment with ezetimibe, statistically significant mean reductions were observed in TC (20.8%), TG (10.1%), apo B (19.8%), and TC:HDL ratio (19.9%) (*P*<0.001). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).
Denke et al[21] Ezetimibe 10 mg QD addition to an ongoing statin	DB, MC, PC, PG, RCT Men and women ≥18 years of age with diabetes, metabolic	N=3,030 6 weeks	Primary: LDL reduction and additional lipid parameters, safety and tolerability	Primary: After 6 weeks of treatment, the addition of ezetimibe to ongoing statin therapy reduced LDL levels in patients with diabetes by 28%, metabolic syndrome by 24%, or elevated LDL levels without diabetes or the metabolic syndrome by 26%, compared with a 3% reduction in the placebo group (*P*<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy vs placebo in addition to an ongoing statin therapy	syndrome without diabetes, or neither disorder who had LDL levels exceeding the NCEP ATP III goals who were taking a stable, approved dose of any statin, had been following a cholesterol –lowering diet for at least 6 weeks prior to study entry with TG levels ≤350 mg/dL		Secondary: Not reported	TG and HDL levels were significantly reduced in patients with diabetes and metabolic syndrome when ezetimibe was added to statin therapy compared to placebo (*P*<0.002). Non-HDL levels, TC, apo B:apo AI ratio, and CRP levels improved significantly in patients with diabetes and patients with elevated LDL levels without diabetes or metabolic syndrome when ezetimibe was added to statin therapy compared to placebo. Drug-related adverse events occurred in 5.2% in the placebo group and 5.1% in the ezetimibe group. Drug-related adverse events that led to drug discontinuation occurred in 1.6% in the placebo group and 0.9% in the ezetimibe group. There were no significant differences between the two groups in elevation of ALT, AST or in muscle CK beyond predefined limits. Secondary: Not reported
Pearson, Denke et al[22] Ezetimibe 10 mg QD vs placebo Patients in both groups continued to receive their current dose of statin therapy.	MC, DB, PC, PG Hypercholesterolemic patients ≥18 years of age with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol-lowering diet for at least 6 weeks	N=3,030 6 weeks	Primary: Percent reduction in LDL-C level from baseline after 6 weeks of double-blind treatment Secondary: Percentage of patients who achieved NCEP ATP III target LDL-C levels in the total population and by NCEP ATP III risk categories (<100 mg/dL for patients with CHD or CHD risk	Primary: Ezetimibe added to a statin significantly reduced mean LDL-C levels by an additional 25.8% compared with a reduction of 2.7% with the addition of placebo to statin (95% CI, –24.4% to –21.7%; *P*<0.001). Secondary: The addition of ezetimibe to statin resulted in an additional 23.8% to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were –24.0%, –19.7%, and –19.9% in the CHD or CHD risk equivalent, multiple risk factors, or <2 risk factors groups, respectively (*P*<0.001 ezetimibe vs placebo for each risk category). No significant differences were found according to age, sex, or race category (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			equivalent, <130 mg/dL for patients with multiple CHD risk factors conferring a 10-year risk of CHD of ≤20%, and <160 mg/dL for patients with <2 CHD risk factors)	
Pearson, Denke et al[23] Ezetimibe 10 mg QD in addition to ongoing statin therapy vs placebo in addition to ongoing statin therapy	DB, MC, PG, PC, RCT Men and women ≥18 years of age including white, African American, Hispanic or other who followed a cholesterol-lowering diet, were taking a stable approved dose of any US-marketed statin for at least 6 weeks before study entry, with LDL levels greater than the NCEP ATP III goal	N=3,030 6 weeks	Primary: LDL-C and additional parameters and percentage of patients reaching LDL goal for the NCEP ATP III in racial and ethnic subgroups Secondary: Safety and tolerability	Primary: The addition of ezetimibe to ongoing statin therapy significantly reduced LDL, TC, non-HDL and HDL levels compared to placebo (*P*<0.001). This effect was consistent across race and ethnicity (*P*>0.50 for treatment-by-race interactions). CRP level reduction was statistically significant in patients receiving ezetimibe compared to placebo (*P*<0.001). The treatment-by-race interaction was not statistically significant (*P*=0.83), indicating a consistent treatment effect of lowering CRP levels across race and ethnicity groups. Ezetimibe added to statin therapy significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63%, Hispanics by 64.8% and whites by 72.3%, compared to placebo (*P*<0.001). Secondary: The addition of ezetimibe to ongoing statin therapy was well tolerated with an overall safety profile similar in all patient groups by race or ethnicity.
Simons et al[24] Ezetimibe 10 mg QD in addition to an ongoing statin therapy	OL, phase 4, single arm Men and women from Australia, mean age 65.6 years, with CHD or diabetes mellitus who had already used	N=130 6 weeks	Primary: LDL reduction and percentage of patients who reached LDL goal of <2.5 mmol/L or <2.0 mmol/L and	Primary: The LDL levels after 6 weeks were reduced by 29% (95% CI, 25 to 34) in patients receiving ezetimibe. Goal LDL-C of <2.5 mmol/L and <2.0 mmol/L were reached in 70% and 50% of patients receiving ezetimibe (95% CI, 59% to 79% and 39% to 60%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo in addition to an ongoing statin therapy	≥40 mg/day of a statin for at least 3 months with current TC of >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL is <1.0 mmol/L		other lipid parameters Secondary: Not reported	TC and TG levels were reduced by 19% and 11%, respectively, in the ezetimibe group compared to placebo (95% CI, –21 to –16 and –16 to –5). There were no significant changes in HDL between the two groups (95% CI, 0 to 6). Secondary: Not reported
Mikhailidis et al[25] Ezetimibe 10 mg QD in combination with a statin vs placebo in combination with a statin or statin monotherapy	MA, systematic review of 19 RCTs, 2 extension studies DB, PG or XO, SB or OL RCTs Adults ≥18 years with diagnoses of nonfamilial or familial hypercholesterolemia, hyperlipidemia, and homozygous familial sitosterolemia; with LDL-C levels above NCEP ATP II/III guideline criteria	N=5,039 Trial durations ranged from 6 to 48 weeks	Primary: Total number of patients attaining LDL-C goal; changes in TC, LDL-C, and HDL-C from baseline to end point Secondary: Not reported	Primary: The analysis of 5 RCTs indicated that when compared to placebo in combination with a statin, the RR of obtaining the LDL-C treatment goal was higher for patients in the ezetimibe and statin groups; $P < 0.0001$. A weighted mean difference (WMD) between treatments significantly favored the ezetimibe and statin combination therapy over placebo and statin: for TC, a WMD of –16.1% (CI, –17.3 to –14.8); for LDL-C, a WMD of –23.6% (CI, –25.6 to –21.7); and for HDL-C, a WMD of 1.7% (CI, 0.9 to 2.5); $P<0.0001$ for all. In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the ezetimibe and statin combination was favored over placebo and statin for the following WMD: LDL-C –23.6% ($P<0.0001$); TC –16.1% ($P<0.0001$); HDL-C +1.7% ($P<0.0001$); TG –10.7%; Apo B –17.3%; RR, LDL-C treatment goal 3.4 ($P<0.0001$). The difference between treatments in all studies favored the ezetimibe and statin combination therapy for all outcomes except TG and HDL-C. An analysis of data from a 48-week extension study correlated with the pooled estimates of the short-term studies in the meta-analysis. This data showed that the ezetimibe and simvastatin combination resulted in significantly lower levels of LDL-C, TC, and TG when compared with the placebo and simvastatin combination (reductions of 20.4%, 13.4% and 13.6%, respectively; $P<0.001$ for the difference between treatments). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ballantyne, Houri et al[26] Ezetimibe 10 mg QD vs atorvastatin 10, 20, 40, or 80 mg QD vs ezetimibe 10 mg QD plus atorvastatin 10, 20, 40, or 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145-250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (*P*<0.01) or ezetimibe alone (*P*<0.01). Mean changes in direct LDL-C ranged from –50% to –60% in the combination group compared to –35% to –51% in the atorvastatin alone group (*P*<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (*P*<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50% vs 51%), TC:HDL-C ratio (43% vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9% vs 3%) with the combination group (*P* value not reported). Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (*P*<0.01 for all) and ezetimibe monotherapy (*P*<0.01 for all). However, increases in HDL_2-C (*P*=0.53), HDL_3-C (*P*=0.06), apo AI (*P*=0.31), and Lp(a) (*P*=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe monotherapy groups for increases in these same parameters: HDL_2-C (*P*=0.08), HDL_3-C (*P*=0.67), apo AI (*P*=0.80), and Lp(a) (*P*=0.92). The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kerzner et al[27] Ezetimibe 10 mg QD vs lovastatin 10, 20, or 40 mg QD vs ezetimibe 10 mg QD plus lovastatin 10, 20, or 40 mg QD vs placebo	DB, MC, PC, RCT Men and women aged ≥18 years with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation, mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease in directly measured LDL-C from baseline to study end point Secondary: Change from baseline to end point for calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, direct LDL-C:HDL-C ratio, adverse events	Primary: The reduction in plasma levels of direct LDL-C from baseline to end point was significantly greater in the combination group of ezetimibe plus lovastatin compared to either lovastatin or ezetimibe monotherapy (*P*<0.01 for both). The mean percentage decrease in direct LDL-C in the combination group was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin monotherapy (*P*<0.01). The mean percentage change in LDL-C achieved with combination ezetimibe plus lovastatin 10 mg was similar to the highest lovastatin dose of 40 mg monotherapy (*P*=0.10). Secondary: In comparison to lovastatin monotherapy, the combination group significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, direct LDL-C:HDL-C ratio (*P*<0.01 for all), and apo AI (*P*=0.04). The combination of ezetimibe plus lovastatin significantly increased HDL-C at lovastatin doses of 20 and 40 mg compared to the same lovastatin monotherapy dose (*P*<0.01 and *P*<0.02, respectively) and significantly decreased TG levels (*P*<0.01 for both). Treatment-related adverse events were reported for 16% of patients receiving lovastatin monotherapy and 17% of patients receiving combination therapy. The safety profile for the combination group was similar to that for the lovastatin monotherapy and placebo group (*P* value not reported).
Melani et al[28] Ezetimibe 10 mg QD vs pravastatin 10, 20, or 40 mg QD	DB, MC, PC, RCT Men and women 20-86 years old with primary hypercholesterolemia (LDL-C 3.8 to 6.5 mmol/L as calculated by the Friedewald equation and TG ≤4.0	N=538 12 weeks	Primary: Percent change in direct LDL-C from baseline to study end point Secondary: Mean change and percent change	Primary: A mean percent change of –38% for the combination therapy and –24% for pravastatin monotherapy was observed. The combination therapy was significantly more effective at reducing plasma levels of direct LDL-C from baseline to end point (*P*<0.01). The combination group had a mean percentage change in direct LDL-C ranging from –34% to –41% compared with –20% to –29% for individual doses of pravastatin monotherapy. When the combination therapy was compared to its corresponding pravastatin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD plus pravastatin 10, 20, or 40 mg QD vs placebo	mmol/L)		from baseline in LDL-C as calculated by the Friedewald equation, TC, TG, HDL-C, direct LDL-C:HDL-C and TC:HDL-C ratio, non–HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C, Lp(a)	dose, the incremental mean percentage reductions in direct LDL-C were statistically significant in favor of the combination therapy ($P \leq 0.01$). In addition, the coadministration of ezetimibe plus pravastatin 10 mg produced a larger mean percentage reduction in direct LDL-C compared to the highest dose of pravastatin monotherapy ($P \leq 0.05$). Secondary: In comparison to pravastatin monotherapy, the combination therapy improved calculated LDL-C, TG, TC, apo B, non–HDL-C, direct LDL-C:HDL-C, and TC:HDL-C ($P<0.01$ for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced in the combination group ($P<0.01$). TG was also significantly reduced in the combination group at pravastatin doses of 10 and 20 mg compared to pravastatin monotherapy ($P<0.05$). Although the combination therapy produced greater increases in HDL-C at the 10 and 40 mg doses, it was not significant. The differences in change in HDL_2-C, HDL_3-C, apo AI, and Lp(a) between the combination group and pravastatin monotherapy were determined to be not significant (P=NS). Coadministration of ezetimibe and pravastatin was well tolerated and the overall safety profile was similar to pravastatin monotherapy and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any nonlaboratory adverse event (P value not reported).
Farnier et al[29] Ezetimibe 10mg vs micronized fenofibrate 160 mg vs	DB, MC, PC, RCT Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	N=619 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared with the other treatment groups ($P<0.001$ compared with micronized fenofibrate and ezetimibe). These reductions were –13.4% in the ezetimibe group, –5.5% in the micronized fenofibrate group, and –20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared with micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non–HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; $P<0.001$. When compared with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ezetimibe 10 mg in combination with micronized fenofibrate 160 mg vs placebo			parameters from baseline to study end point	placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; *P*<0.001. The percent changes from baseline to study end point were as follows: –11.8% in TC, 3.9% in HDL-C, –11.1% in TG, and –6.1% in high sensitivity CRP in the ezetimibe group; –10.8% in TC, 18.8% in HDL-C, –43.2% in TG, and –28.0% in hsCRP in the micronized fenofibrate group; –22.4% in TC, 19.0% in HDL-C, –44.0% in TG, and –27.3% in high sensitivity CRP in the micronized fenofibrate and ezetimibe group; *P*<0.05 for all.
McKenney et al[30] Ezetimibe 10 mg QD and fenofibrate 160 mg (single entities) vs fenofibrate 160 mg	DB, ES, RCT Extension of the preceding study by Farnier et al Patients with mixed hyperlipidemia, LDL-C 130 to 220 mg/dL, TG 200 to 500 mg/dL	N=576 48 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change in TC, HDL-C, TG, non–HDL-C, apo B, apo AI, and hsCRP from baseline	Primary: The combination resulted in significantly reduced LDL-C compared with monotherapy (–22.0 vs –8.6; *P*<0.001). Secondary: The combination resulted in significantly reduced TC, TG, non–HDL-C, and apo B compared with monotherapy (–23.2 vs –13.6; *P*<0.001), (–46.0 vs –41.8; *P*=0.002), (–31.6 vs –19.4; *P*<0.001), (–25.2 vs –16.2; *P*<0.001). The combination resulted in significantly increased HDL-C compared with monotherapy (20.9 vs 17.8; *P*=0.02). There were no significant differences in apo AI or hsCRP (*P*=not significant).
Coll et al[31] Ezetimibe 10 mg QD vs fluvastatin extended release 80 mg QD	RCT HIV patients, ≥6 months on stable HAART, ≥18 years of age, fasting LDL ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe-treated patients experienced a 20% (*P*=0.002) LDL-C reduction and a 10% TC reduction (*P*=0.003). Fluvastatin-treated patients experienced a 24% LDL-C reduction (*P*=0.02) and a 17% TC reduction (*P*=0.06). There were no significant differences in lipid-lowering ability between groups. Ezetimibe-treated patients did not experience significant changes in endothelial function. Fluvastatin-treated patients experienced an increase in the rate of endothelial function by 11% (*P*=0.5). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Blagden et al[32] Ezetimibe 10 mg QD and atorvastatin 10 mg QD vs placebo and atorvastatin 10 mg QD	DB, MC, PC, RCT Men and women with primary hyper-cholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change in LDL-C from baseline to study end point Secondary: Percentage of patients achieving the new Joint British Society 2 (JBS 2) recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L, percentage of patients reaching LDL-C targets, safety and tolerability	Primary: From baseline to week 6, ezetimibe and atorvastatin provided significantly greater reductions in adjusted mean LDL-C level compared with atorvastatin monotherapy, (–50.5% vs –36.5%; *P*<0.0001), equating to an additional 14.1% reduction (95% CI, –17.90 to –10.19). Secondary: A significantly higher proportion of patients on ezetimibe and atorvastatin achieved the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L compared with atorvastatin monotherapy (62% vs 12%; *P*<0.0001 and 93% vs 79%, respectively). Patients receiving ezetimibe and atorvastatin were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; *P*<0.0001) compared with patients receiving atorvastatin monotherapy. Clinical chemistry profiles and the incidence of adverse events were similar in both groups (*P* value not reported).
Stein et al[33] Ezetimibe 10 mg QD in combination with atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80	DB, DD, MC Men and women ≥18 years of age with primary hypercholesterolemia and documented CHD, at least 2 cardiovascular risk factors, or heterozygous familial hypercholesterolemia with an LDL-C level	N=621 14 weeks	Primary: Percentage of subjects in the 2 treatment groups achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of subjects in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively 7% vs 22%; *P*<0.01. Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in subjects in the ezetimibe and atorvastatin; *P*<0.01. Respectively, percent changes between combination vs atorvastatin monotherapy were –22.8 vs –8.6% (mean change) in LDL-C levels, –17.3% vs –6.1% in TC levels (mean change), and –9.3% vs –3.9% (median change) in TG levels; *P*<0.01 for all. Nonsignificant changes were observed in HDL-C levels; *P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day)	≥130 mg/dL despite treatment with 10 mg QD of atorvastatin and diet		lipid parameters 4 weeks after randomization	value not reported.
Ballantyne, Weiss et al[34] Ezetimibe 10 mg QD and rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	MC, OL, PG, RCT Men and women aged ≥18 years with hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category,	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week 6 compared to rosuvastatin alone (94% vs 79.1%; *P*<0.001). Secondary: The non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; *P*<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week 6 (LDL 93.6% vs 74.3%, LDL and TC 90.6% vs 68.3%, respectively; *P*<0.001). At week 6, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (*P*<0.001). Significantly greater reductions in TC, non–HDL-C and TG levels were seen in the combination group compared to the monotherapy group (*P*<0.001). Both treatment groups increased HDL level to a similar extent (*P*=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all *P*<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (*P*<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (*P*=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (–46.4% vs –28.6%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week 6, safety and tolerability	The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event (*P* value not provided). No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were 2 patients (0.8%) in the combination therapy group and 3 patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in 3 patients, all in the combination therapy group.
Patel et al[35] Ezetimibe 10 mg QD and simvastatin 20 mg QD vs simvastatin 20 mg QD	DB, MC, PC, PG, RCT Men and women aged 18-75 years with primary hyper-cholesterolemia (LDL ≥3.3 mmol/L and ≤4.9 mmol/L, TG <3.99 mmol/L) and documented CHD at least 3 months prior to baseline who were not receiving pharmacologic lipid management therapy	N=153 6 weeks	Primary: Mean change in LDL cholesterol level from baseline to 6 weeks and the proportion of patients who reached an LDL goal of <3 mmol/L at end point Secondary: Changes in serum TC, TG and HDL levels, and safety and tolerability	Primary: At 6 weeks, patients receiving ezetimibe and simvastatin combination therapy had a mean LDL reduction of 14.6% (95% CI, 10.1 to 19.1). At 6 weeks, a greater number of patients receiving ezetimibe and simvastatin combination therapy reached an LDL goal <3 mmol/L compared to patients receiving monotherapy (93% vs 75%; *P*<0.001). Secondary: At 6 weeks, there was a significant additional reduction in TC of 0.69 mmol/L in patients receiving ezetimibe and simvastatin combination therapy compared to patients receiving ezetimibe monotherapy (95% CI, 0.48 to 0.90; *P*<0.0001). There was a 20.4% reduction in TG levels in the combination group compared to a 12.4% reduction in the monotherapy group (*P*=0.06). Baseline HDL levels increased by 6% in both treatment groups (*P* value not provided). In the combination group, 40% of patients had at least one treatment-emergent adverse event compared to 25% in the monotherapy group. The overall incidence of adverse events were not significant among the two groups (*P*=0.07). Two patients in the combination therapy group and 1 patient in the monotherapy group experienced a serious adverse event unrelated to the study medications.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Landry et al[36] Ezetimibe 10 mg QD and simvastatin 20 mg QD (single entities) vs placebo and simvastatin 20 mg QD (single entities)	MC, RCT Men and women ≥18 years of age, patients on predialysis with creatinine level ≥1.7 mg/dL, hemodialysis, or peritoneal dialysis	N=203 6 months	Primary: LDL-C, TC, non–HDL-C, HDL-C, TG, apo B, apo AI Secondary: Tolerability and safety	Primary: Both groups had statistically reduced LDL-C at 1, 3, and 6 months compared to baseline (*P*<0.0001). The addition of ezetimibe to simvastatin was associated with 27%, 26%, and 21% reductions in LDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 16%, 16%, and 14% reductions in TC at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 24%, 25%, and 19% reductions in non–HDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 15%, 14%, and 12% reductions in apo B at 1, 3, and 6 months, respectively. There were no significant effects in HDL-C, TG, or apo AI (*P*=not significant) except for 7% increase of HDL-C at 3 months (*P*=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation, or appetite loss between groups (*P*=NS). More patients on ezetimibe reported diarrhea (27% vs 12%; *P*=0.009). There were no significant differences in CK levels or abnormal hepatic transaminase levels (*P* value not reported).
Kastelein et al[37] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries)	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily and ezetimibe 10 mg daily	treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events		Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs 8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Bays et al[38] Ezetimibe 10 mg QD and colesevelam 3.8 g QD vs placebo and colesevelam 3.8 g QD	DB, MC, PC, PG, RCT Men and women with primary hyper-cholesterolemia	N=86 4-8 weeks washout period and 6 weeks of treatment	Primary: Mean percent change in LDL-C, mean absolute and mean percent change in HDL-C, non–HDL-C, TC, apo AI and apo B, and median absolute and percent changes in TG and hsCRP from baseline to end of treatment	Primary: After 6 weeks of treatment, ezetimibe plus colesevelam produced a mean percent decrease in LDL-C of 32.3% vs 21.4% with ezetimibe monotherapy; *P*<0.0001. Ezetimibe plus colesevelam was significantly more effective than ezetimibe alone at producing mean percent reductions in TC, non–HDL-C, apo B and increases in apo AI (*P*<0.005 for all). Neither treatment regimen resulted in significant changes in median TG levels compared with baseline (*P*=NS). Secondary: Both treatment groups were safe and generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Safety and tolerability	
Jelesoff et al[39] Ezetimibe 10 mg daily and niacin (single entities) vs niacin	RETRO Patients who received ezetimibe as add-on therapy to stable doses of niacin and other lipid medications	N=53 Not reported	Primary: TC, LDL-C, TG, HDL-C Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	Primary: The addition of ezetimibe resulted in reductions of 18%, 25%, and 17% (P<0.001) for TC, LDL-C, and TG, respectively. There were no significant differences in HDL-C (P=NS). Secondary: 13% of patients met goals prior to addition of ezetimibe while 45% of patients met goals following addition of ezetimibe (P<0.001).

Drug regimen abbreviations: QD=daily
Study abbreviations: CI=confidence interval, DB=double=blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, SB=single blind, SD=standard deviation, WMD=weighted mean difference, XO=cross over
Miscellaneous abbreviations: apo AI=apolipoprotein AI, apo B=apolipoprotein B, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, FH=familial hypercholesterolemia, HAART=highly active antiretroviral therapy, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, HDL_2=HDL subfraction 2, HDL_3=HDL subfraction 3, HIV=human immunodeficiency virus, hsCRP=high-sensitivity C-reactive protein, IMT=intima-media thickness, JBS=Joint British Society, LDL-C=low-density lipoprotein cholesterol, LDL-C:HDL-C=low-density lipoprotein cholesterol:high-density lipoprotein cholesterol ratio, Lp(a)=lipoprotein(a), NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, non–HDL-C=non-high-density lipoprotein cholesterol, NYHA=New York Heart Association, TC=total cholesterol, TC:HDL-C=total cholesterol:high-density lipoprotein cholesterol ratio, TG=triglyceride, VLDL=very low-density lipoprotein

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on physician visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Cholesterol Absorption Inhibitors

Generic Name	Formulation	Example Brand Name	Brand Cost	Generic Cost
ezetimibe	tablet	Zetia®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

There are no generic or over-the-counter products in this class. At this time, ezetimibe is the only cholesterol absorption inhibitor and appears to be a safe and modestly effective agent for the reduction of low-density lipoprotein cholesterol (LDL-C). Additional data is necessary to determine its effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides.

HMG-CoA reductase inhibitors (statins) are considered first-line agents for treating hyperlipidemia due to their ability to lower total cholesterol and LDL-C. As monotherapy, ezetimibe provides only modest reductions in LDL-C. Ezetimibe's primary role is in combination with a statin in patients unable to achieve or sustain target low-density lipoprotein levels on a statin alone or to reduce the dose of a statin required to achieve target levels. The unique mechanism of action of ezetimibe allows for an additional reduction in LDL-C when administered with a statin. Although studies have shown that the combination of ezetimibe and a statin is more efficacious in lowering LDL-C than monotherapy with either agent, the recently published results of the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in

Patients with Heterozygous Familial Hypercholesterolemia) did not show that these reductions led to better clinical outcomes.[37]

The ENHANCE trial consisted of 720 patients with heterozygous familial hypercholesterolemia and the primary end point was the mean change in the intima-media thickness measured at three sites in the carotid artery.[37] No significant difference was found in this primary end point between simvastatin-ezetimibe 80/10 mg compared to simvastatin 80 mg alone during the two-year study period. Combination therapy with ezetimibe and simvastatin significantly lowered LDL-C by 16.5% compared to simvastatin alone. Additional studies are necessary to determine if the combination of ezetimibe plus a statin results in better clinical outcomes since no trial has yet demonstrated a reduction of cardiovascular outcomes with either ezetimibe alone or in combination therapy with a statin.[40,41]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Fibric Acid Derivatives
AHFS Class 240606
May 14, 2008

I. Overview

The therapeutic class called the fibric acid derivatives encompasses two chemical entities, fenofibrate and gemfibrozil. Fibric acid derivatives are agonists of the peroxisome proliferator-activated receptor (PPAR) and work by increasing lipoprotein lipase activity and triglyceride (TG) clearance. These agents also increase hepatic oxidation of fatty acids, which decreases the secretion of TG-rich lipoproteins and enhances the breakdown of very low-density lipoprotein (VLDL). Finally, fibric acid derivatives may increase secretion of cholesterol into bile.[1,2] Fibric acid derivatives generally decrease TG levels by 25%-50% and increase high-density lipoprotein cholesterol (HDL-C) concentrations by 5%-15%. They promote a shift from small, dense low-density lipoprotein (LDL) to larger, more buoyant particles, which are less susceptible to oxidation and possess higher binding affinity for removal by the nonatherogenic LDL receptor pathway.[1-3]

The fibric acid derivatives are established as effective agents for managing dyslipidemia, particularly in patients with elevated concentrations of TG-rich lipoproteins (VLDL and VLDL remnants) and low levels of HDL-C, typically associated with the dyslipidemia characteristic of type 2 diabetes and the metabolic syndrome. While hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are regarded as the cornerstone of lipid-modifying therapy, based on their proven efficacy in reducing plasma levels of LDL cholesterol (LDL-C), they exert only modest effects on TG (decrease 15%-35%) and HDL-C (typically increase <10%).[1-3]

Gemfibrozil was approved by the Food and Drug Administration (FDA) in 1981 and has been available generically since 1993.[4] Fenofibrate is available in several formulations with generics currently available for the 54 mg and 160 mg micronized tablets, and for the 67 mg, 134 mg, and 200 mg micronized capsules. A nonmicronized formulation of fenofibrate is no longer available in the United States (US).[2] The most recently developed version of fenofibrate is the nanocrystallized formulation, which was approved in 2004.[4]

The fibric acid derivatives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. In accordance with Alabama Medicaid Preferred Drug Legislation, this review does not include information on Fenoglide® (fenofibrate) because it has not been on the market for 6 months or more. This medication will be reviewed at a future time.

Table 1. Fibric Acid Derivatives Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
fenofibrate, micronized	capsule, tablet	Antara®, Lipofen®, Lofibra®*, Triglide®	fenofibrate
fenofibrate, nanocrystallized	tablet	Tricor®	none
gemfibrozil	tablet	Lopid®*	gemfibrozil

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the fibric acid derivatives (fibrates) are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Fibric Acid Derivatives

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management.

Clinical Guideline	Recommendation
(NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[3]	• Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high-risk patients with high TG or low high-density lipoprotein (HDL) levels as the predominant lipoprotein abnormality, consideration can be given to combination therapy with fibrates or nicotinic acid and a low-density lipoprotein cholesterol (LDL-C)-lowering agent. • When an LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • If a high-risk person has high TG or low HDL-C levels, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When TG are >200 mg/dL, non–HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[5]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Fibric Acid Derivatives (Fibrates) • Fibrates can be recommended for persons with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-very low density lipoproteins).

Clinical Guideline	Recommendation
	• Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in persons who have elevated LDL-C and atherogenic dyslipidemia.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[6]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[7]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[8]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[9]	• Statins are considered first-line drugs for lowering LDL cholesterol. • Fibric acid derivatives are considered useful only for the treatment of patients with low HDL, high TG, and other characteristics of insulin resistance syndrome and type 2 diabetes. • Fibrate monotherapy cannot be recommended as first-line therapy in diabetic patients but may be considered in those with persistently low HDL levels or severely elevated TG. • When TG are between ~450-900 mg/dL, fibrates (or statins) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the fibric acid derivatives are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo

clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Fibric Acid Derivatives[10-15]

Indication	Fenofibrate	Gemfibrozil
As adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and apolipoprotein B (apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb)	✔	
As adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)	✔	
Treatment of adult patients with very high elevations of serum TG levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet		✔ *
Reducing the risk of developing coronary heart disease (CHD) only in Type IIb patients without a history of or symptoms of existing CHD, and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG		✔ †

*****Patients who present such risk typically have serum TG over 2,000 mg/dL and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis.
†Indicated only for patients who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid) known to reduce LDL-C and raise HDL-C.

IV. Pharmacokinetics

The pharmacokinetic parameters for the fibric acid derivatives are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Fibric Acid Derivatives[1,10-15]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Metabolites	Elimination (%)	Half-Life (hours)
Fenofibrate	60-90	99	Glucuronidation (liver and kidneys)	Yes; fenofibric acid, fenofibric acid glucuronide, benzhydrol metabolite	Renal (60-93)	16-23
Gemfibrozil	Not reported	99	Hepatic	Yes; carboxyl metabolite, hydroxymethyl metabolite	Renal (70)	1.5

Pharmacokinetic studies have shown that Antara® 130 mg capsule, Lipofen® 150 mg tablet, Lofibra® 160 mg tablet and 200 mg capsule and generic equivalents, Triglide® 160 mg tablet and Tricor® 145 mg nanocrystal tablet produce comparable serum fenofibrate levels. The same has been demonstrated for Lofibra® 54 mg tablet and Lofibra® 67 mg capsule and their generic equivalents. To maximize bioavailability, Lofibra® should be administered with meals, while Antara®, Tricor® and Triglide® may be administered without regard to meals.[2]

Table 5. Fenofibrate Formulations Providing Equivalent Plasma Concentrations of Fenofibric Acid[10-15]

	Antara® Micronized Capsules	Lipofen® Micronized Tablets	Lofibra® Micronized Tablets and Equivalents	Lofibra® Micronized Capsules and Equivalents	Triglide® Micronized Tablets	Tricor® Nanocrystallized Tablets
Comparable strengths			54 mg tablet*	67 mg capsule*		
Comparable strengths	130 mg capsule	150 mg tablet	160 mg tablet*	200 mg capsule*	160 mg tablet‡	145 mg tablet, or three 48 mg tablets

No information was provided in product information for Antara® 43 mg capsules, Lipofen® 50 mg capsules, Lofibra® 134 mg capsules, and Triglide® 50 mg tablets.
*Generic is available.
‡Triglide® 160 mg tablet exhibits a similar extent of absorption but 32% higher rate of absorption compared to the 200 mg micronized fenofibrate capsule under low-fat fed conditions.

V. Drug Interactions

Significant drug interactions with the fibric acid derivatives are listed in Table 6.

Table 6. Significant Drug-Drug Interactions with the Fibric Acid Derivatives[16]

Drug(s)	Significance Level	Interaction	Mechanism
Fibric acid derivatives (both)	1	Warfarin	Coagulation factor synthesis may be affected. Fibric acid derivatives may increase the hypoprothrombinemic effects of oral anticoagulants. Bleeding and death have occurred. Warfarin plasma levels are not affected.
Fenofibrate	1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	The mechanism is unknown. Severe myopathy or rhabdomyolysis may occur. If coadministration of these agents cannot be avoided, use with caution and closely monitor creatine kinase (CK). Fenofibrate has been observed to increase pravastatin area under the curve (AUC) by 28%. The AUC and maximum concentration (C_{max}) of the N-desmethyl rosuvastatin metabolite decreased by 48% and 39%, respectively. Fenofibrate does not appear to affect the pharmacokinetics of rosuvastatin.
Gemfibrozil	1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	The mechanism is unknown. Severe myopathy or rhabdomyolysis may occur. If coadministration of these agents cannot be avoided, use with caution and closely monitor CK. Gemfibrozil has been observed to increase the AUC of pravastatin, atorvastatin, simvastatin, lovastatin, and rosuvastatin. In addition, increased C_{max} has been reported with coadministration of gemfibrozil and pravastatin or rosuvastatin.
Gemfibrozil	2	Repaglinide	Inhibition of repaglinide metabolism (CYP2C8) by gemfibrozil is suspected. Repaglinide plasma concentrations may be greatly increased and prolonged, increasing the risk of severe and protracted hypoglycemia. Avoid coadministration of repaglinide and gemfibrozil. If coadministration is necessary, reduce the dose of repaglinide and closely monitor blood glucose concentrations. Adjust therapy as needed.
Gemfibrozil	2	Thiazolidine-diones (pioglitazone, rosiglitazone)	Inhibition of thiazolidinedione metabolism (CYP2C8) by gemfibrozil is suspected. Plasma concentrations of thiazolidinedione antidiabetic agents may be elevated, increasing hypoglycemic and other adverse effects (eg, peripheral and pulmonary edema) of these agents. If coadministration of a thiazolidinedione and gemfibrozil cannot be avoided, consider initiating therapy at a reduced thiazolidinedione dose, possibly as much as 50% to 70%. Closely monitor blood glucose, glycosolated hemoglobin, and thiazolidinedione adverse effects when starting or stopping gemfibrozil therapy.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Fibric acid derivatives are fairly well tolerated. No clear differences seem to exist with regard to side effects between the drugs in this class. Myopathy and rhabdomyolysis have been rarely reported with fibric acid derivative therapy. The most common adverse drug events reported with the fibric acid derivatives are noted in Table 7.

Table 7. Adverse Drug Events (%) Reported with Fibric Acid Derivatives[10-15]

Adverse Event(s)	Fenofibrate	Gemfibrozil
Cardiovascular		
Angina pectoris	✔	-
Arrhythmia	✔	-

Adverse Event(s)	Fenofibrate	Gemfibrozil
Atrial fibrillation	✔	1
Cardiovascular disorder	✔	-
Coronary artery disorder	✔	-
Edema	✔	-
Electrocardiogram abnormal	✔	-
Hypertension	✔	-
Hypesthesia	-	✔
Hypotension	✔	-
Migraine	✔	-
Myocardial infarction	✔	-
Palpitation	✔	-
Peripheral edema	✔	-
Peripheral vascular disorder	✔	✔
Phlebitis	✔	-
Syncope	-	✔
Tachycardia	✔	-
Varicose vein	✔	-
Vascular disorder	✔	-
Vasodilatation	✔	-
Ventricular extrasystoles	✔	-
Central Nervous System		
Anxiety	✔	-
Confusion	-	✔
Convulsion	-	✔
Depression	✔	✔
Dizziness	✔	✔
Fatigue	-	4
Fever	✔	-
Headache	3	1
Hypertonia	✔	-
Insomnia	✔	-
Libido decreased	✔	✔
Nervousness	✔	-
Neuralgia	✔	-
Paresthesia	✔	✔
Pain	✔	-
Peripheral neuritis	-	✔
Somnolence	✔	✔
Vertigo	✔	2
Dermatological		
Acne	✔	-
Alopecia	✔	-
Angioedema	-	✔
Contact dermatitis	✔	-
Eczema	✔	2
Exfoliative dermatitis	-	✔
Fungal dermatitis	✔	-
Herpes simplex	✔	-
Herpes zoster	✔	-
Nail disorder	✔	-
Maculopapular rash	✔	-
Photosensitivity reaction	✔	✔

Adverse Event(s)	Fenofibrate	Gemfibrozil
Pruritus	✔	-
Rash	-	2
Skin disorder	✔	-
Skin ulcer	✔	-
Stevens-Johnson syndrome	✔	-
Sweating	✔	-
Toxic epidermal necrolysis	✔	-
Urticaria	✔	✔
Vasculitis	-	✔
Endocrine and Metabolic		
Diabetes mellitus	✔	-
Gout	✔	-
Gynecomastia	✔	-
Hypoglycemia	✔	-
Hyperuricemia	✔	-
Gastrointestinal		
Abdominal pain	5	10
Anorexia	✔	-
Cholestatic jaundice	-	✔
Colitis	✔	-
Constipation	2	1
Diarrhea	2	7
Duodenal ulcer	✔	-
Dyspepsia	✔	20
Eructation	✔	-
Esophagitis	✔	-
Flatulence	✔	-
Gastritis	-	-
Gastroenteritis	-	-
Gastrointestinal disorder	-	-
Increased appetite	-	-
Nausea	2	-
Nausea and vomiting	-	2
Peptic ulcer	✔	-
Rectal disorder	-	-
Rectal hemorrhage	-	-
Vomiting	✔	-
Weight gain/loss	✔	-
Genitourinary		
Creatinine increased	✔	-
Cystitis	✔	-
Decreased male fertility	-	✔
Dysuria	✔	-
Impotence	-	✔
Kidney function abnormal	✔	✔
Nephrotoxicity	-	✔
Prostatic disorder	✔	-
Unintended pregnancy	✔	-
Urinary frequency	✔	-
Vaginal moniliasis	✔	-
Hematologic		
Agranulocytosis	✔	-

Adverse Event(s)	Fenofibrate	Gemfibrozil
Anemia	✔	✔
Ecchymosis	✔	-
Eosinophilia	✔	-
Leukopenia	✔	✔
Lymphadenopathy	✔	-
Thrombocytopenia	✔	✔
Hepatic		
Alkaline phosphokinase increased	-	✔
Alanine aminotransferase increased	3	✔
Aspartate aminotransferase increased	3	✔
Bilirubin increased	-	✔
Cholecystitis	✔	✔
Cholelithiasis	✔	✔
Creatinine phosphokinase increased	3	✔
Jaundice	-	✔
Liver fatty deposit	✔	-
Musculoskeletal		
Arthralgia	✔	✔
Arthritis	✔	-
Arthrosis	✔	-
Bursitis	✔	-
Back pain	3	-
Joint disorder	✔	-
Leg cramps	✔	-
Muscle pain	✔	-
Myalgia	✔	-
Myasthenia	✔	✔
Myopathy	✔	✔
Myositis	✔	-
Painful extremities	-	✔
Paresthesia	✔	✔
Rhabdomyolysis	✔	✔
Synovitis	-	✔
Tenosynovitis	✔	-
Weakness	✔	-
Respiratory		
Asthma	✔	-
Bronchitis	✔	-
Cough increased	✔	-
Dyspnea	✔	-
Laryngeal edema	-	✔
Laryngitis	✔	-
Pharyngitis	✔	-
Pneumonia	✔	-
Respiratory disorder	6	-
Rhinitis	2	-
Sinusitis	✔	-
Other		
Allergic reaction	✔	-
Amblyopia	✔	-
Anaphylaxis	-	✔
Appendicitis, acute	-	1

Adverse Event(s)	Fenofibrate	Gemfibrozil
Asthenia	2	-
Blurred vision	-	✔
Cataracts	✔	✔
Chest pain	✔	-
Conjunctivitis	✔	-
Cyst	✔	-
Drug-induced lupus syndrome	-	✔
Dry mouth	✔	-
Ear pain	✔	-
Eye disorder	✔	-
Flu syndrome	2	-
Hernia	✔	-
Infection	✔	-
Intracerebral hemorrhage	-	✔
Hypersensitivity reaction	✔	-
Malaise	✔	-
Otitis media	✔	-
Pancreatitis	-	✔
Raynaud's phenomenon	-	✔
Refraction disorder	✔	-
Retinal edema	-	✔
Seizure	-	✔
Syncope	-	✔
Taste perversion	-	✔
Vision abnormalities	✔	-

✔ Percent not specified
- Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the fibric acid derivatives are summarized in Table 8.

Table 8. Usual Dosing for the Fibric Acid Derivatives[1,10-15,17,18]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate, micronized (Antara®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 130 mg daily Hypertriglyceridemia: Initial: 43-130 mg daily; maximum: 130 mg/day	Safety and efficacy have not been established in children.	Capsules: 43 mg 130 mg
Fenofibrate, micronized (Lipofen®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 150 mg daily Hypertriglyceridemia: Initial: 50-150 mg daily; maximum: 150 mg/day	Safety and efficacy have not been established in children.	Capsules: 50 mg 150 mg
Fenofibrate, micronized (Lofibra® and equivalents)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Tablet: initial, 160 mg daily Capsule: initial, 200 mg daily Hypertriglyceridemia: Tablet: initial, 54-160 mg daily; maximum: 160 mg/ day	Safety and efficacy have not been established in children.	Capsules: 67 mg 134 mg 200 mg Tablet: 54 mg 160 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: initial, 67-200 mg daily; maximum: 200 mg/day		
Fenofibrate, micronized (Triglide®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 160 mg daily Hypertriglyceridemia: Initial: 50-160 mg daily; maximum: 160 mg/day	Safety and efficacy have not been established in children.	Tablets: 50 mg 160 mg
Fenofibrate, nanocrystallized (Tricor®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 145 mg daily Hypertriglyceridemia: Initial: 48-145 mg daily; maximum: 145 mg/day	Safety and efficacy have not been established in children.	Tablets: 48 mg 145 mg
Gemfibrozil	Type IIb Dyslipidemia or Hypertriglyceridemia: Initial and maintenance: 600 mg twice daily; maximum: 1,200 mg/day	Safety and efficacy have not been established in children.	Tablets: 600 mg

VIII. Effectiveness

Table 9 below summarizes clinical studies evaluating the safety and efficacy of the fibric acid derivatives.

Table 9. Comparative Clinical Trials Using the Fibric Acid Derivatives

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Coronary Arteriosclerosis: Prophylaxis				
Keech et al[19] FIELD Fenofibrate 200 mg QD vs placebo	DB, PC, R Patients aged 50-75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization; total mortality	Primary: 5.9% (N=288) of patients on placebo and 5.2% (N=256) of those on fenofibrate had a coronary event (relative reduction of 11%; HR, 0.89; 95% CI, 0.75 to 1.05; *P*=0.16). This finding corresponds to a significant 24% reduction in nonfatal myocardial infarction (HR, 0.76; 95% CI, 0.62 to 0.94; *P*=0.010) and a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; *P*=0.22). Secondary: Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% (HR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.035). This finding included a 21% reduction in coronary revascularization (HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (*P*=0.18).
DAIS[20] Micronized fenofibrate 200 mg QD vs placebo	PC, R Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter Secondary: Not reported	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) than in the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 vs 3.65; *P*=0.02), a significantly smaller decrease in minimum lumen diameter (–0.06 vs –0.10 mm; *P*=0.029), and a nonsignificantly smaller decrease in mean segment diameter (–0.06 vs –0.08 mm; *P*=0.171). The trial was not powered to examine clinical end points. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Frick, Elo et al[21] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, R Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non–HDL-C ≥ 200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 5 years	Primary: Risk of CHD measured by incidence of cardiac events Secondary: Total mortality	Primary: There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; *P*<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.
Frick, Heinonen et al[22] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, R Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	N=311 5 years	Primary: Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (eg, true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al[23] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non–HDL-C greater than or equal to 200 mg/dL in 2 consecutive pretreatment measurements)	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events Secondary: Not reported	Primary: During the posttrial period the numbers of definite CHD events in both groups (54 vs 47; *P*=NS) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group 5 years earlier. Cardiovascular mortality over the entire study period was similar but all-cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (*P*=0.19). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Robins et al[24] VA-HIT Gemfibrozil 1,200 mg daily vs placebo	DB, MC, PC, R Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes Secondary: Not reported	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3% gemfibrozil vs 21.7% placebo; *P*=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20% gemfibrozil vs 26% placebo; *P*<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7% gemfibrozil vs 17.4% placebo; *P*=0.23). Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C (*P*=0.02). Events were reduced even further with gemfibrozil beyond that explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events. Secondary: Not reported
Hypertriglyceridemia				
Rosenson et al[25] Fenofibrate 160 mg QD vs placebo	DB, PC, R Patients with fasting hypertriglycer-idemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP III criteria for the metabolic syndrome	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response Secondary: Not reported	Primary: Fenofibrate treatment lowered fasting TG (–46.1%; *P*<0.0001) and postprandial (area under the curve) TG (–45.4%; *P*<0.0001) due to significant reductions in postprandial levels of large (–40.8%; *P*<0.0001), medium (–49.5%; *P*<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated subjects (–19.0%; *P*=0.0033) primarily due to reductions in small LDL particles (–40.3%; *P*<0.0001); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated subjects compared with placebo-administered subjects (–15.3%; *P*=0.0013, and 31.0%; *P*<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				fasting and postprandial soluble VCAM-1 decreased by –10.9% for fasting VCAM-1 (*P*=0.0005), and by –12.0% for postprandial VCAM-1 (*P*=0.0001); and fasting and postprandial soluble ICAM-1 decreased by –14.8% for fasting ICAM-1 (*P*<0.0001) and by –15.3% for postprandial ICAM-1 (*P*<0.0001). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles (*P*<0.0001) as well as postprandial oxidized fatty acids (*P*<0.0005). Secondary: Not reported
Davidson et al[26] TRIMS Micronized fenofibrate 130 mg QD vs placebo	DB, MC, PC, RCT Patients between the ages of 21 and 79 years, with fasting TG levels ≥300 and <1,000 mg/dL, and at least two of four additional components of the metabolic syndrome as defined by the NCEP ATP III	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-of-treatment in fasting TG Secondary: Changes or percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non–HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared with essentially no change in the placebo group (*P*<0.001). Secondary: There was no significant difference in TC change between the fenofibrate treatment and the placebo groups (*P*=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared with 3.2% in the placebo group (*P*=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared with 0.8% for placebo (*P*<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared with placebo (–14.2% vs 0.8%; *P*<0.001). VLDL-C declined by 33% with fenofibrate compared with a 1.6% decline with placebo treatment (*P*<0.001). Non–HDL-C decreased significantly more in the fenofibrate group (–7.5% vs –1.1%; *P*=0.009). There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3% vs 2.0%; *P*=0.212). Apo B declined significantly with fenofibrate compared with placebo (*P*<0.001,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively). Apo CIII was markedly reduced in the fenofibrate group (*P*<0.001 compared with placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (–35.1% vs an increase of 12.3%; *P*<0.001).
Koh et al[27] Fenofibrate 200 mg QD plus placebo vs fenofibrate 200 mg QD plus candesartan 16 mg QD vs candesartan 16 mg QD plus placebo	DB, PC, R, XO Patients with hypertriglyceri-demia (≥150 mg/dL) and hypertension (≥140/90 mm Hg)	N=46 6 months	Primary: Blood pressure, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adioponectin, and insulin resistance Secondary: Not reported	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced blood pressure. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone (*P*<0.001). When compared with candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non–HDL-C levels (all *P*<0.001) and increased HDL-C levels (*P*<0.001) when compared with baseline. These reductions were significantly greater than those observed with candesartan alone (*P*<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (*P*=NS). All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared with monotherapy (*P*<0.001, *P*=0.002, *P*=0.050, and *P*=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (*P*=0.246 for adiponectin levels and *P*=0.153 for insulin sensitivity). Secondary: Not reported
Treatment of Primary Hypercholesterolemia or Mixed Dyslipidemia				
Farnier, Freeman et al[28] Fenofibrate 160 mg QD	DB, MC, PA, PC, R Patients with mixed	N=625 12 weeks	Primary: Percent change in LDL-C from baseline to study end point after	Primary: There was a significantly greater percent reduction in LDL-C among patients in the fenofibrate plus ezetimibe group vs the fenofibrate only group (*P*>0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fenofibrate 160 mg QD plus ezetimibe 10 mg QD vs ezetimibe 10 mg QD vs placebo	hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria		treatment with fenofibrate plus ezetimibe vs fenofibrate alone Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo B, apo AI	Non–HDL-C and apo B were significantly reduced with fenofibrate plus ezetimibe when compared with fenofibrate or ezetimibe alone (*P*>0.001). TG levels were significantly decreased and HDL-C was significantly increased with fenofibrate plus ezetimibe when compared with placebo (*P*<0.001).
Farnier, Roth et al[29] Fenofibrate 160 mg QD vs simvastatin-ezetimibe 20 mg-10 mg combination tablet QD plus fenofibrate 160 mg QD vs simvastatin-ezetimibe 20 mg-10 mg combination tablet QD	DB, MC, PA, PC, R Patients 18 to 79 years old with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo AI, and apo B	Primary: LDL-C level was significantly reduced with simvastatin-ezetimibe plus fenofibrate (–45.8%) compared with fenofibrate (–15.7%) or placebo (–3.5%; *P*<0.01), but not when compared with simvastatin-ezetimibe (–47.1%; *P*>0.2). Secondary: HDL-C and apo AI levels were significantly increased with simvastatin-ezetimibe plus fenofibrate (18.7% and 11.1%; *P*<0.01, respectively) treatment compared with simvastatin-ezetimibe (9.3% and 6.6%; *P*<0.01) or placebo (1.1% and 1.6%; *P*<0.01), but not when compared with fenofibrate (18.2% and 10.8%; *P*>0.2). TG, non–HDL-C, and apo B levels were significantly reduced with simvastatin-ezetimibe plus fenofibrate (–50.0%, –50.5%, and –44.7%; *P*<0.01, respectively) vs all other treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				
McKenney et al[30] Fenofibrate 160 mg QD vs fenofibrate 160 mg QD plus ezetimibe 10 mg QD vs ezetimibe 10 mg QD for first 12 weeks, then switched to fenofibrate plus ezetimibe QD for 48 week extension phase vs placebo for first 12 weeks, then switched to fenofibrate for 48 week extension phase	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non–HDL-C , apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared with fenofibrate alone (–22.0 vs –8.6; *P*<0.001). Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (–23.2 vs –13.6; *P*<0.001), TG (–46.0 vs –41.0; *P*=0.002), non–HDL-C (–31.6 vs –19.4; *P*<0.001), and apo B (–25.2 vs –16.2; *P*<0.001) compared with fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; *P*=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; *P*=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (–25.3 vs –21.1; *P*=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.
Insua et al[31] Gemfibrozil 900 mg daily	DB, DD, R, XO Patients between the ages of 45	N=21 6 weeks	Primary: Cholesterol-lowering effectiveness	Primary: Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (*P*<0.01 for all calculations, except *P*<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs micronized fenofibrate 200 mg QD	and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa and IIb		Secondary: Not reported	Neither drug affected Lp (a) lipoprotein, whereas uric acid was reduced only by fenofibrate (*P*<0.01). The percentage decrease in TC and LDL cholesterol was greater with fenofibrate than with gemfibrozil (–22% versus –15%; *P*<0.02; and –27% versus –16%; *P*<0.02, respectively). In contrast, reductions in levels of TG (–54% vs –46.5%), apo B, and fibrinogen, as well as the increase in HDL (+9% for both drugs), showed no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL concentrations. Secondary: Not reported
Conversion Between Fibric Acid Derivatives				
Corbelli et al[32] Gemfibrozil, mean daily dose 1,200 mg/day to fenofibrate, mean daily dose of 201 mg/day	RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects	N=92 23 months	Primary: Mean TC, TG, HDL, and non-HDL Secondary: Not reported	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL, and non-HDL (*P*<0.005). Specifically, more patients achieved a TG goal < 200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; *P*<0.0005). The study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MC=multicenter, PA=parallel arm, PC=placebo controlled, R=randomized, RCT=randomized controlled trial, RETRO=retrospective study, XO=crossover
Miscellaneous abbreviations: apo=apoliprotein, CHD=coronary heart disease, DAIS=Diabetes Atherosclerosis Intervention Study, FIELD=Fenofibrate Intervention and Event Lowering in Diabetes, HDL=high-density lipoprotein, HDL-C= high-density lipoprotein cholesterol, ICAM-1=intercellular adhesion molecule-1, LDL=low-density lipoprotein, LDL-C=LDL cholesterol, MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, non–HDL-C=non–high-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, TRIMS=Triglyceride Reduction in Metabolic Syndrome, VA-HIT=Veterans Affairs High-Density Lipoprotein Intervention Trial, VCAM-1=vascular cell adhesion molecule-1, VLDL=very low-density lipoprotein, VLDL-C=very low-density lipoprotein cholesterol

Additional Evidence

Dose Simplification:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy:
A study was conducted to determine lipid effects from a conversion of gemfibrozil to fenofibrate in patients on stable statin therapy.[32] Subjects (N=92) were converted from gemfibrozil (mean dose 1,200 mg) to fenofibrate (mean dose 201 mg). The mean duration of therapy was 23 months for gemfibrozil and 18 months for fenofibrate. The primary reason for conversion from gemfibrozil was inadequate lipid response or adverse effects. Compared to gemfibrozil, fenofibrate showed statistically significant improvements in mean total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and non-HDL ($P<0.005$). Specifically, more patients achieved a TG goal <200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; $P<0.0005$). In summary, the study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months.

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Fibric Acid Derivatives

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
fenofibrate	tablet, capsule	Lipofen®, Triglide®	$$$	N/A
fenofibrate, micronized	capsule	Antara®, Lofibra®*	$$$-$$$$	$$$
fenofibrate, nanocrystallized	tablet	Tricor®	$$$	N/A
gemfibrozil	tablet	Lopid®*	$$$	$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

It has been shown that lowering cholesterol (including low-density lipoprotein cholesterol [LDL-C]) significantly reduces cardiovascular risk. Because LDL-C is the major atherogenic lipid component, the NCEP ATP III guidelines focus primarily on attaining designated LDL-C goals. While LDL-C is the primary treatment target, very high triglycerides (TG) should also be treated to avoid pancreatitis and reduce coronary heart disease (CHD) risk. Finally, consideration should be given to treating low levels of high-density lipoprotein cholesterol (HDL-C) despite LDL-C goal attainment.

Fibric acid derivatives are used less frequently than HMG-CoA reductase inhibitors (or statins), primarily because of a reduced LDL-C lowering capacity compared to statins; however, they have a greater capacity to reduce TG compared to statins. The main place in therapy for fibric acid derivatives is for the treatment of hypertriglyceridemia in patients at risk for pancreatitis and hypertriglyceridemia in patients with low HDL-C, especially with underlying diabetes, insulin resistance or the metabolic syndrome.[33]

Gemfibrozil and fenofibrate are available generically. There are numerous formulations of fenofibrate, among which no particular product offers a distinct clinical advantage over another. There are no major clinically relevant differences between gemfibrozil and fenofibrate with regard to TG-lowering efficacy, tolerability, or safety. Notably, both gemfibrozil and fenofibrate are supported by clinical trials that show reductions in patient-oriented outcomes (CHD morbidity and/or mortality)[19,21-24] However, neither product has demonstrated a decrease in all-cause mortality as has been shown with the statins. The national and international consensus treatment guidelines do not give preference to one fibric acid derivative over another. Both gemfibrozil and fenofibrate should be administered cautiously with a concomitant statin; however, there is evidence to suggest that fenofibrate may have less of an effect on statin metabolism and/or levels.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HMG-CoA Reductase Inhibitors
Single Entity Agents
AHFS Class 240608
May 14, 2008

I. Overview

The single entity hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. All agents are formulated for oral administration, with lovastatin and fluvastatin available as sustained-release tablet formulations. Lovastatin, pravastatin, and simvastatin are available generically. Statins work by inhibiting HMG-CoA reductase.[1] HMG-CoA reductase is the rate-limiting enzyme in hepatic cholesterol synthesis, which catalyzes the conversion of HMG-CoA to mevalonate, a cholesterol precursor. Reduced hepatic cholesterol synthesis leads to the up-regulation of hepatic low-density lipoprotein cholesterol (LDL-C) receptors and subsequently a decreased production and an enhanced clearance of circulating LDL-C. In addition, HMG-CoA reductase inhibition leads to a reduction in total cholesterol (TC), apolipoprotein B (apo B), triglycerides (TG), as well as an increase in apolipoprotein A (apo A) and high-density lipoprotein cholesterol (HDL-C). The mechanism by which statins increase HDL-C is not fully determined.[1,2]

The single entity statins are all Food and Drug Administration (FDA) approved for the treatment of primary hyperlipidemia, and, with the exception of rosuvastatin, for primary and secondary prevention of cardiovascular events in high-risk patients.[1,2] The agents in this class have demonstrated a significant benefit in reducing TC, LDL-C, and modestly increasing HDL-C. In addition, statins have been shown to reduce the risk of cardiovascular mortality, morbidity (ie, strokes, myocardial infarctions [MIs], congestive heart failure [CHF], major vascular events), and all-cause mortality among patients with and without a prior history of coronary heart disease (CHD). Individual statins differ in their potency, pharmacokinetic parameters, drug-drug interactions, and side-effect profile. All statins may cause an elevation in liver enzymes and creatine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure. Consequently, liver function tests should be performed routinely with statin therapy.

CHD is the leading cause of death in the United States (US).[3] In 2008, 1,200,000 Americans are expected to experience either a new or a recurrent MI, associated with an up to 38% mortality rate.[3] Despite an increased awareness of benefits associated with statin therapy, less than 50% of eligible patients actually receive one. Since CHD is a significant contributor to morbidity and mortality, it is important to identify and treat patients at risk.. The HMG-CoA reductase inhibitors have demonstrated significant improvements in overall mortality in primary and secondary prevention of cardiovascular diseases.

The single entity HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Single Entity HMG-CoA Reductase Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
atorvastatin	tablet	Lipitor®	Lipitor®
fluvastatin	capsule, sustained-release tablet	Lescol®, Lescol XL®	Lescol®, Lescol XL®
lovastatin	sustained-release tablet, tablets	Altoprev®, Mevacor®*	lovastatin
pravastatin	tablet	Pravachol®*	pravastatin
rosuvastatin	tablet	Crestor®	Crestor®
simvastatin	tablet	Zocor®*	simvastatin

*Generic is available in at least one dosage form or strength.

All statins lower cholesterol levels. However, the degree to which individual agents lower cholesterol levels vary. The lipid-lowering effects with single entity statins are noted in Table 2.

Table 2. Effects of the Single Entity HMG-CoA Reductase Inhibitors on Cholesterol and Triglyceride Levels[4-10] *

Statin	Daily Dosage (mg)	TC ↓ (%)	LDL-C ↓ (%)	TG ↓ (%)	HDL-C ↑ (%)
Atorvastatin	10-80	25-58	26.5-60	17-53	5-14
Fluvastatin IR/fluvastatin SR	20-80 IR; 80 SR	17-27 IR; 25 SR	22-36 IR; 35 SR	12-18 IR; 19 SR	3-6 IR; 7 SR
Lovastatin IR/lovastatin SR	10-80 IR; 10-60 SR	16-34; 17.9-29.2 SR	21-42; 23.8-40.8 SR	6-27; 9.9-25.1 SR	2-9.5; 7.4-13.1 SR
Pravastatin	10-80	16-33	22-41	6-24	2-12
Rosuvastatin	5-40	24-46	28-63	10-43	3-22
Simvastatin	5-80	19-52	26-47	8-41	7-16

IR=immediate release, SR=sustained release, TC=Total Cholesterol, LDL-C=Low-density Lipoprotein Cholesterol, TG=Triglycerides, HDL-C=High-density Lipoprotein Cholesterol
*The data presented in the table above are pooled from different studies incorporating various indications and may not be directly comparable.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 3. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Combination HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[11]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). For the treatment of homozygous FH • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH.

Clinical Guideline	Recommendation
	For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP). **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)**[12]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.
American Heart Association (AHA)/ American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[13]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[14]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile cid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age.

Clinical Guideline	Recommendation
Association (2007)[15]	• Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[16]	• Statins are considered first-line drugs for lowering LDL-C. • When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity HMG-CoA reductase inhibitors (statins) are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials. All product information for the statins stresses that, as recommended by the NCEP ATP III guidelines, therapy with lipid-altering agents should be used in conjunction with a diet restricted in saturated fat and cholesterol for the reduction of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[1,2, 4-10] The effects of rosuvastatin on cardiovascular morbidity/mortality end points have not been established.[9]

Table 4. FDA-Approved Indications for the Single Entity HMG-CoA Reductase Inhibitors[4-10]

Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Prevention of Cardiovascular Disease						
Primary prevention of cardiovascular events (patients without clinically evident coronary heart disease (CHD); to reduce the risk of:	✔ *†		✔	✔ §		✔ ‖
Angina	✔ *		✔ ‡ (Unstable)			
Mortality				✔ § (Cardiovascular)	Effect not determined¶	✔ ‖ (CHD death)
Myocardial infarction	✔ *†		✔ ‡	✔ §		✔ ‖ (Nonfatal MI)
Revascularization procedures	✔ *		✔ ‡ (Coronary)	✔ § (Myocardial)		✔ ‖ (Coronary and noncoronary)
Stroke	✔ *†					✔ ‖
Secondary prevention of cardiovascular events (patients with clinically evident CHD); to reduce the risk of:	✔	✔		✔		✔ ‖
Angina	✔					
Hospitalization for congestive heart failure	✔					
Mortality				✔ (Coronary death)	Effect not determined¶	✔ ‖ (CHD death)
Myocardial infarction	✔ (Nonfatal MI)			✔		✔ ‖ (Nonfatal MI)
Revascularization procedures	✔	✔ (Coronary)		✔ (Myocardial)		✔ ‖ (Coronary and noncoronary)
Stroke	✔ (Fatal and nonfatal)			✔ (Stroke and TIA)		✔ ‖
Coronary atherosclerosis, slowing its progression in patients with CHD, as part of a treatment strategy to lower total and LDL-C to target levels		✔	✔	✔	✔ #	

Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Treatment of Dyslipidemias						
Primary hypercholesterolemia (heterozygous familial and nonfamilial; Fredrickson Type IIa) and mixed dyslipidemia (Fredrickson Type IIb)	✔ #	✔ #	✔ #	✔ #	✔ #	✔
To reduce:						
TC	✔	✔	✔	✔	✔	✔
LDL-C	✔	✔	✔	✔	✔	✔
Apolipoprotein B (Apo B)	✔	✔		✔	✔	✔
Triglyceride (TG)	✔	✔		✔	✔	✔
Non–high-density lipoprotein cholesterol (HDL-C)					✔	
To increase:						
HDL-C	✔	✔		✔	✔	✔
Homozygous familial hyperlipidemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein (LDL) apheresis) or if such treatments are unavailable	✔				✔ (Adult patients)	✔
To reduce:						
TC	✔				✔	✔
LDL-C	✔				✔	✔
Apo B					✔	
Primary dysbetalipoproteinemia (Fredrickson Type III)	✔	**	**	✔ #	**	✔
Hypertriglyceridemia, elevated serum TG levels (Fredrickson Type IV)	✔	**	**	✔	✔ (Adult patients)	✔
Elevated chylomicrons (Fredrickson Types I and V)	**	**	**		**	**
Heterozygous familial hypercholesterolemia (HeFH) in pediatric patients††	✔ # (10-17 years old) (boys and postmenarchal girls)	✔ # (10-16 years old) (boys and post-menarchal girls)	✔ # (10-17 years old) (boys and post-menarchal girls)	✔ # (>8 years old)		✔ # (10-17 years old) (boys and postmenarchal girls)

TIA=transient ischemic attack
*In adult patients with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease
†In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension
‡In individuals with average to moderately elevated TC and LDL-C, and below average HDL-C
§Hypercholesterolemic patients
|| Patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease
¶ The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.
#As an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures
**Has not been studied for this condition
††To reduce TC, LDL-C and apolipoprotein B levels if after an adequate trial of diet therapy the following findings are present:
1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and either (a) there is a positive family history of premature cardiovascular disease (CVD) or (b) 2 or more other CVD risk factors are present

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 5. Minor clinical differences exist between the statins in regards to pharmacokinetic parameters. All statins possess low systemic bioavailability indicating extensive first-pass metabolism, which is advantageous since the major site of cholesterol synthesis is in the liver. Half-life is one parameter that separates some statins from others. In particular, atorvastatin, fluvastatin sustained-release (SR) and rosuvastatin have long half-lives, allowing for more flexible dose scheduling. All of the statins are available in a dosage form whereby they can be administered once a day.

Table 5. Pharmacokinetic Parameters of the Single Entity HMG-CoA Reductase Inhibitors[2, 4-10,17,18]

Drug(s)	Absolute Bioavailability (%)	Protein Binding (%)	Lipid Solubility	Metabolism	Active Metabolites	Half-Life (hours)
Atorvastatin	14	≥98	Lipophilic	Hepatic, CYP3A4	Yes, 2-hydroxy- and 4-hydroxy-atorvastatin acid	14; metabolites: up to 30
Fluvastatin IR/ fluvastatin SR	IR 24; SR 29	98	Hydrophilic*	Hepatic, CYP2C9 (75%), CYP2C8 (5%), CYP3A4 (20%)	No	IR 2.5-2.8; SR 9
Lovastatin IR/ lovastatin SR	<5; SR/IR=190/100	>95	Lipophilic	Hepatic, CYP3A4	Yes, β-hydroxyacid and 6-hydroxy derivatives	IR 1.1-1.7; SR not reported
Pravastatin	17	50	Hydrophilic	Oxidation, isomerization, conjugation, hydroxylation	No important active metabolites	2.0-3.2; metabolites and parent drug: 77
Rosuvastatin	20	88	Hydrophilic	Hepatic (minor), CYP2C9	Yes, N-desmethyl rosuvastatin	19
Simvastatin	5	95	Lipophilic	Hepatic, CYP3A4	Yes, β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives	Not reported

IR=immediate release, SR=sustained release

*Several sources differed from the package insert, noting fluvastatin to possess lipophilic properties.[19-21]

V. Drug Interactions

Clinically important drug interactions exist for the HMG-CoA reductase inhibitors (statins), with minor differences between the drugs within the class when evaluating their use in the general population. Since atorvastatin, lovastatin and simvastatin are metabolized via CYP3A4, they share similar drug interactions. Fluvastatin and rosuvastatin are primarily metabolized via CYP2C9 whereas pravastatin is not appreciably metabolized by the CYP system. As a result, pravastatin may exhibit a lower potential for drug interactions given its unique metabolism. Significant drug interactions with the single entity statins are listed in Table 6.

Table 6. Significant Drug-Drug Interactions with the Single Entity HMG-CoA Reductase Inhibitors[2,18]

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (atorvastatin,	1	Amiodarone	Amiodarone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic effects (ie, myositis, rhabdomyolysis) of

Drug(s)	Significance Level	Interaction	Mechanism
lovastatin, simvastatin)			HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin, pravastatin, and rosuvastatin are not significantly metabolized by CYP3A4 and may be safer alternatives.
HMG-CoA reductase inhibitors (all)	1	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their first-pass hepatic metabolism via CYP3A4/CYP2C9 isoenzymes resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Itraconazole is contraindicated with HMG-CoA reductase inhibitors metabolized by CYP3A4. If other azole antifungals are to be used, the HMG-CoA reductase inhibitor dose should be decreased accordingly. Patients should be monitored for toxicity. Pravastatin may be a safer alternative since its levels are affected least by azole coadministration.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Cyclosporine	Cyclosporine may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism and resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity.
HMG-CoA reductase inhibitors (all)	1	Fibric acid derivatives (fenofibrate, gemfibrozil)	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis via an unknown mechanism. Decrease HMG-CoA reductase inhibitor dose accordingly; obtain creatine kinase levels and monitor for toxicity.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Grapefruit	Grapefruit may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of these HMG-CoA reductase inhibitors. Avoid concomitant administration of atorvastatin, lovastatin, and simvastatin with grapefruit products.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and ketolides (clarithromycin, erythromycin and telithromycin)	Macrolides may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, myopathy or rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Nefazodone	Nefazodone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentrations and increased pharmacologic and toxic (ie, rhabdomyolysis or myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	1	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz,	Delavirdine and nevirapine may inhibit the metabolism of HMG-CoA reductase inhibitors via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis or myopathy) effects of HMG-CoA reductase inhibitors. In contrast, efavirenz may induce CYP3A4 metabolism, resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. With

Drug(s)	Significance Level	Interaction	Mechanism
		nevirapine)	concurrent administration, adjust HMG-CoA reductase inhibitor dose accordingly; monitor plasma low-density lipoprotein cholesterol level, and adverse effects.
Lovastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of lovastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of lovastatin. Decrease lovastatin dose accordingly; monitor for toxicity. Lovastatin is contraindicated in patients receiving concomitant nelfinavir. In addition, lovastatin should not be coadministered with ritonavir, atazanavir, or darunavir.
Pravastatin	1	Protease inhibitors (nelfinavir, ritonavir, saquinavir)	Protease inhibitors may increase the elimination of pravastatin by inducing its metabolism via glucuronidation resulting in decreased concentration and consequently decreased pharmacologic effects of pravastatin. Monitor patients for a decrease in clinical effect with coadministration of pravastatin and certain protease inhibitors.
Simvastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of simvastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of simvastatin. Simvastatin is contraindicated in patients receiving nelfinavir. In addition, coadministration of simvastatin with ritonavir or darunavir should be avoided.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Carbamazepine may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. Monitor patients for a decrease in clinical effect. Pravastatin and rosuvastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Diltiazem	Diltiazem may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Pravastatin may be a safer alternative.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their first-pass metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. The dose of the HMG-CoA reductase inhibitor may need to be increased. Pravastatin levels may be increased in some patients.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Verapamil	Verapamil may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	2	Warfarin	HMG-CoA reductase inhibitors may decrease the elimination of warfarin by inhibiting its hepatic metabolism resulting in increased anticoagulant effect of warfarin. Monitor patients' anticoagulant parameters when starting or discontinuing concurrent therapy with warfarin and HMG-CoA reductase inhibitors. Atorvastatin and pravastatin may be safer alternatives.
Atorvastatin	2	Protease inhibitors (amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of atorvastatin by inhibiting its first-pass metabolism via CYP3A4 resulting in increased concentrations and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of atorvastatin. Monitor patients receiving atorvastatin for toxicity, especially with ritonavir/saquinavir combination. Decrease atorvastatin dose accordingly; monitor for toxicity.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

HMG-CoA reductase inhibitors (statins) are generally well tolerated with only mild side effects, such as abdominal pain, constipation, flatulence, and headache.[1,2,4-10,18] Patients who do not tolerate one statin may experience improved tolerability with another. More serious but rare side effects of statins include increases in liver enzymes and myopathy (defined as muscle ache in conjunction with creatine kinase [CK] elevation >10 times the upper limit of normal [ULN]), which can progress to rhabdomyolysis and acute renal failure secondary to myoglobinuria. Age >65 years, poorly controlled hypothyroidism, and renal impairment may increase the risk of myopathy among patients taking statins. In clinical trials with rosuvastatin, doses above the recommended 40 mg maximum daily dose were associated with an increased risk of myopathy and rhabdomyolysis.[9] Increases in hepatic transaminases >3 times the ULN have been reported with each statin (0.5%-2.3%) and also appear to be dose-dependent (risk increases as the statin dose increases).[1] Those abnormalities are reversible with statin discontinuation. Routine liver function monitoring is recommended with each statin. It is suggested that liver function tests be performed before the initiation of therapy, at 12 weeks following change in dose, and semiannually thereafter. Statins are contraindicated in patients with active liver disease, including those with unexplained elevations of hepatic transaminase levels. In June 2004, in response to labeling changes in the European Union for rosuvastatin, the FDA reviewed the need to adjust rosuvastatin package labeling in the United States (US) to highlight the risk of myopathy. The FDA reviewed postmarketing adverse event reports and found the labeling current at that time to be sufficient.[22] However, the FDA advisory reinforced the importance of following the recommendations stated in the product label.

The most common adverse reactions reported with the single entity statins are noted in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Single Entity HMG-CoA Reductase Inhibitors [2,4-10,17]

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Cardiovascular						
Angina pectoris	<2	-	-	3.1	-	-
Arrhythmia	<2	-	-	-	-	-
Chest pain	≥2	-	0.5-1.0/–	0.1-2.6	-	-
Hypertension	<2	-	-	-	-	-
Migraine	<2	-	-	-	-	-
Phlebitis	<2	-	-	-	-	-
Palpitation	<2	-	-	-	-	-
Postural hypotension	<2	-	-	-	-	-
Vasodilatation	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Syncope	<2	-	-	-	-	-
Central Nervous System/Neurological						
Abnormal dreams	<2	-	-	-	-	-
Amnesia	<2	-	-	-	-	-
Anxiety	-	✔	✔	1.0	-	✔
Chills	-	✔	✔	✔	-	✔
Cranial nerve dysfunction	-	✔	✔	✔	-	✔
Depression	<2	✔	✔	1.0	-	✔
Dizziness	≥2	✔	0.5-1.2/2	1.0-2.2	≤4	✔
Emotional lability	<2	-	-	-	-	-
Facial paralysis/paresis	<2	✔	-	✔	-	✔
Fever	<2	✔	✔	<1.0	-	✔
Flushing	-	✔	✔	<1.0	-	✔
Headache	2.5-16.7	8.9/4.7	2.1-3.2/7	1.7-1.9	3.1-8.5	3.5
Hyperkinesia	<2	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-
Hypesthesia	<2	-	-	-	-	-
Impairment of extraocular movement	-	✔	-	✔	-	-
Incoordination	<2	-	-	-	-	-
Insomnia	≥2	2.7/0.8	0.5-1.0/–	1.0	-	✔
Libido decreased	<2	✔	✔	<1.0	-	✔
Memory loss	-	✔	✔	<1.0	✔	✔
Neck rigidity	<2	-	-	-	-	-
Paresthesia	<2	✔	0.5-1.0/–	<1.0	-	✔
Peripheral nerve palsy	-	✔	✔	✔	-	✔
Peripheral neuropathy	<2	✔	✔	<1.0	-	✔
Psychiatric disturbances	-	✔	✔	-	-	✔
Somnolence	<2	-	-	-	-	-
Torticollitis	<2	-	-	-	-	-
Tremor	-	✔	✔	<1.0	-	✔
Vertigo	-	✔	✔	<1.0	-	✔
Dermatological						
Acne	<2	-	-	-	-	-
Alopecia	<2	✔	0.5-1.0/–	<1.0	-	✔
Contact dermatitis	<2	-	-	-	-	-
Dry skin	<2	✔	✔	<1.0	-	✔
Eczema	<2	-	-	-	-	0.8
Erythema multiforme	<2	✔	✔	✔	-	✔
Pruritus	<2	✔	0.5-1.0/–	<1.0	<2	0.5
Rash	1.1-3.9	-	0.8-1.3/–	1.3-2.1	<2	0.6
Seborrhea	<2	-	-	-	-	-
Skin ulcer	<2	-	-	-	-	-
Stevens-Johnson syndrome	✔	✔	✔	✔	-	✔
Sweating	<2	-	-	-	-	-
Toxic epidermal necrolysis	✔	✔	✔	✔	-	✔
Urticaria	<2	✔	✔	<1.0	<2	-
Endocrine and Metabolic						
Gout	<2	-	-	-	-	-
Hyperglycemia	<2	-	-	-	-	-
Hypoglycemia	<2	-	-	-	-	-
Peripheral edema	≥2	-	-	-	-	-
Weight gain	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Gastrointestinal						
Abdominal pain	0.0-3.8	4.9/3.7	2.0-2.5/–	2.0-2.4	≤2.4	0.9-3.2
Acid regurgitation	-	-	0.5-1.0/–	-	-	-
Anorexia	<2	✔	✔	-	-	✔
Biliary pain	<2	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	✔	✔	✔
Cirrhosis	-	✔	✔	✔	-	✔
Colitis	<2	-	-	-	-	-
Constipation	0.0-2.5	-	2.0-3.5/–	1.2-2.4	2.1-4.7	2.3
Diarrhea	0.0-5.3	4.9/3.3	2.2-2.6/3	2.0	-	0.5-1.9
Decreased appetite	-	-	-	<1.0	-	-
Dry mouth	<2	-	0.5-1.0/–	-	-	-
Duodenal ulcer	<2	-	-	-	-	-
Dyspepsia/heartburn	1.3-2.8	7.9/3.5	1.0-1.6/–	2.0-3.5	-	0.6-1.1
Dysphagia	<2	-	-	-	-	-
Enteritis	<2	-	-	-	-	-
Eructation	<2	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-
Flatulence	1.1-2.8	2.6/1.4	3.7-4.5	1.2-2.7	-	0.9-1.9
Fulminant hepatic necrosis	-	✔	✔	✔	-	✔
Gastritis	<2	-	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-
Glossitis	<2	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-
Hepatitis	<2	✔	✔	✔	✔	✔
Hepatoma	-	✔	✔	✔	-	✔
Increased appetite	<2	-	-	-	-	-
Melena	<2	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-
Nausea	≥2	3.2/2.5	1.9-2.5	-	0.0-6.3	0.4-1.3
Nausea/vomiting	-	-	-	1.6-2.9	-	-
Pancreatitis	<2	✔	✔	✔	<2	✔
Rectal hemorrhage	<2	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-
Tenesmus	<2	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-
Vomiting	<2	✔	0.5-1.0/–	-	-	✔
Genitourinary						
Abnormal ejaculation	<2	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-
Cystitis	<2	-	-	-	-	-
Dysuria	<2	-	-	<1.0	-	-
Epididymitis	<2	-	-	-	-	-
Erectile dysfunction	-	✔	✔	<1.0	-	✔
Fibrocystic breast	<2	-	-	-	-	-
Gynecomastia	-	✔	✔	✔	-	✔
Hematuria	≥2	-	-	-	-	-
Impotence	<2	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Metrorrhagia	<2	-	-	-	-	-
Nephritis	<2	-	-	-	-	-
Nocturia	<2	-	-	<1.0	-	-
Urinary abnormality	-	-	-	0.7-1.0	-	-
Urinary frequency	<2	-	-	<1.0	-	-
Urinary incontinence	<2	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-
Urinary tract infection	≥2	1.6/2.7	–/2	-	-	-
Urinary urgency	<2	-	-	1.0	-	-
Uterine hemorrhage	<2	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-
Hematologic						
Anemia	<2	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-
Eosinophilia	-	✔	✔	✔	-	✔
Hemolytic anemia	-	✔	✔	✔	-	✔
Leukopenia	-	✔	✔	✔	-	✔
Lymphadenopathy	<2	-	-	-	-	-
Petechia	<2	-	-	-	-	-
Purpura	-	✔	✔	✔	-	✔
Thrombocytopenia	<2	✔	✔	-	-	✔
Vasculitis	-	✔	✔	✔	-	✔
Laboratory Test Abnormalities						
Bilirubin elevation	-	✔	✔	-	✔	✔
Creatine phosphokinase increased	<2	-	-	-	2.6	✔
Eosinophil sedimentation rate increase	-	✔	✔	✔	-	✔
Hematuria	-	-	-	-	✔	-
Liver enzyme abnormalities	-	✔	✔	✔	2.2	✔
Positive antinuclear antibody	-	✔	✔	✔	-	✔
Proteinuria	-	-	-	-	✔	-
Thyroid level abnormality	-	✔	✔	✔	✔	✔
Musculoskeletal						
Arthralgia	0.0-5.1	–/3.2	0.5-1.0/5	6.0	10.1	✔
Arthritis	≥2	2.1/1.3	0.5-6/5.0	✔	-	✔
Back pain	0.0-3.8	-	–/5	-	-	-
Bursitis	<2	-	-	-	-	-
Dermatomyositis	-	-	-	✔	-	-
Leg cramps	<2	-	-	-	-	-
Leg pain	-	-	0.5-1.0/–	-	-	-
Localized pain	-	-	-	1.4	-	-
Muscle cramps	-	✔	0.6-1.1/–	2.0	-	✔
Myalgia	0.0-5.6	5.0/3.8	1.8-3.0/3	0.6-1.4	1.9-12.7	1.2
Myopathy	-	✔	-	✔	-	✔
Myositis	<2	-	-	-	-	-
Myasthenia	<2	-	-	<1.0	-	-
Polymyalgia rheumatica	-	✔	✔	✔	-	✔
Rhabdomyolysis	✔	✔	✔	✔	-	✔
Shoulder pain	-	-	0.5-1.0/–	-	-	-
Tendinous contracture	<2	-	-	-	-	-
Tenesynovitis	<2	-	-	-	-	-
Respiratory						
Asthma	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Bronchitis	≥2	1.8/2.6	-	-	-	-
Cough	-	-	-	0.1-1.0	-	-
Dyspnea	<2	✔	✔	1.6	-	✔
Epistaxis	<2	-	-	-	-	-
Pharyngitis	0.0-2.5	-	-	-	-	-
Pneumonia	<2	-	-	-	-	-
Rhinitis	≥2	-	-	0.1	-	-
Sinusitis	0.0-6.4	2.6/3.5	-/4	-	-	-
Upper respiratory infection	-	-	-	1.3	-	2.1
Other						
Accidental injury	0.0-4.2	5.1/4.2	-/6	-	-	-
Allergic reaction	0.0-2.8	2.3/1.0	-	<1.0	-	-
Amblyopia	<2	-	-	-	-	-
Anaphylaxis	✔	✔	✔	✔	-	✔
Angioedema	-	✔	✔	✔	<2	✔
Angioneurotic edema	✔	-	-	-	-	-
Asthenia	0.0-3.8	✔	1.2-2.0/3	✔	0.9-4.7	1.6
Blurred vision	-	-	0.9-1.2/–	-	-	-
Cataracts	-	✔	✔	-	-	0.5
Deafness	<2	-	-	-	-	-
Dry eyes	<2	-	-	-	-	-
Eye hemorrhage	<2	-	-	-	-	-
Eye irritation	-	-	0.5-1.0/–	-	-	-
Facial/general edema	<2	-	-	<1.0	-	-
Fatigue	✔	2.7/1.6	-	1.9-3.4	-	-
Flu syndrome	0.0-3.2	5.1/7.1	-/5	-	-	-
Glaucoma	<2	-	-	-	-	-
Infection	2.8-10.3	-	-/11	-	-	-
Lens opacity	-	-	-	<1.0	-	-
Lupus erythematosus-like syndrome	-	✔	✔	✔	-	✔
Malaise	<2	✔	✔	✔	-	✔
Ophthalmoplegia	-	✔	✔	-	-	✔
Pain	-	-	-/3	-	-	-
Parosmia	<2	-	-	-	-	-
Photosensitivity reaction	<2	✔	✔	✔	-	-
Refraction disorder	<2	-	-	-	-	-
Taste loss	<2	-	-	-	-	-
Taste disturbance	<2	✔	-	<1.0	-	-
Tinnitus	<2	-	-	-	-	-
Visual disturbance	-	-	✔	1.6	-	-
Weight loss	-	-	-	-	-	-

*Checks in this column refer to adverse events reported with drugs in this class, but not to the specific agent.
✔ Percent not specified
-Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 8. All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin immediate-release products, which should be divided into twice-daily dosing. Atorvastatin, rosuvastatin, and fluvastatin sustained-release are the only statins that may be administered at any time in the day. The other statins should be administered in the evening or at bedtime to target the time of maximum cholesterol synthesis.

Table 8. Usual Dosing for the Single Entity HMG-CoA Reductase Inhibitors[2,4-10,17]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Atorvastatin	Hypercholesterolemia; heterozygous familial/nonfamilial hypercholesterolemia; secondary prevention of cardiovascular events: Initial, 10-20 mg once daily; maximum, 80 mg daily. For low-density lipoprotein cholesterol (LDL-C) reduction >45%, initiate at 40 mg once daily. Primary prevention of cardiovascular events: Initial, 10 mg once daily Homozygous familial hypercholesterolemia: 10-80 mg once daily Hypertriglyceridemia: Initial, 10 mg once daily; maximum, 80 mg daily	Heterozygous familial hypercholesterolemia: (Adolescents 10-17 years old): Initial, 10 mg once daily; maximum, 20 mg daily Homozygous familial hypercholesterolemia: Initial, 10 mg once daily; maximum, 80 mg daily Safety and efficacy in children younger than 10 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg
Fluvastatin/ fluvastatin SR	Coronary arteriosclerosis: Capsule: initial, 40 mg once or twice daily (LDL-C reduction goal of ≥25%) or 20 mg once daily in the evening (LDL-C reduction goal of <25%); maintenance, 20-80 mg daily, divided into 2 daily doses Sustained-release tablet: 80 mg once daily Primary hypercholesterolemia, heterozygous familial and nonfamilial and mixed lipidemia and LDL-C reduction goal of ≥25%: Capsule: initial, 40 mg once or twice daily; maintenance, 20-80 mg daily Sustained-release tablet: initial, 80 mg once daily Patients with LDL-C reduction goal of ≤25%: Capsule: as above, except that a starting dose of 20 mg/day may be used	Heterozygous familial hypercholesterolemia: (Adolescents 10-16 years old): Initial: 20 mg capsule once daily in the evening; maintenance, 20-80 mg daily; maximum, 80 mg daily, either two 40 mg capsules in divided doses, or one sustained-release tablet Safety and efficacy in children younger than 10 years of age have not been established.	Capsule: 20 mg 40 mg Sustained-release tablet: 80 mg
Lovastatin/ lovastatin SR	Hypercholesterolemia, primary and mixed: Tablet: initial, 20 mg once daily at bedtime; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once daily at bedtime Coronary arteriosclerosis: Tablet: initial, 20 mg once daily at bedtime; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once daily at bedtime Coronary arteriosclerosis, primary; prophylaxis: Tablet: initial, 20 mg once daily at bedtime; maintenance, 10-80 mg; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once at bedtime	Heterozygous familial hypercholesterolemia: (Adolescents 10-17 years old): Tablet: initial, 10 mg daily at bedtime; maximum, 40 mg daily Safety and efficacy of doses higher than 40 mg daily have not been established in children. Safety and efficacy of sustained-release tablets have not been established in children.	Sustained-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Pravastatin	Hyperlipidemia: Initial, 40 mg once daily at bedtime; maintenance, 40-80 mg once daily Primary prevention of cardiovascular events: 40 mg once daily at bedtime Secondary prevention of cardiovascular events: 40 mg once daily at bedtime	Heterozygous familial hypercholesterolemia: (8-13 years old): 20 mg once daily at bedtime Doses greater than 20 mg daily have not been studied in children 8-13 years old. (14-18 years old): 40 mg once daily at bedtime Doses greater than 40 mg daily have not been studied in children 8-13 years old.	Tablet: 10 mg 20 mg 40 mg 80 mg
Rosuvastatin*	Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, slowing of the progression of atherosclerosis: Initial, 5-10 mg once daily or 20 mg once daily for patients with LDL-C greater than 190 mg/dL and when aggressive lipid reduction is desired; maintenance, 5-40 mg once daily (the 40 mg dose should be reserved for patients who failed therapy with the 20 mg dose); maximum, 40 mg daily Homozygous familial hypercholesterolemia: Initial, 20 mg once daily; maintenance, 20-40 mg once daily; maximum, 40 mg daily	Safety and efficacy in children younger than 18 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Coronary arteriosclerosis; prophylaxis: Initial, 20-40 mg once daily in the evening; dose range, 5-80 mg daily Homozygous familial hypercholesterolemia: Initial, 40 mg once daily in the evening or 80 mg daily in 3 divided doses (20 mg, 20 mg, and 40 mg in the evening) Hypercholesterolemia: Initial, 20-40 mg once daily in the evening; dose range, 5-80 mg daily	Heterozygous familial hypercholesterolemia: (Adolescents 10-17 years old): Initial, 10 mg daily in the evening; maintenance, 10-40 mg daily; maximum, 40 mg daily Safety and efficacy in children younger than 10 years of age or in premenarchal girls have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg

*Lower initial dose should be considered for patients requiring less aggressive LDL-C reduction, predisposed to myopathy, taking cyclosporine, gemfibrozil, or lopinavir/ritonavir, Asian patients, and patients with severe renal insufficiency.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Delaying the Progression of Atherosclerosis				
Furberg et al[23] ACAPS Lovastatin 20 to 40 mg once daily in addition to warfarin 1 mg once daily vs lovastatin 20 to 40 mg once daily in addition to warfarin placebo once daily vs lovastatin placebo once daily in addition to warfarin 1 mg once daily vs lovastatin placebo once daily in addition to warfarin placebo once daily	DB, MC, PC, RCT Asymptomatic men and women 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and moderately elevated LDL cholesterol (LDL levels between the 60th and 90th percentiles)	N=919 3 years	Primary 3-year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of the common carotid, the bifurcation, and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	Primary The progression rate of mean maximum IMT was less in the lovastatin and warfarin combination group than in the lovastatin group alone (*P*=0.04). The overall annualized progression rates of mean maximum IMT in the lovastatin group and placebo group were –0.009 and 0.006 mm/year, respectively (*P*=0.001). Secondary: The changes in single maximum IMT in the lovastatin group and placebo group were –0.036±0.022 mm/year and 0.000±0.011 mm/year, respectively (*P*=0.12). Fourteen of the 459 patients in the lovastatin-placebo groups had a major cardiovascular event (4 CHD deaths, 5 strokes and 5 nonfatal myocardial infarction) compared with 5 of the 460 patients in the lovastatin group (*P*=0.04). There was 1 death in patients treated with lovastatin and 8 deaths in patients receiving lovastatin-placebo therapy (*P*=0.02). All 6 cardiovascular deaths were in the lovastatin-placebo group, the remaining 3 deaths were cancer deaths. The lovastatin and lovastatin-placebo groups showed no difference in ALT elevations of ≥200% the ULN.
Byington et al[24] PLAC-II Pravastatin 20 mg once daily in the evening,	DB, PC, RCT Patients with a history of CHD and ≥1 extracranial carotid lesion with the	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the common, internal, and bifurcation	Primary: Pravastatin treatment did not result in a statistically significant reduction in the progression of mean maximum IMT (*P*=0.44). Pravastatin treatment was associated with a 35% statistically significant reduction in IMT progression in the common carotid artery

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated up to 40 mg daily vs placebo once daily in the evening	maximum IMT ≥1.3 mm		carotid artery segments Secondary: Effects on individual carotid artery segments and clinical events	(*P*=0.03). There was no significant effect on bifurcation (*P*=0.49) or on the internal carotid artery (*P*=0.93) with pravastatin therapy. Secondary: Pravastatin treatment was associated with a 60% reduction in clinical coronary events (*P*=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen in the pravastatin group (*P*=0.04).
Crouse et al[25] METEOR Rosuvastatin 40 mg once daily vs placebo once daily	DB, RCT Adult patients between the ages of 45 and 70 years, with LDL-C between 120 and 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C between 120 and 160 mg/dL for individuals with ≥2 CHD risk factors and a 10-year risk of CHD events of <10%, HDL-C level ≤60 mg/dL, level of TG <500 mg/dL, and maximum CIMT between 1.2 mm and 3.5 mm from 2 separate ultrasounds; patients were excluded if they had used lipid-lowering therapies in the previous 12 months,	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery) Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb, and internal carotid artery sites, and annualized rate of change in mean CIMT	Primary: Rosuvastatin therapy was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared with placebo (*P*<0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant 49% reduction in LDL-C from baseline compared with placebo (*P*<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (*P*<0.001), carotid bulb (*P*<0.001), and internal carotid artery sites (*P*=0.02) from baseline compared with placebo. Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (*P*<0.001) from baseline compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	had clinical evidence of CAD or other peri-pheral atherosclerotic disease, prior revascularization procedures, 10-year CHD risk ≥10%, diabetes, uncontrolled hypertension or familial hypercholesterolemia, or serum creatinine >2 mg/dL			
Nissen, Nicholls et al[26] ASTEROID Rosuvastatin 40 mg once daily	MC, OL, PRO Patients ≥18 years old, requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months; patients were excluded if they had a triglyceride level ≥500 mg/dL or poorly controlled diabetes	N=507 24 months	Primary: Percent atheroma volume (PAV), absolute change in total atheroma volume (TAV) in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: With rosuvastatin treatment, patients experienced a significant reduction in PAV from baseline (–0.79%; 95% CI, –1.21% to –0.53%; *P*<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (–5.6 mm^3; 95% CI, –6.82 mm^3 to –3.96 mm^3; *P*<0.001). Secondary: With rosuvastatin treatment, patients experienced a significant reduction from baseline in normalized TAV (–12.5 mm^3; 95% CI, –15.08 mm^3 to –10.48 mm^3; *P*<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in the total normalized TAV (–6.8%; 95% CI, –7.82% to –5.60%; *P*<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in TC (33%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%), and non–HDL-C (47.2%; *P*<0.001). With rosuvastatin treatment, patients experienced a significant increase from baseline in HDL-C (14.7%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kastelein et al[27] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs 8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Yu et al[28] Atorvastatin 80 mg once daily	DB, RCT Patients with CHD (confirmed by angiographic evidence	N=112 26 weeks	Primary: Improvement in IMT Secondary: Reduction in CRP	Primary: While atorvastatin 10 mg therapy was not associated with a statistically significant improvement in either left or right carotid IMT (*P* value not reported), atorvastatin 80 mg therapy led to a significant improvement in left carotid IMT (*P*=0.02) as well as the right carotid IMT from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 10 mg once daily	of coronary stenosis, previous MI, PCI, or angina pectoris), hypercholesterolemia and an LDL-C >100 mg/dL		level, and proinflammatory cytokines at week 26	baseline (*P*=0.01). Secondary: While atorvastatin 10 mg therapy was not associated with a statistically significant change in CRP (*P* value not reported), atorvastatin 80 mg therapy led to a significant reduction in CRP level from baseline (*P*=0.01). In terms of proinflammatory cytokines, atorvastatin 10 mg therapy was associated with a statistically significant reduction in interleukin-8 (*P*=0.01), interleukin-18 (*P*<0.001), and tumor necrosis factor (*P*<0.001). Atorvastatin 80 mg therapy led to a significant reduction in all the proinflammatory cytokines from baseline (*P*<0.05).
Schmermund et al[29] Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily	DB, MC, RCT Patients between the ages of 32 and 80 years without a history of MI, coronary revascularization, or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification [CAC] score ≥30), LDL-C between 130 and 250 mg/dL in the absence of statin therapy or between 100 and 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors	N=471 12 months	Primary: The percent change in total CAC volume score Secondary: Change in LDL-C	Primary: There was no significant difference in the primary end point between the two groups (*P*=0.6477). Secondary: Atorvastatin 80 mg therapy was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg therapy (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nissen, Tuzcu, Schoenhagen, Brown et al[30] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change in atheroma volume from baseline Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-sections with the greatest and the least atheroma volume	Primary: Atorvastatin therapy was associated with a significant delay in atheroma volume progression compared to pravastatin therapy (*P*=0.02). Secondary: Atorvastatin therapy was associated with a significant nominal change in total atheroma volume compared to pravastatin therapy (*P*=0.02). Atorvastatin therapy was associated with a significant change in the percentage of atheroma volume compared to pravastatin therapy (*P*<0.001). Atorvastatin therapy was associated with a significant change in atheroma volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin therapy (*P*=0.01). Progression of coronary atherosclerosis from baseline occurred in the 2.7% of the pravastatin-treated patients (*P*=0.001) and none of the atorvastatin-treated patients (*P*=0.98). Atorvastatin 80 mg daily therapy was associated with a significant reduction in TC, LDL-C, TG, apo B, and CRP (*P*<0.001) compared with the pravastatin group.
Schoenhagen et al[31] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT Serial intravascular ultrasound observations from the REVERSAL study. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210	N=654 18 months	Primary: Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion, remodeling ratio Secondary: Not reported	Primary: Atorvastatin therapy was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (*P*<0.0001). Atorvastatin therapy was associated with a significant 7.3% increase in the lumen area lesion from baseline (*P*=0.0002). Atorvastatin therapy was associated with a significant 7.9% increase in the plaque area lesion from baseline (*P*=0.0002). Atorvastatin therapy was associated with a significant 3.3% reduction in remodeling ratio from baseline (*P*=0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long			Pravastatin therapy was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (*P*=0.0002). Pravastatin therapy was associated with a significant 9.5% increase in the lumen area lesion from baseline (*P*=0.0003). Pravastatin therapy was associated with a significant 9.9% increase in the plaque area lesion from baseline (*P*=0.0022). Pravastatin therapy was associated with a significant 2.7% reduction in remodeling ratio from baseline (*P*=0.0013). There was no statistically significant difference between the atorvastatin intensive therapy and the pravastatin groups in terms of increase in plaque area from baseline (7.9% vs 9.9%, respectively; *P*=0.57). There was no statistically significant difference between the atorvastatin (intensive) therapy and the pravastatin (moderate) groups in terms of reduction in remodeling ratio from baseline (3.3% vs 2.7%, respectively; *P*=0.68). Secondary: Not reported
Nicholls et al[32] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT, SA Subanalysis of REVERSAL study in obese patients. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume Secondary: Not reported	Primary: Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly lower reduction in TC (40% vs 36%; *P*=0.007), LDL-C (55% vs 49%; *P*=0.008), and TG (35% vs 23%; *P*=0.04). Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly higher reduction in CRP (33% vs 40%; *P*=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin therapy (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m^2 or BMI<29.6 kg/m^2			Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly greater benefit on the total atheroma volume (*P*=0.01) and percent atheroma volume (*P*=0.0005). In contrast, pravastatin therapy was associated with a significant 6.5% increase in atheroma volume in the obese group (*P*=0.006). Secondary: Not reported
Nissen, Tuzcu, Schoenhagen, Crowe et al[33] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT Subanalysis of REVERSAL study evaluating the effect of statin therapy on LDL, CRP, and CAD. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m^2 or BMI<29.6 kg/m^2	N=654 18 months	Primary: Percent change in TC, TG, CRP, non–HDL-C, HDL-C, atheroma volume Secondary: Not reported	Primary: Patients in both treatment groups experienced a significant reduction from baseline in the TC (63%; *P*<0.001), LDL-C (56%; *P*<0.001), TG (40%; *P*=0.002), CRP (22.4%; *P*<0.001) and non–HDL-C (33%; *P*<0.001). HDL-C was not significantly increased from baseline in either group (4.2%; *P*=0.11). Patients randomized to atorvastatin experienced a slower rate of disease progression (atheroma volume) compared to patients receiving pravastatin therapy (0.2% vs 1.6%; *P* value not reported). Patients whose LDL-C and CRP reductions were greater than the median experienced a significantly slower rate of disease progression compared with patients with lower LDL-C and CRP reductions (*P*=0.001). Secondary: Not reported
Familial Hypercholesterolemia (FH)				
Rodenburg et al[34] Pravastatin 20 mg (children <14 years of age) or	FU Children diagnosed with FH, between 8 and	N=214 2 years (mean duration of	Primary: Percentage change in TC, LDL-C, TG, HDL-C, predictors of	Primary: Statin therapy was associated with a 22.5% reduction in TC from baseline (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pravastatin 40 mg (children ≥14 years of age)	18 years of age, on a fat-restricted diet ≥3 months, with LDL-C ≥4.0 mmol/L and triglyceride levels <4.0 mmol/L on 2 different occasions, using adequate contraception, not on any treatment for hypercholesterolemia, including plant sterol or stanol products	total treatment with a statin was 4.5 years)	smaller carotid IMT, and safety Secondary: Not reported	Statin therapy was associated with a 29.2% reduction in LDL-C from baseline (*P* value not reported). Statin therapy was associated with a 3.1% increase in HDL-C from baseline (*P* value not reported). Statin therapy was associated with a 1.9% reduction in TG from baseline (*P* value not reported). The study found several independent predictors of smaller carotid IMT: IMT at statin initiation (*P*<0.001), age at statin initiation (*P*=0.016), male sex (*P*<0.001), and the duration of statin therapy (*P*<0.001). Secondary: Not reported
Avis et al[35] Standard statin therapy (pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo	MA Randomized, placebo-controlled trials, evaluating statin therapy in patients, aged <18 years, with heterozygous FH; studies were excluded if lipid lowering co-medication was used, if treatment was unblinded, abstracts, or if none of the following outcome measures were reported: lipid profile, IMT, or safety parameters	N=798 (6 studies) Up to 2 years	Primary: Percentage change in TC, LDL-C, TG, HDL-C, apo B, apo AI, the difference in absolute changes in IMT, and safety Secondary: Not reported	Primary: Statin therapy was associated with a 23% reduction in TC compared with placebo (95% CI, 19 to 27; *P* value not reported). Statin therapy was associated with a 30% reduction in LDL-C compared with placebo (95% CI, 24 to 36; *P* value not reported). Statin therapy was associated with a 3.6% increase in HDL-C compared with placebo (95% CI, 1.33 to 5.94; *P* value not reported). Statin therapy was associated with a 25% reduction in apo B compared with placebo (95% CI, 19 to 31; *P* value not reported). Statin therapy was associated with a 2.4% reduction in apo AI compared with placebo (95% CI, 0.41 to 4.45; *P* value not reported). Statin therapy was associated with a significant carotid IMT regression compared with placebo (*P*=0.02). Statin therapy was not associated with a significant risk of adverse events compared with placebo (RR, 0.99; 95% CI, 0.79 to 1.25; *P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26; *P* value not reported), ALT (RR, 2.03; 95% CI, 0.24 to 16.95; *P* value not reported), or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82; *P* value not reported) compared with placebo. Secondary: Not reported
Shafiq et al[36] Statins (lovastatin up to 40 mg/day, pravastatin up to 20 mg/day, simvastatin [no dose reported], atorvastatin up to 20 mg/day) vs placebo	MA Randomized, double-blind, controlled trials comparing statins with placebo in pediatric and adolescent patients with FH	6 studies N=798 12-104 weeks	Primary Percent change in LDL-C, TC, TG, HDL-C Secondary Not reported	Primary Statin therapy was associated with a significant reduction in LDL-C compared with placebo (*P* value not reported). Statin therapy was associated with a significant reduction in TC compared with placebo (*P* value not reported). Statin therapy was associated with a significant reduction in TG compared with placebo (*P* value not reported). Statin therapy was associated with a significant increase in HDL-C compared with placebo (*P* value not reported). Secondary: Not reported
Marais et al[37] Rosuvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week	RCT, DB, XO Patients >10 years of age, weighing ≥32 kg, with homozygous FH, fasting LDL-C >500 mg/dL, TG <600 mg/dL, and either xanthomata before 10 years of age or both parents with FH; patients were excluded if had active liver	N=44 24 weeks (16-weeks OL titration phase)	Primary Percent change in LDL-C from baseline to week 18 Secondary Response rate, percent change in TC, apo B, TG, HDL-C	Primary Patients receiving rosuvastatin 20-80 mg experienced a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; *P*<0.0001). Patients without a portacaval shunt and those not receiving plasmaphoresis who were treated with rosuvastatin 20-80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy (*P* value not reported). Secondary: Rosuvastatin treatment was associated with an overall 72% response rate, defined as ≥15% reduction in baseline LDL-C (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dietary lead-in period vs atorvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week dietary lead-in period	disease, unexplained elevations in ALT/AST, bilirubin ≥3 times ULN, unexplained CK >3 times ULN, serum creatinine >220 µmol/L, or uncontrolled hypertension			reported). Patients receiving rosuvastatin 20-80 mg experienced a significant reduction in TC and apo B from baseline after 18 weeks of therapy (20%; *P*<0.0001). Patients receiving rosuvastatin 20-80 mg experienced a non-significant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3% and 3.1%, respectively; *P*>0.05). At week 24, patients randomized to rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1% vs 18%; *P*=0.67). At week 24, there was no statistically significant difference between patients randomized to rosuvastatin and atorvastatin in reductions from baseline in TC (17.6% vs 17.9%; *P*=0.91), TG (6.3% vs 13.9%; *P*=0.21), or apo B (11.4% vs 11.7%; *P*=0.90). The only statistically significant difference between the two groups was in apo AI change from baseline. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (*P*=0.001).
Arca et al[38] Atorvastatin 10 mg daily, titrated to LDL-C goal, up to 80 mg daily for 24 weeks, following a 6-week dietary lead-in period vs fenofibrate 200 mg daily for 24 weeks, following a 6-week dietary lead-in period	OL, R Patients between 30 and 75 years old with diagnosis of familial combined hyper-lipidemia with TC and/or triglyceride levels ≥90th Italian population percentiles, and/or hyperapobeta-lipoproteinemia; patients were excluded if they had type III	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A, endothelin-1 Secondary: Not reported	Primary: At 24 weeks, a greater percentage of patients on atorvastatin therapy was able to reach recommended lipid targets, compared to patients randomized to fenofibrate therapy (*P*=0.02). Atorvastatin therapy was associated with a significant 9% reduction in TC compared with fenofibrate therapy (95% CI, 3% to 15.1%; *P*=0.004). Atorvastatin therapy was associated with a significant 17% reduction in LDL-C compared with fenofibrate therapy (95% CI, 8% to 26.1%; *P*<0.001). Fenofibrate therapy was associated with a significant 15.5% reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hyperlipidemia, were obese, had uncontrolled diabetes mellitus, or were taking lipid-lowering drugs			in TG compared with atorvastatin therapy (95% CI, 3.35% to 27.7%; *P*=0.013). Fenofibrate therapy was associated with a significant 14.2% increase in HDL-C compared with atorvastatin therapy (95% CI, 3.8% to 24.6%; *P*=0.008). Fenofibrate therapy was associated with a significant 5.2% and 22% increase in apo AI and apo AII compared with atorvastatin therapy (*P*=0.044 and *P*<0.001, respectively). Fenofibrate therapy was associated with a significant 16.7% reduction in endothelin-1 from baseline (*P*<0.05). Atorvastatin was not associated with a significant change in endothelin-1 (*P* value not reported). Secondary: Not reported
Hypercholesterolemia				
Lewis et al[39] Pravastatin 80 mg once daily vs placebo once daily	DB, MC, PC, RCT Adult patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with at least 6-months history of compensated liver disease	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC, and TG, ALT event rate (ALT ≥2 times the ULN for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline) Secondary: Not reported	Primary: Pravastatin was associated with a statistically significant reduction in LDL-C, TC, and TG at week-12 of the study compared to placebo (*P*<0.0001). There was no statistically significant difference between the two study groups in the ALT event rate at any time during the study (*P*>0.05). By the 36th week of the study, 7.5% of patients on pravastatin and 12.5% of patients taking placebo had at least one ALT event (*P*=0.1379). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stein et al[40] Rosuvastatin 40 mg daily for ≤96 weeks, after a 6-week dietary lead-in period	MC, OL Adult patients ≥18 years of age with LDL-C ≥190 and ≤260 mg/dL and TG <400 mg/dL; patients were excluded if they had homozygous familial hypercholesterolemia, significant liver enzyme elevations, active arterial disease within the previous 3 months, uncontrolled hyper-tension, serum CK >3 times ULN, serum creatinine >2.5 mg/dL, uncontrolled diabetes or hypothyroidism	N=1,380 ≤96 weeks	Primary: Percentage of patients who achieved NCEP ATP III LDL-C goals (<160, <130, or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apoliprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B	Primary: At 12 weeks, 83% of patients achieved the NCEP ATP III LDL-C goal (95% CI, 81% to 85%; *P* value not reported). Secondary: At 48 weeks, rosuvastatin therapy was associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (*P*<0.0001). At 48 weeks, rosuvastatin therapy was associated with a significant increase from baseline in HDL-C (11%; *P*<0.0001). During the 96-week study period, 13% of patients experienced a serious adverse event, 0.4% of these patients died, and 2% of the patients experienced myalgia (*P* value not reported).
Meredith et al[41] Simvastatin 20 mg once daily vs simvastatin 80 mg once daily vs placebo once daily	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD, and an hsCRP >3 mg/L; patients were excluded if they had been hospitalized within 90 days with an ACS, had undergone a coronary revascularization procedure within 90 days, or if they had a known acute or long-	N=107 16 weeks	Primary: Change in hsCRP from baseline Secondary: Change in LDL-C, TC, TG from baseline	Primary: There was no statistically significant difference between simvastatin 20 and 80 mg groups in terms of change in hsCRP from baseline (*P*=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in LDL-C reduction from baseline (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in hsCRP reduction from baseline (*P*=0.007). Simvastatin, regardless of dose, was more effective than placebo in TC reduction from baseline (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	term inflammatory process			triglyceride reduction from baseline (*P*=0.01).
Wolffenbuttel et al[42] CORALL Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 20 mg daily for 6 weeks, titrated to 40 mg daily for 6 weeks vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 40 mg daily for 6 weeks, titrated to 80 mg daily for 6 weeks	MC, OL, PG, R Adult patients ≥18 years of age with type 2 diabetes for ≥3 month, LDL ≥3.36 mmol/L in statin naïve patients or LDL between 2.99 mmol/L and 5.0 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L, and HbA_{1C}<10%	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B, percentage of patients who achieved LDL-C goals (<2.6 mmol/L or <2.5 mmol/L) at 18 weeks Secondary: Not reported	Primary: Both rosuvastatin and atorvastatin were associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (*P*<0.001). Rosuvastatin therapy was associated with significant reduction in LDL-C (*P*<0.01), apolipoprotein ratio (*P*<0.05), LDL:HDL ratio (*P*<0.01), TC (*P*<0.05), TC:HDL ratio (*P*<0.05), non–HDL-C(*P*<0.05), and apo B (*P*<0.05), compared to atorvastatin therapy. Significantly greater percentage of patients randomized to rosuvastatin therapy achieved LDL-C goals at 18 weeks of therapy compared with the control (*P*<0.05). The incidence of treatment-related adverse events was similar in the rosuvastatin and atorvastatin groups (47% vs 50%, respectively; *P* value not reported). Secondary: Not reported
Deedwania, Gupta et al[43] IRIS Rosuvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs rosuvastatin 20 mg daily for 6 weeks, after a 6-week dietary lead-in period vs	MC, OL, R South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10-year CHD risk 10%-20%, and LDL-C ≥130 mg/dL or 0-1 risk factor and LDL-C ≥160 mg/dL, LDL-C had to be within 15% of each other and ≤300 mg/dL on 2	N=740 12 weeks	Primary: Percentage change in LDL-C from baseline at 6 weeks Secondary: Achievement of NCEP ATP III LDL-C goals, percentage change from baseline in non–HDL-C, HDL-C, TC, TG, and safety	Primary: At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C from baseline compared with atorvastatin 10 mg therapy (*P*=0.0023). The difference in LDL-C reduction from baseline at 6 weeks between the rosuvastatin 20 mg and atorvastatin 20 mg groups was not statistically significant (*P* value not reported). Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar in the rosuvastatin 10 mg and 20 mg and atorvastatin 10 mg and 20 mg groups (79%, 89%, 76%, and 85%, respectively). At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C:HDL-C ratio from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs atorvastatin 20 mg daily for 6 weeks, after a 6-week dietary lead-in period	consecutive measurements, with TG <500 mg/dL			baseline compared with atorvastatin 10 mg therapy (*P*<0.017). There were no clinically relevant differences between statins in adverse events or incidence of creatine kinase >10 times the ULN, ALT>3 times the ULN, proteinuria, or hematuria over a 6-week study period (*P* value not reported).
Betteridge and Gibson[44] ANDROMEDA Rosuvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	DB, MC, PG, RCT Adult patients ≥18 years of age, with type 2 diabetes, with ≥2 FBG levels of ≥7.0 mmol/L, and a triglyceride level of ≤6.0 mmol/L; patients were excluded if they had type 1 diabetes, HbA_{1C} >9%, a history of cardiovascular disease or familial hypercholesterolemia, ALT/AST level ≥1.5 times the ULN, resting diastolic or systolic blood pressure >95 mmHg or >200 mmHg, respectively, or an unexplained serum CK level >3 times the ULN	N=509 16 weeks	Primary: Percentage changes from baseline in LDL-C levels at 16 weeks Secondary: Percentage changes from baseline in: LDL-C, TC, HDL-C, TG, non–HDL-C, cholesterol ratios, apo B, apolipoprotein ratio, HbA_{1C}, the proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in LDL-C from baseline compared with atorvastatin therapy (57.4% vs 46%; *P*=0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant reduction in apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, and apo B from baseline compared with atorvastatin therapy (*P*<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in HbA_{1C} from baseline compared with atorvastatin therapy (*P*=0.049). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies LDL-C goal compared to the atorvastatin group at 16 weeks of therapy (95.6% vs 87.3%; *P*=0.002). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies TC goal compared to the atorvastatin group at 16 weeks of therapy (93.4% vs 86%; *P*=0.01).
Betteridge, Gibson, Sager et al[45]	DB, DD, MC, PG, RCT, SA of ANDROMEDA study	N=509 16 weeks	Primary: A composite end point of CRP <2mg/L	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in the primary end point from baseline compared with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rosuvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	Adult patients ≥18 years of age, with type 2 diabetes, with ≥2 FBG levels of ≥7.0 mmol/L, and a triglyceride level of ≤6.0 mmol/L (see above for exclusion criteria)		and LDL-C <70 mg/dL Secondary: Not reported	atorvastatin therapy (58% vs 37%; *P*<0.001). Secondary: Not reported
Ferdinand et al[46] ARIES Rosuvastatin 10 mg one daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 20 mg once daily for 6 weeks, after a 6-	OL, R African-American adult patients ≥18 years of age with LDL ≥160 mg/dL but ≤300 mg/dL, TG <400. Patients were excluded if they had a history of homozygous familial hypercholesterolemia, type I, III, or V hypercholesterolemia, active arterial disease, uncontrolled hypertension, poorly controlled diabetes, active liver disease, transaminase elevation, bilirubin levels ≥2 times the ULN, unexplained serum creatine kinase levels >3 times the ULN, or	N=774 6 weeks	Primary: The change from baseline in LDL-C at 6 weeks Secondary: Changes from baseline in other lipids, apolipoproteins	Primary: Patients in the rosuvastatin group experienced a statistically significant reduction in LDL-C levels compared to the atorvastatin groups (*P*<0.017). Secondary: Patients in the rosuvastatin group experienced a statistically significant reduction in TC, non–HDL-C levels, apo B concentrations, lipoprotein, and apolipoprotein ratios compared to the atorvastatin groups (*P*<0.017). Patients in the rosuvastatin group experienced a statistically significant increase in HDL-C levels compared to the atorvastatin groups (*P*<0.017). Side effects were similar in the rosuvastatin and atorvastatin treatment groups (34.4% and 33.6%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week lead-in period	serum creatinine 2.0 mg/dL.			
Lloret et al[47] STARSHIP Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period	MC, OL, RCT Hispanic-American adult patients ≥18 years of age with a 10-year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 mg/dL but ≤300 mg/dL on two measurements within 15% of each other, TG <400. Patients were excluded if they had a history of homozygous familial hypercholesterolemia, type I, III, or V hyper-cholesterolemia, active arterial disease, uncontrolled hypertension, poorly controlled diabetes, active liver disease, transaminase elevation, bilirubin levels ≥2 times the ULN, unexplained serum creatine kinase levels >3 times the ULN, or serum creatinine 2.0 mg/dL.	N=696 6 weeks	Primary: Percent change from baseline in LDL-C at 6 weeks Secondary: Proportion of patients reaching NCEP ATP III lipid goals, percent change from baseline in TC, apo B, non–HDL-C, TG, HDL, apo AI, LDL:HDL-C ratio, TC:HDL ratio, apo B:apo AI ratio, side effects at 6 weeks	Primary: Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (45%, 50%, 36%, and 42%, respectively; *P*<0.0001). Secondary: More patients randomized to the rosuvastatin 10 mg and 20 mg groups achieved NCEP ATP III LDL-C goals compared to the atorvastatin 10 mg and 20 mg groups at 6 month (78%, 88%, 60%, 73%, respectively; *P* value not reported). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.017, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL:HDL cholesterol ratio from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (*P*<0.0001). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in non-HDL:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B:apo AI from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (*P*<0.01). Side effects were similar across treatment groups (*P* value not reported). There were no cases of myopathy, rhabdomyolysis, or clinically significant increases in serum creatine kinase.
Insull et al[48] SOLAR Rosuvastatin 10 mg daily for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs simvastatin 20 mg for 6	MC, RCT Patients were 18 years or older, enrolled in a managed care health plan, and classified as high risk by NCEP ATP III risk assessment. The NCEP ATP III defines high risk as the presence of CHD or CHD risk equivalents that consist of other clinical atherosclerotic disease, diabetes, or multiple CHD risk factors conferring a 10-year CHD risk of more than 20%; exclusion criteria included active vascular disease (such as unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, CABG, or	N=1,632 12 weeks	Primary: Achievement of the NCEP ATP III high-risk LDL-C goal (<100 mg/dL) at week 6 Secondary: Proportions of patients who reached the high-risk LDL-C goal at 12 weeks, proportions of hypertriglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non–HDL-C goal (<130 mg/dL) for high-risk patients, and changes in LDL-C and other lipid parameters at 6 and 12 weeks	Primary: Significantly greater proportion of patients randomized to rosuvastatin achieved their LDL-C target compared with the atorvastatin and simvastatin arms at 6 weeks of therapy (65%, 41%, and 39%, respectively; *P*<0.001). Secondary: After 12 weeks, 76% of patients taking rosuvastatin reached the LDL-C goal compared with 58% and 53% of patients on atorvastatin and simvastatin, respectively (*P*<0.001). After 6 weeks, 44% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 19% of patients on simvastatin, respectively (*P*<0.001). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 31% of patients on simvastatin, respectively (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TC level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved	angioplasty within 3 months of study entry), uncontrolled hypertension, an FSG level of 180 mg/dL or higher or an HbA_{1c} level of ≥9%, active liver disease, unexplained serum CK elevation of more than 3 times the ULN, or a serum creatinine level of more than 2.0 mg/dL			Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C:HDL-C ratio from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant increase in HDL-C from baseline compared to the atorvastatin and simvastatin groups at 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to the simvastatin group at 6 and 12 months (*P*<0.001). The frequency and types of adverse events were similar in all treatment groups (*P* value not reported).
Leiter et al[49] POLARIS Rosuvastatin 40 mg once daily vs atorvastatin 80 mg once daily	DB, PG, R Patients between 45-80 years of age, with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis, or a 10-year Framingham CHD-risk score >20%, with LDL-C ≥160 but <250 mg/dL, and TG <400 mg/dL	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week 8 Secondary: Safety, the percentage change from baseline in LDL-C levels at week 26, the percentage change from baseline in other lipids and lipoproteins at weeks 8 and 26, and the proportion of patients	Primary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy (56% vs 52%; *P*<0.001). Secondary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 26 weeks compared to atorvastatin 80 mg therapy (57% vs 53%; *P* value not reported). Rosuvastatin 40 mg was associated with a significantly greater reduction in TG (27% vs 22.2%; *P*<0.05), non–HDL-C (50.8% vs 48.3%; *P*<0.01), LDL-C:HDL-C ratio (58.5% vs 53.6%; *P*<0.001), TC:HDL-C (44.4% vs 41.1%; *P*<0.001), non–HDL-C:HDL-C (53.6% vs 49.6%; *P*<0.001), apo B (44.6% vs 42.3%; *P*<0.05), and apo AI (4.2% vs –0.5%; *P*<0.001) from baseline at 8 weeks compared to atorvastatin 80 mg therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			reaching NCEP ATP III and 2003 European lipid goals at 8 and 26 weeks	Rosuvastatin 40 mg was associated with a significantly greater increase in HDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy (9.6% vs 4.4%; *P*<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the NCEP ATP III LDL-C goal of <100 mg/dL compared with patients in the atorvastatin group (80% vs 72%; *P*<0.01). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved NCEP ATP III LDL-C goal of <70 mg/dL compared with patients in the atorvastatin group (36 vs 18%; *P*<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the 2003 European lipid goals compared with patients in the atorvastatin group (79% vs 69%; *P*<0.001). The incidence of drug-related adverse effects was low in both rosuvastatin and atorvastatin treatment groups (0.5% vs 0.2%; *P* value not reported).
Jones et al[50] STELLAR Rosuvastatin once daily vs pravastatin once daily vs atorvastatin once daily vs simvastatin once daily	OL, PG Men and nonpregnant women ≥18 years of age with hypercholesterolemia, with LDL-C level ≥160 and <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change in LDL-C from baseline to 6 weeks Secondary: Percent change in HDL-C, triglyceride, and TC levels	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C from baseline (*P*<0.001 for both). When compared to baseline, the following changes in LDL-C were observed: a 45.8% to 55.0% reduction with rosuvastatin, a 36.8% to 51.1% reduction with atorvastatin, a 28.3% to 45.8% reduction with simvastatin, and a 20.1% to 29.7% reduction with pravastatin. The highest LDL reductions observed were a 55% reduction achieved in the rosuvastatin 40 mg group and a 51% reduction achieved in the atorvastatin 80 mg group (*P*=0.006). Secondary: A 7.7% to 9.6% increase in HDL, a 19.8% to 26.1% reduction in TG, and a 32.9% to 40.2% reduction in TC was observed with rosuvastatin 10 mg to 40 mg group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(treatments ranged from 10 mg to 80 mg)				A 2.1% to 5.7% increase in HDL, 20.0% to 28.2% reduction in TG, and a 27.1% to 38.9% reduction in TC was observed with the atorvastatin 10 mg to 80 mg group (*P* value not reported). A 5.2% to 6.8% increase in HDL, 11.9% to 18.2% reduction in TG, and a 20.3% to 32.9% reduction in TC was observed with the simvastatin 10 mg to 80 mg group (*P* value not reported). A 3.2% to 5.6% increase in HDL, 7.7% to 13.2% reduction in TG, and a 14.7% to 21.5% reduction in TC was observed with the pravastatin 10 mg to 40 mg group (*P* value not reported).
Stalenhoef et al[51] Rosuvastatin 10 mg daily for 6 weeks, titrated up to rosuvastatin 20 mg daily for another 6 weeks vs atorvastatin 10 mg daily for 6 weeks, titrated up to atorvastatin 20 mg daily for another 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin 20 mg daily for another 6 weeks	DB, DD, MN, PG, RCT Men and women aged ≥18 years with metabolic syndrome (defined as at least 3 of the following: waist circumference >102 cm for men and >88 cm for women, TG ≥1.70 mmol/L, HDL-C <1.04 mmol/L for men and <1.30 mmol/L for women, BP ≥130/85 mm Hg or receiving antihypertensive therapy, FBG ≥6.11 mmol/L), LDL-C ≥3.36 mmol/L, and 10-year CHD risk score of >10%	N=401 12 weeks	Primary: Percentage change from baseline in LDL-C at 6 weeks Secondary: Percentage change from baseline in TC, LDL-C, HDL-C, non–HDL-C at 12 weeks	Primary: Rosuvastatin 10 mg reduced LDL-C significantly more than placebo (42.7% vs 0.3%, respectively; *P*<0.001) after 6 weeks of therapy. At 6 weeks, rosuvastatin had a significantly greater percentage change in LDL-C levels from baseline compared to atorvastatin (41.7% vs 35.7%, respectively; *P*<0.001). Secondary: At 12 weeks, significant reductions in LDL-C were observed in the rosuvastatin combined group in comparison to the atorvastatin group (48.9% vs 42.5%, respectively; *P*<0.001). Significantly more patients taking rosuvastatin achieved LDL-C goal (3.0 mmol/L) than patients taking atorvastatin at both 6 weeks (*P*<0.05) and 12 weeks (*P*<0.05). Percentage improvements in TC (*P*<0.001), HDL-C (*P*<0.01), and non–HDL-C(*P*<0.001) from baseline were significantly greater in patients taking rosuvastatin compared to patients taking atorvastatin at both 6 and 12 weeks.
Ballantyne, Bertolami et al[52] MERCURY II	MC, OL, R Patients ≥18 years of age, at high risk for	N=1,993 16 weeks	Primary: The proportion of patients achieving LDL-C<100 mg/dL	Primary: At 16 weeks, more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rosuvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 10 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 40 mg daily for 8 weeks after a 6-week dietary lead-in period After 8 weeks of treatment, patients received an additional 8 weeks of either initial or rosuvastatin therapy.	CHD events, fasting LDL-C level ≥130 to <250 mg/dL on two separate measurements within 15% of each other, and a fasting TG <400 mg/dL; patients were excluded if were pregnant, lactating, had a history of homozygous familial hypercholesterolemia, hyperlipoproteinemia types I, III, IV, or V, unstable arterial disease within 3 months, uncontrolled hypertension, FSG >180 mg/dL, active liver disease, serum creatinine >2 mg/dL or unexplained serum creatine kinase levels >3 times the ULN		at week 16 Secondary: The proportion of patients meeting the LDL-C target at week 8, change in lipid and lipoprotein measures at weeks 8 and 16, adverse events	mg, and simvastatin 40 mg for the duration of the study (83%, 42%, 64%, 32%, and 56%, respectively; *P* value not reported). At 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial medication regimen (*P*<0.001). Secondary: At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001). At 8 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (82%, 43%, 62%, 33%, and 55%, respectively; *P*<0.0001). At 16 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C level <70 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (37%, 7%, 13%, 1%, and 10%, respectively; *P* value not reported). At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001). At 16 weeks, significantly more hypertriglyceridemic patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL and non–HDL-C targets compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (80%, 20%, 42%, 19%, and 29%, respectively; *P* value not reported). The frequency and type of adverse events were similar in all treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups (*P* value not reported). In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Rogers et al[53] Simvastatin 10, 20, 40, or 80 mg daily vs atorvastatin 10, 20, 40, or 80 mg daily	MA Randomized, comparative studies comparing atorvastatin with simvastatin in patients >18 years of age with elevated levels of serum TC and LDL-C; studies were excluded if they involved animals, had a crossover, dose-titration, or forced dose-titration design, or did not include a washout period of previous statin or other lipid-lowering therapy	N=8,320 (18 studies) Up to 12 weeks	Primary: Reductions in TC, LDL-C, TG and increases in HDL-C Secondary: Not reported	Primary: Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at 4 times the dose of atorvastatin (*P*>0.05). Simvastatin 20 mg and 40 mg were less effective at reducing LDL-C level from baseline compared to atorvastatin 40 mg and 80 mg, respectively (*P*<0.001). Simvastatin, dosed 40 mg to 80 mg, was comparable to atorvastatin 20 mg in terms of triglyceride reduction from baseline (*P*=0.22 and *P*=0.53, respectively). Atorvastatin, dosed 40 mg to 80 mg, was more effective in reducing triglyceride level from baseline compared to all simvastatin doses studied (*P*<0.001). Simvastatin 10 mg, 20 mg, and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (*P*<0.05). Secondary: Not reported
Milionis et al[54] ATOROS Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 20 mg daily for 18 weeks vs atorvastatin 20 mg once daily for 6 weeks, after a 6-	OL, PG, R Patients, average age of 53.6 years, free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL, and TG <350 mg/dL; patients were	N=180 24 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Change from baseline in LDL-C, HDL-C, TC, TG, non-HDL, and apo B at 24 weeks	Primary: At 6 weeks, 75% and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin therapies, respectively (*P* value not reported). Secondary: Both rosuvastatin and atorvastatin were associated with statistically significant reductions in LDL from baseline (48.7% vs 44.6%; *P*<0.001). Rosuvastatin therapy was associated with a significant 5% increase from baseline in HDL-C (*P*<0.001). Atorvastatin therapy was associated with a significant 2.1% reduction from baseline in HDL-C (*P*<0.001). Compared to atorvastatin, rosuvastatin was associated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week dietary lead-in period, titrated to 40 mg daily for 18 weeks	excluded if they had abnormal liver function tests, impaired renal function, diabetes, elevated thyroid-stimulating hormone, or any other condition potentially interfering with successful completion of study protocol; a control group of healthy volunteers was included in the analysis			a significantly greater increase in HDL-C (*P*=0.002). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TC from baseline (36.1% vs 36.9%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TG from baseline (29% vs 27.8%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in non-HDL from baseline (45% vs 46%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in apo B from baseline (29% vs 26%; *P*<0.001). The incidence of myalgia was similar in both treatment groups (3 %; *P* value not reported). There were no reports of significant ALT or CK elevations.
Clearfield et al[55] PULSAR Rosuvastatin 10 mg once daily for 6 weeks vs atorvastatin 20 mg once daily for 6 weeks	OL, PG, R, MC Patients ≥18 years of age with hypercholesterolemia and either a history of CHD or a CHD-risk equivalent, with the mean of the two most recent LDL levels (within 15% of each other) ≥130 mg/dL and <220 mg/dL, as well as TG <400 mg/dL; patients were excluded if they had an MI, unstable angina, myocardial revascularization, a	N=996 6 weeks	Primary: Percentage change from baseline in LDL-C at 6 weeks Secondary: Percentage of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk (CVD, diabetes, LDL-C ≥6mmol/L, TC ≥8 mmol/L, or blood pressure ≥180/110	Primary: Compared to atorvastatin, rosuvastatin was associated with a statistically greater reduction from baseline in LDL-C at 6 weeks (42.7% vs 44.6%; *P*<0.05). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III and the 2003 European LDL-C goals, compared with the atorvastatin-treated group (68% vs 63%; *P*<0.05). In addition, more rosuvastatin-treated patients at greatest risk for CHD reached the 2003 European LDL-C goals, compared to patients treated with atorvastatin (65.6% vs 60.3%; *P*>0.05). While more patients reached the NCEP ATP III non–HDL-C goal with rosuvastatin compared with atorvastatin, the difference was not statistically significant (69.7% vs 65%; *P*>0.05). While more patients reached the NCEP ATP III combined LDL-C:TC goal with rosuvastatin compared with atorvastatin, the difference was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	TIA, or stroke within 8–12 weeks of study onset, had a history of statin-induced myopathy, were awaiting a planned myocardial revascularization, had CHF NYHA class III-IV, a history of malignancy, homozygous FH, current active liver disease, unexplained CK elevation ≥3 the ULN, serum creatinine >2.0 mg/dL, uncontrolled, alcohol or drug abuse within the last 5 years, hormone-replacement therapy or oral contraceptives within 3 months of study onset		mm Hg), the NCEP ATP III non-HDL-C goal (<130 mg/dL, combined LDL-C:TC goal <175-190 mg/dL, the percentage change from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, lipoprotein(a) frequency and severity of adverse events	not statistically significant (55.2% vs 53.3%; *P*>0.05). Rosuvastatin was associated with a statistically significant increase in HDL-C from baseline compared to atorvastatin (6.4% vs 3.1%; *P*<0.001). There was no statistically significant difference in the change from baseline in TC, TG, non–HDL-C, and apo B observed with rosuvastatin and atorvastatin (*P*>0.05). Rosuvastatin was associated with a statistically significant reduction in LDL-C:HDL-C from baseline compared to atorvastatin (47.6% vs 44%; *P*<0.001). Rosuvastatin was associated with a statistically significant reduction in TC:HDL-C from baseline compared to atorvastatin (34.6% vs 32.3%; *P*<0.01). Rosuvastatin was associated with a statistically significant reduction in non-HDL-C:HDL-C from baseline compared to atorvastatin (43.3% vs 40.2%; *P*<0.001). Atorvastatin was associated with a statistically significant increase in lipoprotein(a) from baseline compared to rosuvastatin (13.3% vs 2.1%; *P*<0.001). The frequency and type of adverse events were similar with the rosuvastatin and atorvastatin groups (27.5% vs 26.1%; *P* value not reported). The most commonly reported adverse effects were myalgia and urinary tract infections.
Bullano, Kamat et al[56] Rosuvastatin (11 mg mean daily dose) vs	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin between August 1, 2003 and	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with the atorvastatin-treated group (35% vs 26%; *P*<0.001). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin (15 mg mean daily dose)	September 30, 2004 with at least one lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and posttherapy initiation		patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in HDL-C, TC, TG, non-HD-CL	ATP III LDL-C goals, compared with the atorvastatin-treated group, when adjusted for age, sex, LDL-lowering required to reach goal, risk category, and duration of therapy (74% vs 65%; *P*<0.05). Unadjusted attainment rates were similar in both treatment groups (*P*=0.088). Moreover, patients in the rosuvastatin group required greater LDL-C reduction to reach their LDL goal compared to patients treated with atorvastatin (26.3% vs 23.5%; *P*<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to atorvastatin group (61% vs 48%; *P*<0.05). There was no statistically significant difference between the change in HDL-C obtained with rosuvastatin and atorvastatin (*P*=0.234). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TC from baseline compared with the atorvastatin-treated group (26% vs 20%; *P*<0.001). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (*P*=0.192). Patients treated with rosuvastatin experienced a statistically greater percent reduction in non–HDL-C from baseline compared with the atorvastatin-treated group (33% vs 25%; *P*<0.001).
Bullano, Wertz et al[57] Rosuvastatin 5-40 mg daily vs other statins (atorvastatin 10-80 mg/day, simvastatin 5-80 mg/day, pravastatin 10-80 mg/day, lovastatin 10-80 mg/day, fluvastatin 20-160 mg/day)	RETRO Patients ≥18 years of age, initiated on a statin between August 1, 2003 and September 30, 2004 with at least one LDL-C level obtained prior to and after therapy initiation	N=8,251 Up to 122 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with other statin groups (33% vs atorvastatin 24%, simvastatin 20%, pravastatin 18%, fluvastatin 13% and lovastatin 16%; *P*<0.05). Moreover, rosuvastatin 10 mg was associated with a greater percentage of LDL-C reduction from baseline compared to either atorvastatin 10-20 mg (*P*<0.05) or simvastatin 10-20 mg (*P*<0.05). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III LDL-C goals, compared with the other statin treatment groups (*P*<0.05). Moreover, patients in the rosuvastatin group required greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			HDL-C, TC, and TG	LDL-C reduction to reach their LDL goal compared to patients treated with other statins (29% vs 23-27%; *P*<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to other statins (58% vs 29-48%; *P*<0.05). There was no statistically significant difference between the HDL-C reduction obtained with rosuvastatin and other statins (*P*>0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in total cholesterol from baseline compared with other statin groups (24% vs atorvastatin 18%, simvastatin 14%, pravastatin 13%, fluvastatin 10%, and lovastatin 12%; *P*<0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TG from baseline compared with other statin groups (11% vs simvastatin 6%, pravastatin 4%, fluvastatin 4%, and lovastatin 5%; *P*<0.05). However there was no statistically significant difference in TG reduction from baseline between rosuvastatin and atorvastatin-treated groups (11% vs 10%; *P*>0.05).
Ai et al[58] STELLAR Rosuvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks	OL Patients ≥18 years of age, with hypercholesterolemia, with LDL-C levels ≥160 mg/dL and <250 mg/dL, as well as TG <400 mg/dL	N=271 6 weeks	Primary: Change in direct LDL-C and small dense LDL-C Secondary: Percentage change from baseline in HDL-C, TC, TG, non-HDL-C, TC:HDL-C ratio	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared with atorvastatin (52% vs 50%; *P*=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (53% vs 46%; *P*<0.001). Secondary: Rosuvastatin was associated with a significant increase from baseline in HDL-C compared with atorvastatin (10% vs 2%; *P*<0.001). There was no statistically significant difference between the TC reduction obtained with rosuvastatin and atorvastatin (*P*=0.10). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (*P*=0.50).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Rosuvastatin was associated with a significant reduction from baseline in non–HDL-C compared with atorvastatin (51% vs 48%; *P*<0.0078). Rosuvastatin was associated with a significant reduction from baseline in TC:HDL-C compared with atorvastatin (46% vs 39%; *P*<0.001).
Fox, Gandhi, Ohsfeldt, Blasetto et al[59] Rosuvastatin at an average dose of 11.7 mg vs other statins (atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin) dosed 17-64 mg	RETRO Adult patients with diabetes (ICD 9 code 250, on antidiabetic medication, or FBG >126 mg/dL), newly prescribed a statin between August 2003 and March 2006	N=4,754 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction in LDL-C from baseline, percentage of patients achieving LDL-C goal <100 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%), and fluvastatin (15.8%) (*P*<0.0001). Compared to other statins, a greater percentage of patients receiving rosuvastatin were able to reach their LDL-C goal <100 mg/dL (*P*<0.05). Secondary: Not reported
Harley et al[60] Rosuvastatin after simvastatin therapy (5-80 mg) vs atorvastatin after simvastatin therapy (5-80 mg) vs lovastatin after simvastatin monotherapy (5-80 mg) vs	RETRO Adult patients ≥18 years of age, receiving simvastatin monotherapy between July 2005 and June 2006, switched to other statin therapy	N=134,160 1 year	Primary: Percentage of patients achieving NCEP ATP III LDL goal after switching from simvastatin to another statin Secondary: Not reported	Primary: Of those patients not at NCEP ATP III LDL goal with simvastatin monotherapy, 73% reached their LDL goal following the switch to another statin (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pravastatin after simvastatin monotherapy (5-80 mg) vs fluvastatin after simvastatin monotherapy (5-80 mg) vs simvastatin in combination with ezetimibe after simvastatin monotherapy (5-80 mg)				
Fox, Gandhi, Ohsfeldt, and Davidson [61] Rosuvastatin switch vs simvastatin switch	RETRO Adult patients ≥18 years of age switching to either rosuvastatin or simvastatin from another statin between August 2003 and March 2006, not receiving other antidyslipidemic medications in the 12 months before or after initiating statin therapy	N=277 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction in LDL-C from baseline Secondary: Not reported	Primary: Patients switched to rosuvastatin experienced a significant reduction in LDL-C from baseline compared to simvastatin-treated patients (18.5% vs 5.8%; *P*<0.05). LDL-C reduction of >25% was achieved by a significantly greater percentage of patients switched to rosuvastatin therapy than those switched to simvastatin therapy (44% vs 29%; *P*<0.05). Patients switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C from baseline compared to those switched to simvastatin therapy (14.6% vs 4.6%; *P*<0.05). Secondary: Not reported
Piorkowski et al[62] Atorvastatin 40 mg once daily vs	RCT Patients between 18 and 80 years of age with clinically stable angiographically documented CHD and	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL, LDL, and TG from baseline, percentage of patients achieving the ATP III	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL in either group (*P* value not reported). Both groups exhibited a statistically significant reduction in LDL-C from baseline (*P*<0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 10 mg once daily in addition to ezetimibe 10 mg daily, separate entities	LDL-C >2.5 mmol/L despite ongoing atorvastatin 10-20 mg daily, receiving aspirin and clopidogrel; patients were excluded if they had a history of an MI or CK elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal insufficiency, active liver disease, liver cirrhosis, unexplained transaminase elevation, recent antibiotic therapy, or known alcohol abuse		LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline (*P* value not reported). Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in triglyceride level from baseline ($P<0.005$ and $P<0.05$, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) (*P* value not reported). Secondary: Not reported
Constance et al[63] Atorvastatin 20 mg daily for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 20 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1C} ≤10%, ALT/AST levels <1.5 times the ULN, CK <1.5 times the ULN; patients were excluded if they had congestive heart failure New York Heart Association classes III- IV, MI, CABG or angioplasty within 3 months, uncontrolled hypertension or endocrine/metabolic	N=661 6 weeks	Primary: Change from baseline in LDL-C at 6 weeks Secondary: Change from baseline in TC, HDL-C, TG, non–HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin 20 mg monotherapy group ($P\leq0.001$). Secondary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TC, non-HDL, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared with the atorvastatin 20 mg monotherapy group ($P\leq0.001$). Patients on the ezetimibe/simvastatin 10/40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared with the atorvastatin 20 mg monotherapy group ($P=0.006$). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period	disease, renal dysfunction or nephrotic syndrome, alcohol consumption >14 drinks per week and treatment with excluded concomitant medications			achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5%, 87%, and 70.4%, respectively; *P*≤0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5%, 0.5%, and 2.3%, respectively; *P* value not reported).
Pearson et al[64] Atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 6 weeks vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for up to 12 weeks vs placebo for 12 weeks	MA Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to ezetimibe/simvastatin or atorvastatin for 6 weeks	N=4,373 (4 studies) up to 12 weeks	Primary: Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (52.5% vs 38%; *P*<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin monotherapy group (53.4% vs 45.3%; *P*<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant CRP reduction from baseline compared with the simvastatin monotherapy group (31% vs 14.3%; *P*<0.001). Patients on the ezetimibe/simvastatin combination therapy experienced a similar CRP reduction from baseline compared with the atorvastatin monotherapy group (25.1% vs 24.8%; *P* value not reported). The reduction in CRP from baseline was not significantly different between simvastatin 10 mg and placebo groups (*P*>0.10). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9% vs 43.1%; *P*<0.001). Significantly greater proportion of patients randomized to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37% vs 5.7%; *P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8% vs 61.9%; *P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2% vs 16.8%; *P*<0.001). Secondary: Not reported
Goldberg et al[65] VYTAL Atorvastatin 10 mg daily vs atorvastatin 20 mg daily vs atorvastatin 40 mg daily vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily, separate entities vs	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and a triglyceride level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week 6 Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dl, percent change from baseline in HDL-C, non–HDL-C, TC, TG, and CRP	Primary: Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 10 mg or 20 mg daily (53.6%, 38.3%, and 44.6%, respectively; *P*<0.001). Patients randomized to simvastatin 40 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 40 mg daily (57.6% and 50.9%, respectively; *P*<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (59.7%, 21.5%, and 35%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 40 mg daily (74.4% and 55.2%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily, separate entities				A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (90.3%, 70%, and 82.1%, respectively; *P*=0.007). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 40 mg daily (93.4% and 88.8%, respectively; *P*=0.07). Patients randomized to simvastatin/ezetimibe combination therapy, at all doses, experienced a significant increase in HDL level (*P*≤0.001), a greater reduction in TC, and non–HDL-C (*P*<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and triglyceride level compared to patients receiving atorvastatin (*P*=0.02). Side effects were similar in the simvastatin/ezetimibe and atorvastatin groups (19.85 vs 22.7%; *P* value not reported).
Ballantyne, Weiss et al[66] EXPLORER Rosuvastatin 40 mg daily for 6 weeks vs ezetimibe 10 mg, in addition to rosuvastatin 40 mg daily, separate entities, for 6 weeks	MC, OL, PG, RCT Patients ≥18 years of age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%), and mean LDL-C between 160 mg/dL and 250 mg/dL with the two last measurements within	N=469 6 weeks	Primary: Percentage of patients achieving the ATP III LDL-C goal (<100 mg/dL) at 6 weeks Secondary: Change from baseline in LDL-C, TC, non–HDL-C, TG, LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B, CRP, HDL, apo	Primary: Significantly greater proportion of patients randomized to the combination therapy achieved their ATP III LDL-C goal compared to the monotherapy group (94% vs 79.1%; *P*<0.001). Secondary: Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL-C compared to the monotherapy group (70% vs 57%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC compared to the monotherapy group (51% vs 42%; *P*<0.001). Patients on the combination therapy experienced a significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	15% of each other, and TG <400 mg/dL; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or creatine kinase >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled hypertension, or body mass index ≥30 kg/m^2		AI, adverse effects	reduction from baseline in non–HDL-C compared to the monotherapy group (65% vs 52%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TG compared to the monotherapy group (35% vs 25%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL:HDL cholesterol compared to the monotherapy group (72% vs 60%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC:HDL cholesterol compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL/HDL cholesterol compared to the monotherapy group (67% vs 55%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in apo B compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in CRP compared to the monotherapy group (46% vs 29%; *P*<0.001). There was no statistically significant difference in HDL-C increase (*P*=0.151) or apo AI reduction (*P*=0.202) between the combination therapy and rosuvastatin monotherapy groups. The frequency and types of adverse events were similar across the combination and monotherapy groups (31.5% and 33.5%, respectively; *P* value not reported).
Ose et al[67] Simvastatin 10 mg, 20 mg,	DB, MC, RCT Extension of a 12-week	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG,	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
40 mg, or 80 mg daily for 14 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for 14 weeks vs ezetimibe 10 mg once daily for 14 weeks vs placebo once daily for 14 weeks	study in patients, aged 22 to 83 years, with primary hyper-cholesterolemia (LDL-C between 145 mg/dL and 250 mg/dL and TG <350 mg/dL) who were randomized to ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg combination tablet, simvastatin 10, 20, 40, or 80 mg monotherapy, ezetimibe 10 mg, or placebo		TC, non-HDL, CRP, LDL:HDL cholesterol ratio, TC:HDL ratio, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL) Secondary: Not reported	baseline compared with the simvastatin monotherapy group (53.7% vs 38.8%; *P*<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TG, TC, non-HDL, CRP, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the simvastatin monotherapy group (*P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2% vs 47.9%; *P*<0.001). A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4% vs 7%; *P*<0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin and simvastatin monotherapy groups (7.4% vs 5.5%, respectively; *P* value not reported). Secondary: Not reported
Patel et al[68] Simvastatin 20 mg, in addition to placebo for 6 weeks vs ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 6 weeks	DB, MC, PG, RCT Patients 18-75 years of age with primary hypercholesterolemia and CHD (at least 3 months prior to baseline), not on lipid management therapy; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/l) at 6 weeks Secondary: Change in serum cholesterol, TG, HDL	Primary: Patients on the combination therapy experienced an additional LDL-C reduction of 14.6% compared to the simvastatin monotherapy group (95% CI, 10.1 to 19.1; *P*<0.0001). Significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (93% vs 75%, respectively; *P*<0.001). Patients on combination therapy were 5.1 times more likely to reach target LDL-C levels compared to patients on simvastatin alone (95% CI, 1.8 to 15.0; *P*=0.003). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or creatine kinase >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled hypertension, or body mass index ≥30 kg/m^2			Patients on the combination therapy experienced an additional TC reduction of 0.69 mmol/L compared to the simvastatin group (95% CI, 0.48 to 0.90; *P*<0.0001). Significantly greater proportion of patients in the combination therapy group reached TC target (<4 mmol/L) compared to simvastatin group (*P*<0.001). Greater reduction in TG was observed in the combination therapy group compared to the simvastatin group (20.4% vs 12.4%; *P*=0.06). There was no difference in the change of HDL level from baseline between the two groups (~6% increase in each group; *P* value not reported). There was no statistically significant difference in treatment emergent adverse events between the combination therapy and simvastatin groups (40% vs 25%; *P*=0.07).
Chenot et al[69] Simvastatin 40 mg daily vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities vs no lipid-lowering therapy	RCT Patients, average age 61 years, admitted for an AMI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission; patients were excluded if they had a thyroid disorder, inflammatory disease, neoplasia, serious hepatic disease, creatinine level >1.7 mg/dL, creatinine clearance <30 mL/min,	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL Secondary: Not reported	Primary: Patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (27%, 41%, and 51%, respectively; *P*<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (15%, 27%, and 25%, respectively; *P*<0.001). There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (*P*≥0.09). Patients on the ezetimibe/simvastatin combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day 4 (*P*=0.03) and day 7 (*P*=0.002) of the study. A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	CK >3 times the ULN, LDL-C <90 mg/dL, or were receiving potent 3A4 inhibitors			mg/dL, compared to the simvastatin monotherapy group at day 4 and day 7 (45% vs 5%, and 55% vs 10%, respectively; *P* value not reported). Secondary: Not reported
McKenney et al[70] COMPELL Rosuvastatin 10 mg for the first 4 weeks, titrated up to 20 mg on weeks 5-8, and 40 mg on weeks 9-12 vs atorvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to niacin SR 500 mg for the first 4 weeks, separate entities, titrated up to 1,000 mg on weeks 5-8, and 2,000 mg on weeks 9-12 vs simvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to ezetimibe 10 mg, separate entities, for 12 weeks vs	MC, OL, PG, RCT Adult patients ≥21 years of age with hypercholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with two consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL; patients were excluded if they had secondary dyslipidemia, known hypersensitivity to the study drugs, major organ system disease, severe hypertension, diabetes, major cardiovascular event within 12 months, severe heart failure, history of myopathy, active gout, life expectancy <2 years, active liver disease, creatinine clearance <30 mL/min, or uric acid >3 times the ULN	N=292 12 weeks	Primary: LDL-C level at week 12 Secondary: HDL-C level at week 12, non–HDL-C, TG, Lp(a), apo B, side effects	Primary: Patients randomized to atorvastatin/niacin SR, rosuvastatin/niacin SR, simvastatin/ezetimibe, and rosuvastatin therapies experienced similar reductions in LDL-C from baseline at week 12 of the study (56%, 51%, 57%, 53%, respectively; *P*=0.093). Secondary: Patients randomized to atorvastatin/niacin SR experienced a statistically significant increase in HDL-C from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (22%, 10%, and 7%, respectively; *P*≤0.05). There was no significant difference in the reduction of non–HDL-C from baseline among treatment groups (*P*=0.053). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in TG from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (47%, 33%, and 25%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in Lp(a) from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin 20 mg groups (–14%, +7%, and +18%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in apo B from baseline at week 12 of the study compared to the rosuvastatin group (43% vs 39%, respectively; *P*≤0.05). Side effects were similar across treatment groups (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
rosuvastatin 10 mg for the first 8 weeks, titrated up to 20 mg on weeks 9-12, in addition to niacin SR 500 mg, separate entities, for the first 4 weeks, titrated up to 1,000 mg on weeks 5-12				reported). There were no cases of myopathy or hepatotoxicity reported during the study period.
Primary Prevention of Coronary Heart Disease (CHD) Events				
Colhoun et al[71] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Patients between 40 and 75 years of age with type 2 diabetes without a history of CHD, LDL-C level ≤160 mg/dL, TG ≤600 mg/dL and at least one other CHD risk factor; patients were excluded if they had a past history of an MI, angina, coronary vascular surgery, cerebrovascular accident, severe vascular disease, serum creatinine >150 µmol/L, severe renal dysfunction, nephritic syndrome, HbA_{1c}>12%, or serum creatine kinase levels >3 times the ULN	N=2,838 3.9 years	Primary: Major cardiovascular events (CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral vascular disease requiring hospitalization or surgery), reduction in coronary revascularization,	Primary: Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point compared to control (95% CI, 17 to 52; *P*=0.001). Secondary: Atorvastatin treatment led to a 27% reduction in the relative risk of all-cause mortality compared to control (95% CI, 1 to 48; *P*=0.059). Atorvastatin treatment led to a 32% reduction in the relative risk of any cardiovascular end point compared to control (95% CI, 15 to 45; *P*=0.001). Atorvastatin therapy was associated with a significant reduction in stroke compared to control (1.5% vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89; *P* value not reported). Atorvastatin therapy was not associated with a significant reduction in coronary revascularization compared to control (HR, 0.69; 95% CI, 0.41 to 1.16; *P* value not reported). Atorvastatin treatment was associated with a 40% reduction in the LDL-C levels from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 26% reduction in the TC levels from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 1% increase in the HDL-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			lipid reduction	C level from baseline compared with control (*P*=0.0002). Atorvastatin treatment was associated with a 36% reduction in non–HDL-C level from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 19% reduction in the TG level from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 23% reduction in apo B level from baseline compared with control (*P*<0.0001). The frequency of adverse events was similar in all study groups (*P* value not reported).
Neil et al[72] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Post hoc analysis of CARDS study, evaluating safety and efficacy of atorvastatin in patients ≥65 years of age (see above)	N=2,838 3.9 years	Primary: Major cardiovascular events (acute CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality, acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral vascular disease	Primary: Atorvastatin treatment led to a 38% reduction in the relative risk of the primary end point in patients ≥65 years of age (95% CI, 8 to 58; absolute risk reduction [ARR], 3.9%, *P*=0.017). Consequently, 21 patients would need to be treated for 4 years to prevent one major cardiovascular event. Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; *P*=0.019). Consequently, 33 patients would need to be treated for 4 years to prevent one major cardiovascular event. Secondary: There was no statistically significant effect on all-cause mortality in either the <65 (*P*=0.98) or the ≥65 year old population (*P*=0.245). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the LDL-C levels among both the younger and the older patients (38% and 41%, respectively; *P*<0.001). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the TC levels among both the younger and the older patients (26% and 27%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			requiring hospitalization or surgery) among patients ≥65 and <65 years of age	Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the triglyceride level among both the younger and the older patients (*P*<0.001). The frequency of adverse events was similar in all treatment groups (*P* value not reported).
Hitman et al[73] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Subanalysis of CARDS study, evaluating stroke prevention with atorvastatin therapy (see above)	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke, type of stroke, risk factors for stroke Secondary: Not reported	Primary: Atorvastatin therapy was associated with a significant 48% reduction in stroke compared to control (1.5% vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; *P*=0.016). Atorvastatin therapy was associated with a significant 50% reduction in non-hemorrhagic stroke compared to control (1.1% vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; *P*=0.024). Atorvastatin therapy was associated with a significant 42% reduction in stroke or transient ischemic attacks compared to control (2.1% vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; *P*=0.019). Independent risk factors predicting stroke were age (HR, 2.3; *P*<0.001), microalbuminuria (HR, 2.0; *P*=0.007), and glycemic control (HR, 2.7; *P*=0.007). Women were at a lower risk for stroke than men (HR, 0.3; *P*=0.004). Secondary: Not reported
Sever, Dahlöf et al[74] ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood	DB, MC, RCT Patients between 40 and 79 years of age with either untreated or treated hypertension, TC ≤6.5 mmol/L, and not currently taking a statin or a fibrate; patients were also required to have >3 of	N=10,305 3.3 years	Primary: Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular	Primary: Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.50 to 0.83; *P*=0.0005). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 38% reduction in the primary end point, excluding silent MIs (HR, 0.62; 95% CI, 0.47 to 0.81; *P*=0.0005). Atorvastatin 10 mg daily was not associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pressure goals of <140 mm Hg and 90 mm Hg, respectively) vs placebo, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)	the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or transient ischemic attack, age >55 years, microalbuminuria or proteinuria, male sex, smoking, ratio of plasma TC to HDL-C of >6, or family history of CHD; patients were excluded if they had a previous MI, currently treated angina, cerebrovascular event within 3 months, fasting TG >4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormality		mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary end points, and total cardiovascular events and procedures	reduction in all-cause mortality (*P*=0.1649), cardiovascular mortality (*P*=0.5066), or fatal and nonfatal heart failure (*P*=0.5794) compared with control. Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for fatal and nonfatal strokes (HR, 0.73; 95% CI, 0.56 to 0.96; *P*=0.0236). Compared to placebo, atorvastatin 10 mg daily was associated with a 29% reduction in the risk for total coronary events (HR, 0.71; 95% CI, 0.59 to 0.86; *P*=0.005). Compared to placebo, atorvastatin 10 mg daily was associated with a 21% reduction in the risk for total cardiovascular events and procedures (HR, 0.79; 95% CI, 0.69 to 0.90; *P*=0.0005).
Sever, Poulter et al[75] ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as	DB, MC, RCT A two-year extension of the ASCOT-LLA trial (see above)	N=10,305 5.5 years	Primary: Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events,	Primary: Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.53 to 0.78; *P*≤0.0001). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 19% reduction in the risk for total cardiovascular events and procedures (HR, 0.81; 95% CI, 0.73 to 0.89; *P*≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively) vs placebo, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)			all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary end points, and total cardiovascular events	Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for total coronary events (HR, 0.73; 95% CI, 0.63 to 0.85; $P \leq 0.0001$). Compared to placebo, atorvastatin 10 mg daily was associated with a 37% reduction in the primary end point, excluding silent MIs (HR, 0.63; 95% CI, 0.51 to 0.77; $P \leq 0.0001$). Compared to placebo, atorvastatin 10 mg daily was associated with a 23% reduction in the risk for fatal and nonfatal strokes (HR, 0.77; 95% CI, 0.63 to 0.95; $P=0.0127$). Compared to placebo, atorvastatin 10 mg daily was associated with a 15% reduction in the risk for all-cause mortality (HR, 0.85; 95% CI, 0.74 to 0.98; $P=0.0219$). Atorvastatin 10 mg daily was not associated with a significant reduction in cardiovascular mortality ($P=0.1281$), or fatal and nonfatal heart failure ($P=0.9809$) compared with control.
Winkler et al[76] Fluvastatin 20 mg, 40 mg, and 80 mg (pooled group) vs placebo	MA Double-blind, randomized, placebo-controlled trials assessing ≥6 weeks of fluvastatin therapy in dyslipidemic patients with and without metabolic syndrome	N=7,043 (30 studies) ≥6 weeks	Primary: Major adverse cardiovascular events (MACEs) defined as CVD-related death, nonfatal MI, and cardiac revascularization, LDL-C, HDL-C, TC, TG, non–HDL-C, apo B Secondary: Not reported	Primary: Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of any MACE compared to placebo (16% vs 22%; HR, 0.728; 95% CI, 0.6 to 0.9; $P=0.001$). The difference in the incidence of MACE between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant ($P=0.083$). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death compared to placebo (3% vs 4.9%; HR, 0.62; 95% CI, 0.4 to 0.95; $P=0.03$). The difference in the incidence of cardiovascular death between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant ($P=0.478$). Among patients with metabolic syndrome, pooled fluvastatin was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				associated with a statistically significant reduction in the risk of a cardiovascular intervention compared to placebo (12% vs 16%; HR, 0.75; 95% CI, 0.59 to 0.93; *P*=0.011). The difference in the incidence of cardiovascular intervention between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.125). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death or nonfatal MI compared to placebo (6.6% vs 9.9%; HR, 0.65; 95% CI, 0.48 to 0.87; *P*=0.005). The difference in the incidence of cardiovascular death or nonfatal MI between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.288). There was no statistically significant difference in the incidence of nonfatal MI, all-cause mortality, or noncardiovascular-related death between pooled fluvastatin- and placebo-treated patients whether or not they had the metabolic syndrome (*P*>0.05). In all patients, pooled fluvastatin was associated with a significant reduction from baseline in LDL-C, TC, TG, non–HDL-C, and apo B compared to placebo (*P*<0.001). Patients with and without the metabolic syndrome taking fluvastatin experienced similar benefits in terms of LDL-C, TC, non–HDL-C, and apo B reduction from baseline (*P* value not reported). Patients with the metabolic syndrome experienced a greater increase in HDL-C and a greater reduction in TG from baseline compared to patients without the metabolic syndrome (*P*<0.01).
Downs et al[77] AFCAPS/TexCAPS Lovastatin 20 to 40 mg once daily	DB, MC, PC, RCT Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years on a	N=6,605 5.2 years	Primary First acute major coronary event, defined as fatal or nonfatal MI, unstable angina, or sudden	Primary After an average follow-up of 5.2 years, lovastatin-treated patients experienced a 37% lower incidence of the first acute major coronary event than patients receiving placebo (95% CI, 0.50 to 0.79; *P*<0.001). Secondary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo once daily	low-saturated fat, low-cholesterol diet, with TC 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL ≤45 mg/dL for men or ≤ 47 mg/dL for women and TG ≤400 mg/dL; without a prior history of MI, angina, claudication, cerebrovascular accident, or transient ischemic attack; patients with LDL-C between 125-129 mg/dL were included when the ratio of TC to HDL was more than 6		cardiac death during at least 5 years of follow-up without clinical evidence of atherosclerotic cardiovascular disease Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety and discontinuation rates	Lovastatin-treated patients had 33% reduction in revascularization (95% CI, 0.52 to 0.85; *P*=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; *P*=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; *P*=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; *P*=0.003), 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; *P*=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular mortality and CHD mortality events based on prespecified criteria (1.0% in lovastatin group vs 1.4% in placebo group and 0.6% in lovastatin group vs 0.9% in lovastatin group, respectively). The overall mortality rate and fatal and nonfatal cancer rates were similar in the lovastatin and placebo groups (*P* value not reported). Discontinuation rates due to adverse events were 13.6% in the lovastatin group and 13.8% in the placebo group (*P* value not reported). Both treatment groups had similar rates of serious adverse events (34.2% in lovastatin group vs 34.1% in placebo group; *P* value not reported).
The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP)[78] Pravastatin 20 to 40 daily vs placebo daily	DB, MC, PC, RCT Men and postmenopausal or surgically sterile women (mean of 55 years of age)	N=1,062 26 weeks	Primary: Lipid levels at 13 and 26 weeks and occurrence of cardiovascular events Secondary: Not reported	Primary: At week 13, when compared to placebo, pravastatin treatment was associated with significant reductions in LDL-C (26%), TC (19%), and TG (12%) and significant elevations in HDL-C (7%) (*P*<0.001). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the pravastatin and placebo groups. No MIs or cerebral infarctions occurred in the pravastatin group, and a total of 6 MIs and 3 cerebral infarctions occurred in the placebo group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group[79] ALLHAT-LLT Pravastatin 40 mg daily vs usual care Vigorous cholesterol-lowering therapy in the usual care group was discouraged.	MC, OL, RCT Patients aged ≥55 years, with stage 1 or stage 2 hypertension, at least 1 additional CHD risk factor, previously enrolled in the ALLHAT study, fasting LDL-C 120-189 mg/dL for patients with no known CHD or 100-129 mg/dL for patients with known CHD, fasting TG <350 mg/dL	N=10,355 Mean 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers	Primary: All-cause mortality did not differ significantly between treatment groups (RR, 0.99; 95% CI, 0.89 to 1.11; *P*=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower in the pravastatin group compared to the usual care group (RR, 0.91; 95% CI, 0.79 to 1.04; *P*=0.16). There were 209 total strokes in the pravastatin group and 231 in the usual care group (RR, 0.91; 95% CI, 0.75 to 1.09; *P*=0.31). Heart failure rates were similar in the pravastatin and usual care groups (RR, 0.99; 95% CI, 0.83 to 1.18; *P*=0.89). The 6-year cancer rates were similar in both groups (RR, 1.03; 95% CI, 0.89 to 1.19; *P*=0.66).
Nakamura et al[80] MEGA Pravastatin 10-20 mg daily in addition to the NCEP step I diet vs NCEP step I diet	OL, PRO, R Men and post-menopausal women aged 40-70 years weighing ≥40 kg, with hypercholesterolemia, without a history of CHD or familial hypercholesterolemia	N=8,214 Mean 5.2 years	Primary: CHD occurrence, sudden cardiac deaths, MIs, coronary revascularization Secondary: CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	Primary: Pravastatin therapy was associated with a reduced incidence of CHD compared to the control (3.3% vs 5%; HR, 0.67; 95% CI, 0.49 to 0.91; *P*=0.01). There was no statistically significant difference between the groups in either the incidence of sudden cardiac deaths or anginal episodes (*P*>0.05). Secondary: Pravastatin therapy was associated with a reduced incidence of MIs compared to the control (0.9% vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; *P*=0.03). Pravastatin therapy was associated with a reduced incidence of coronary revascularizations compared to the control (2% vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; *P*=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Pravastatin therapy was associated with a reduced incidence of CHD and cerebral infarctions compared to the control (5% vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; *P*=0.005). Pravastatin therapy was associated with a reduced incidence of all cardiovascular events compared to the control (6.4% vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01). There was no statistically significant difference between the groups in either all-cause mortality or the incidence of strokes (*P*>0.05).
Shepherd, Cobbe et al[81] WOSCOPS Pravastatin 40 mg daily vs placebo daily	DB, PC Men 45 to 64 years of age (mean of 55 years of age)	N=6,595 4.9 years	Primary: Occurrence of nonfatal MI or death from CHD as a first event Secondary: Occurrence of death from CHD and nonfatal MI	Primary: When compared to placebo, pravastatin produced a 31% reduction in the risk of the combined primary end point of definite nonfatal MI and death from CHD (95% CI, 17% to 43%; *P*<0.001). The absolute difference in the risk at five years was 2.4%. Secondary: The reduction in the risk of nonfatal MI was significant whether the definite cases of MI were considered alone or in combination with suspected cases (*P*≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with treatment (95% CI, 1% to 55%; *P*=0.042), but not in the analysis of definite cases alone (*P* value not reported). When the effect of pravastatin treatment on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3% to 53%; *P*=0.033). Additionally, pravastatin treatment was associated with a 31% reduction in the frequency of coronary angiography (95% CI, 10% to 47%; *P*=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11% to 56%; *P*=0.009).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ford et al[82] WOSCOPS Pravastatin 40 mg daily for 5 years, with follow-up for subsequent 10 years vs placebo daily for 5 years, with follow-up for subsequent 10 years	DB, RCT Extension of the WOSCOPS study. Male patients, 45 to 64 years of age, with hypercholesterolemia without a history of previous MI, two determinations of LDL-C level ≥155 mg/dL, with at least 1 value that was ≥174 mg/dL and 1 value that was ≤232 mg/dL	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality Secondary: Not reported	Primary: Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15-year period (11.8% vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; *P*<0.001). Pravastatin treatment led to a statistically significant reduction in the risk of death from all causes compared to placebo over a 15-year period (18.7% vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; *P*=0.03). Pravastatin treatment led to a statistically significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15-year period (7.6% vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96; *P*=0.01). Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD compared to placebo over a 15-year period (5.1% vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; *P*=0.02). Pravastatin treatment was associated with a small increase in the risk of death from stroke compared to placebo over a 15-year period (1.6% vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; *P*=0.14). Secondary: Not reported
Asselbergs et al[83] Pravastatin 40 mg once daily and fosinopril 20 mg once daily vs placebo two matching tablets once daily	DB, PC, RCT Patients aged 28-75 years with persistent microalbuminuria, blood pressure <160/100 mm Hg (not on antihypertensive medications), TC level <8.0 mmol/L, or <5.0 mmol/L in case of previous MI, and no use	N=864 46±7 months	Primary: Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity (nonfatal or myocardial ischemia, heart failure, peripheral vascular disease and/or	Primary: Pravastatin therapy was associated with a 13% reduction in the risk of the primary end point compared to placebo (4.8% vs 5.6%; *P*=0.649). The incidence of noncardiovascular mortality was 2.1% in the pravastatin group compared to 1.9% in the placebo group (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of lipid-lowering medication		cerebrovascular accident) Secondary: Not reported	
Heart Protection Study (HPS) Group[84] MRC/BHF Simvastatin 40 mg once daily vs placebo once daily	DB, MC, PC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and >65 years), with TC >135 mg/dL; patients were excluded if statins were contraindicated, if they had had an MI, stroke, or hospital admission for angina within the previous 6 months, if they had chronic liver disease or evidence of liver dysfunction, severe renal dysfunction, inflammatory muscle disease or evidence of muscle problems, concurrent treatment with cyclosporine, fibrates, or high-dose niacin, child-bearing potential, severe heart failure, or other conditions that might	N=20,536 (5,963 diabetics and 14,573 patients with occlusive arterial disease without diabetes) 5 years	Primary: Incidence of first nonfatal MI or coronary death, fatal or nonfatal stroke, revascularization procedures, first occurrence of major coronary events, strokes, and revascularizations Secondary: Not reported	Primary: Simvastatin treatment was associated with a 27% reduction in the incidence of first nonfatal MI or coronary death following randomization (95% CI, 21 to 33; *P*<0.0001) compared to placebo. Among diabetic patients, a 27% reduction in the incidence of first nonfatal MI or coronary death was observed with simvastatin therapy compared with placebo (95% CI, 19 to 34%; *P*<0.0001). Simvastatin treatment was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes following randomization (95% CI, 15 to 34; *P*<0.0001) compared to placebo. Simvastatin treatment was associated with a significant 26% reduction in the incidence of fatal strokes following randomization (95% CI, 14 to 36; *P*=0.0002) compared to placebo. Among diabetic patients, a 24% reduction in the incidence of fatal strokes was observed with simvastatin therapy compared to placebo (95% CI, 6 to 39; *P*=0.01). Simvastatin treatment was associated with a 24% proportional reduction in the incidence of first revascularization procedure following randomization compared with placebo (95% CI, 17 to 30; *P*<0.0001). Among diabetic patients, a 17% reduction in the incidence of first revascularization procedure was observed with simvastatin therapy compared to placebo (95% CI, 3 to 30; *P*=0.02). Simvastatin treatment was associated with a 24% reduction in the first occurrence of major coronary events, strokes, and revascularizations

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	limit long-term compliance			compared to placebo (95% CI, 19 to 28; *P*<0.0001). Among diabetic patients, a 22% reduction in the incidence of first occurrence of major coronary events, strokes, and revascularizations was observed with simvastatin therapy compared to placebo (95% CI, 13 to 30; P<0.0001). Secondary: Not reported
HPS Collaborative Group[85] Simvastatin 40 mg once daily vs placebo once daily	DB, MC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and ≥65 years), with TC ≥135 mg/dL; patients were excluded if statins were contraindicated, if they had had an MI, stroke, or hospital admission for angina within the previous 6 months, if they had chronic liver disease or evidence of liver dysfunction, severe renal dysfunction, inflammatory muscle disease or evidence of muscle problems, concurrent treatment with cyclosporine, fibrates, or high-dose	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), and first major vascular event (major coronary event, stroke or revascularization) Secondary: Not reported	Primary: In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of a major vascular event, compared to placebo (19.8% vs 25.2%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant 22% reduction in the first occurrence of a major vascular event, compared to placebo (26.4% vs 32.7%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant 25% reduction in the first occurrence of a major vascular event, compared to placebo (16.5% vs 21.5%; *P*<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.05). In the overall study sample, simvastatin resulted in a significant 27% reduction in the first occurrence of a major coronary event, compared to placebo (8.7% vs 11.8%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (10.9% vs 13.8%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (7.7% vs 10.8%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	niacin, child-bearing potential, severe heart failure, or other conditions that might limit long-term compliance			The difference in the reduction of the risk of major coronary events with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.03). In the overall study sample, simvastatin resulted in a significant 25% reduction in the first occurrence of stroke, compared to placebo (4.3% vs 5.7%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (5.3% vs 7.2%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (3.8% vs 5%; *P*<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.07). In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of revascularization, compared to placebo (9.1% vs 11.7%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (13.8% vs 17.9%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (6.9% vs 8.7%; *P*<0.0001). The difference in the reduction of the risk of revascularization with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the overall study sample, simvastatin resulted in a significant 16% reduction in the risk of first occurrence of a peripheral vascular event, compared to placebo (4.7% vs 5.5%; *P*=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes, or coronary disease (*P* value not reported). Secondary: Not reported
Baigent et al[86] Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 studies) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups, effect on stroke, cancer, and vascular procedures, vascular events	Primary: There was a 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL cholesterol (RR, 0.88, 95% CI, 0.84 to 0.91; *P*<0.0001). Statin therapy was associated with a 19% reduction in CHD mortality compared with control (3.4% vs 4.4%; RR, 0.81, 95% CI, 0.76 to 0.85; *P*<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared with control (1.2% vs 1.3%; RR, 0.93, 95 % CI, 0.83 to 1.03; *P* value not reported). Secondary: Statin therapy was associated with a 17% reduction in vascular mortality compared with control (4.7% vs 5.7%; RR, 0.83, 95% CI, 0.79 to 0.87; *P*<0.0001). Statin therapy was associated with a 21% reduction in major vascular events (RR, 0.79, 95% CI, 0.77 to 0.81; *P*<0.0001). Statin therapy was associated with a 26% reduction in nonfatal MI (RR, 0.74, 99% CI, 0.70 to 0.79; *P*<0.0001). Statin therapy was associated with a 23% reduction in any major coronary event (RR, 0.77, 95% CI, 0.74 to 0.80; *P*<0.0001). Statin therapy was associated with a 24% reduction in any coronary revascularization (RR, 0.76, 95% CI, 0.73 to 0.80; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Statin therapy was associated with a 21% reduction in any stroke (RR, 0.79, 95% CI, 0.77 to 0.81; *P*<0.0001). Statin therapy was not associated with a significant increase in the incidence of rhabdomyolysis compared to control (*P*=0.4).
Cholesterol Treatment Trialists' Collaborators[87] Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA, SA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 studies) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death), major vascular events among diabetic and non-diabetic patients	Primary: Among patients with diabetes, there was a 9% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.91, 99% CI, 0.82 to 1.01; *P*=0.02). Patients without diabetes experienced a 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.82 to 0.92; *P*<0.0001). Secondary: Patients with diabetes experienced a 13% reduction in vascular mortality per mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.76 to 1.00; *P*=0.008) and no effect on nonvascular mortality (RR, 0.97, 99% CI, 0.82 to 1.16; *P*=0.7). Among patients with diabetes, there was a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.72 to 0.86; *P*<0.0001). Patients without diabetes experienced a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.76 to 0.82; *P*<0.0001). Patients with diabetes experienced a 22% reduction in MI or coronary death (RR, 0.78, 99%CI, 0.69 to 0.87; *P*<0.0001), 25% reduction in coronary revascularization (RR, 0.75, 99% CI, 0.64 to 0.88; *P*<0.0001), and 21% reduction in stroke (RR, 0.79, 99% CI, 0.67 to 0.93; *P*=0.0002). After 5 years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				CI, 30 to 55; *P* value not reported). The benefit was greater among patients with diabetes and known vascular disease at baseline.
Secondary Prevention of CHD Events				
Pitt et al[88] AVERT Atorvastatin 80 mg daily vs percutaneous coronary transluminal angioplasty	MC, OL, R Patients, mean age 58.5 years, with stable CAD, LDL-C ≥115 mg/dL and TG ≤500 mg/dL, stenosis ≥50% in at least one coronary artery and had been recommended for treatment with percutaneous revascu-larization, asympto-matic or with Canadian Cardiovascular Society (CCS) class I or II angina, able to complete at least four minutes of a treadmill test or a bicycle exercise test without marked ECG changes indicative of ischemia; patients were excluded if they had left main CAD, triple-vessel disease, unstable angina or MI within the previous two weeks, and an ejection fraction <40%.	N=341 18 months	Primary: Number of ischemic events and/or need for revascularization, angina symptoms, adverse events Secondary: Not reported	Primary: Compared to revascularization procedure, atorvastatin 80 mg daily was associated with a lower incidence of ischemic events (21% vs 13%; *P*=0.048). Compared to revascularization procedure, atorvastatin 80 mg daily resulted in a significantly longer time to the first ischemic event (*P*=0.03). Compared to revascularization procedure, atorvastatin 80 mg/day resulted in a significantly smaller improvement in the CCS classification of angina symptoms (54% vs 41%; *P*=0.009). The adverse events observed in the study were similar in the two treatment groups (*P* value not reported). Secondary: Not reported
Knopp et al[89] ASPEN	DB, MC, PG, RCT Adult patients between	N=2,410 4 years	Primary: Time to occurrence of the composite	Primary: There was no statistically significant difference between atorvastatin and placebo groups in the time to first primary event (HR, 90; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atorvastatin 10 mg once daily vs placebo once daily	40 and 75 years of age with type 2 diabetes, defined by the World Health Organization, for at least 3 years prior to screening, LDL cholesterol ≤140 mg/dL (if they had a history of an MI, or an interventional procedure >3 months before screening) or LDL cholesterol ≤160 mg/dL, triglyceride level ≤600 mg/dL. Patients were excluded if they had type 1 diabetes, MI, interventional procedure, or episode of unstable angina ≤3 months before screening, HbA_{1C} >10%, active liver disease or hepatic dysfunction, severe renal insufficiency or nephritic syndrome, congestive heart failure treated with digoxin, creatine phosphokinase ≥3 times the ULN, blood pressure >160/100 mm Hg, BMI>35 kg/m^2, alcohol or drug abuse, hypersensitivity to the		clinical end point including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest, worsening or unstable angina requiring hospitalization Secondary: Time to occurrence of cardiovascular death, noncardiovascular death, transient ischemic attack, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed PAD, and acute ischemic heart failure requiring hospitalization, cholesterol level reduction, side effects	0.73 to 1.12; *P*=0.034). Less patients in the atorvastatin group experienced primary end points (13.7%) compared to the placebo group (15%) during the study period (*P*=0.034). Secondary: Atorvastatin group experienced a statistically significant decrease from baseline in the mean LDL-C (~29%) compared to the placebo group (1.6%; *P*<0.0001). Among patients without a prior history of an MI or interventional procedure, 10.4% of atorvastatin- and 10.8% of placebo-treated patients experienced a primary end point (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2% of atorvastatin- and 30.8% of placebo-treated patients experienced a primary end point (HR, 82; 95% CI, 0.59 to 1.15). Relative risk reductions in fatal and nonfatal MI were 27% overall (*P*=0.10), 19% for patients treated for primary protection (*P*=0.41), and 36% for patients treated for secondary protection (*P*=0.11). Adverse events were similar in both treatment groups for the total, primary, and secondary prevention groups (*P* value not reported). Serious adverse events occurred in 37.7% of patients in the atorvastatin groups and 35.4% of patients receiving placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	study drug, placebo run-in compliance rate <80%, current or planned pregnancy, use of excluded medications, or participation in another study within 30 days			
Schwartz et al[90] MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an acute coronary syndrome (ACS) vs placebo daily within 96 hours of hospital admission with an ACS	DB, I, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change from their usual anginal pattern; patients were excluded if the serum TC level at screening >270 mg/dL or were planned to have coronary revascul-arization, had Q-wave AMI within 4 weeks, CABG surgery within 3 months, PCI within 6 months, left bundle-branch block or paced ventricular rhythm, severe congestive heart	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospital-ization but without new objective evidence of ischemia, coronary revascu-larization, time to occurrence of any of	Primary: Compared to placebo, atorvastatin 80 mg daily resulted in a 16% reduction in the risk of a composite end point of death, nonfatal AMI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4% vs 14.8%; *P*=0.048). Secondary: Compared to placebo, atorvastatin 80 mg daily resulted in a 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; *P*=0.02). Compared to placebo, atorvastatin 80 mg daily resulted in a 50% reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; *P*=0.045). There were no significant differences between groups in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least 1 secondary end point, or occurrence of at least 1 primary or secondary end point (*P* value not reported). Liver transaminase elevation was more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	failure, severe anemia, renal failure requiring dialysis, hepatic dysfunction, insulin-dependent diabetes, pregnancy, were lactating or taking concurrent treatment with other lipid-regulating agents or drugs associated with rhabdomyolysis		the above, and percent change in lipid levels from baseline, safety	
Olsson et al[91] MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an ACS vs placebo daily within 96 hours of hospital admission with an ACS	DB, I, MC, RCT Post hoc analysis of MIRACL study evaluating atorvastatin therapy in patients ≥65 years of age; patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change from their usual anginal pattern (see above for exclusion criteria)	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring	Primary: Compared to placebo, atorvastatin treatment led to a 14% reduction in the relative risk of the primary end point in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; *P*=0.18). Compared to placebo, atorvastatin treatment led to a 22% reduction in the relative risk of the primary end point in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; *P*=0.11). Secondary: There was no statistically significant difference in any of the secondary end points between the ≥65 and the <65 age groups (*P*>0.05). The frequency of adverse events was similar in all treatment groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hospitalization but without new objective evidence of ischemia, coronary revascularization, time to occurrence of any of the above, and percent change in lipid levels from baseline among patients ≥65 and <65 years of age	
Athyros, Papageorgiou et al[92] GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, congestive heart failure, revascularization (coronary morbidity), and stroke Secondary: Safety	Primary: Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 51% reduction in the risk for CHD recurrent events or death (24.5% vs 12%; *P*<0.0001). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 43% reduction in all-cause mortality (5% vs 2.9%; *P*=0.0021). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of stroke (2.1% vs 1.1%; *P*=0.034). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of coronary mortality (4.8% vs 2.5%; *P*=0.0017). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 54% reduction in the risk of coronary morbidity (*P*<0.0001). Atorvastatin 10 mg titrated to 80 mg daily was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31%, non–HDL-C by 44%, and an increase in HDL-C by 7% (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP LDL-C treatment goals (3% vs 95%, respectively; *P* value not reported). Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP non–HDL-C treatment goals (14% vs 97%, respectively; *P* value not reported). Secondary: Withdrawals due to adverse effects were similar in the atorvastatin and placebo groups (0.75% vs 0.4%; *P* value not reported).
Athyros, Mikhailidis et al[93] GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents, for other risk factors (ie, diabetes, hypertension)	SA Post hoc analysis of the GREACE study; adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria, stratified by the presence of metabolic syndrome	N=1,600 3 years	Primary: Vascular events, estimated GFR, serum uric acid level Secondary: Not reported	Primary: Compared to the usual care, daily statin therapy was associated with a 43% reduction in LDL-C from baseline ($P<0.0001$). Among patients with metabolic syndrome, statin therapy was associated with a significant 57% reduction in the incidence of vascular events compared with usual therapy (12.1% vs 28%; RR, 0.43; 95% CI, 0.20 to 0.64; $P<0.0001$). Among patients without metabolic syndrome, statin therapy was associated with a significant 41% reduction in the incidence of vascular events compared with usual therapy (RR, 0.59; 95% CI, 0.41 to 0.79; $P<0.0001$). Statin therapy was associated with a significant increase in GFR and a reduction in serum uric acid level from baseline ($P<0.05$), regardless of metabolic syndrome status. Usual therapy was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline ($P<0.05$), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with statin therapy ($P=0.02$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Serruys et al[94] LIPS Fluvastatin 40 mg twice daily vs placebo twice daily	DB, MC, PC, RCT Men and women aged 18 to 80 years with angina or silent ischemia following successful completion of their first PCI, with baseline TC levels between 135 and 270 mg/dL, with fasting TG <400 mg/dL	N=1,677 3-4 years	Primary: Development of major adverse cardiac events (MACE), defined as cardiac death, nonfatal MI or a reintervention procedure of CABG or repeat PCI Secondary: MACE excluding reintervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, cardiac mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI, and treatment effects on measured lipid levels, discontinuation rates, tolerability, and safety	Primary: MACE-free survival time was significantly longer in the fluvastatin group (*P*=0.01) compared to placebo. Significantly less patients in the fluvastatin group had a MACE compared to patients in the placebo group (21.4% vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; *P*=0.01). During the follow-up period, 13 patients in the fluvastatin group (1.5%) compared to 24 patients in the placebo group (2.9%) died from cardiac causes, 30 patients in the fluvastatin group (3.6%) compared to 38 patients in the placebo group (4.6%) had a nonfatal MI and 167 patients in the fluvastatin group (19.8%) compared to193 patients in the placebo group (23.2%) underwent CABG or PCI (*P* value not reported). Secondary: The risk of MACE, excluding reintervention procedures (surgical or PCI), occurring in the first 6 months of follow-up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; *P*<0.001) in the fluvastatin group than in the placebo group. There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI between the two groups (*P*=0.07, *P*=0.07 and *P*=0.08, respectively). At week 6, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25% to 29%) compared with an 11% reduction seen in the placebo group (95% CI, 9% to 13%; *P*<0.001). Triglyceride reductions were greater in the fluvastatin group compared to placebo (22% vs 14%; *P* value not reported). Levels of HDL increased by a median of 22% in both groups (*P* value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reported). Discontinuation rates due to adverse events were 21.2% in the fluvastatin group and 24.0% in the placebo group. Death rates due to noncardiac causes were 2.7% in the fluvastatin group and 3.0% in the placebo group. There were 3 reported cases of elevations in creatine kinase levels of ≥10 times the ULN in the placebo group. There were 10 patients in the fluvastatin group and 3 patients in the placebo group who had elevations of ≥3 times the ULN level in AST or ALT on 2 consecutive occasions. Cancers were reported in 46 patients in the fluvastatin group and 49 in the placebo group.
Liem et al[95] FLORIDA Fluvastatin 80 mg daily vs placebo daily	DB, PC, PG, RCT Patients, mean age 61 years, with an AMI and TC of <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes, or a new pathological Q wave of ≥0.04 seconds duration, or ≥25% of the corresponding R wave amplitude, both in at least two contiguous leads	N=540 1 year	Primary Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event during the study Secondary: 6-week and 12-month occurrence of ischemia on the ambulatory ECG, the 6-week and 12-month change in ischemic burden, the 12-month change in lipid profile, safety and tolerability	Primary At 12 months, fluvastatin treatment did not significantly affect ischemia on ambulatory ECG (*P*=0.67), nor the occurrence of any major clinical event (*P*=0.24) when compared to placebo. Secondary In patients with ischemia at baseline, 29% in the fluvastatin group and 38% in the placebo group were ischemic on the ambulatory ECG at 6 weeks and 27% in the fluvastatin group and 21% in the placebo group were again positive for ischemia at 12 months (*P* value not reported). The 6-week and 12-month ischemic burden was lowered by 6.1% and 7.7%, respectively in the fluvastatin group and by 10.5% and 13%, respectively in the placebo group (*P*=0.81 and *P*=0.43, respectively between treatment groups) After 12 months, treatment with fluvastatin lowered LDL-C by 21% compared to a 9% increase in the placebo group (*P*<0.001). There were 62 patients in the fluvastatin group and 68 patients in the placebo group who had at least one major clinical event (*P*=0.764). All-cause mortality was 2.6% in the fluvastatin group vs 4% in the placebo group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sacks et al[96] CARE Pravastatin 40 mg once daily vs placebo once daily	DB, MC, RCT Post MI patients, mean age 59 years, (including men and postmenopausal women), with plasma TC levels <240 mg/dL, LDL-C between 115-174 mg/dL, triglyceride <350 mg/dL, glucose levels ≤220 mg/dL, left ventricular ejection fractions ≥25 percent, and no symptomatic congestive heart failure	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden death, death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum creatine kinase Secondary: Not reported	Primary: When compared with the placebo group, a 24% lower incidence of the primary end point was observed in the pravastatin group (13.2% vs 10.2%; 95% CI, 9% to 36%; *P*=0.003). Pravastatin therapy was associated with a 23% risk reduction in nonfatal MIs compared with placebo (*P*=0.02). The pravastatin group experienced a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, –5 to 62; *P*=0.07) and a 25% reduction in the rate of total MIs (95% CI, 8 to 39; *P*=0.06) compared with placebo. Secondary: Not reported
The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group[97] Pravastatin 40 mg once daily vs placebo once daily	DB, MC, PC Men and women 31 to 75 years of age, who were post MI or had a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry	N=9,014 6.1 years	Primary: Death from CHD Secondary: Incidence of MI, stroke, rate of CABG surgery	Primary: The incidence of the primary study end point of death from CHD was 6.4% in the pravastatin group, as compared with 8.3% in the placebo group (relative reduction in risk, 24%; 95% CI, 12% to 35%; *P*<0.001). Secondary: Pravastatin therapy was associated with a significant 29% reduction in the incidence of MI compared with placebo (7.4% vs 10.3%; *P*<0.001). Pravastatin therapy was associated with a significant 19% reduction in the incidence of stroke compared with placebo (3.7% vs 4.5%; *P*=0.048). Pravastatin therapy was associated with a significant 22% reduction in the risk of CABG surgery compared with placebo (9.2% vs 11.6%; *P*<0.001). Pravastatin therapy was associated with a significant 19% reduction in the risk of coronary angioplasty compared with placebo (4.7% vs 5.6%; *P*=0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Pravastatin therapy was associated with a significant 12% reduction in the risk of unstable angina compared with placebo (22.3% vs 24.6%; *P*=0.005).
Shepherd, Blauw et al[98] PROSPER Pravastatin 40 mg once daily vs placebo once daily	DB, MC, PC, RCT Men and women aged 70-82 years with pre-existing vascular disease (coronary, cerebral, or peripheral) or at an increased risk of such disease due to risk factors (smoking, hypertension, or diabetes), with plasma TC 4.0-9.0 mmol/L, TG <6.0 mmol/L	N=5,804 Mean 3.2 years (range 2.8 to 4.0 years)	Primary: Combined end point of definite or suspect death from CHD, nonfatal MI, and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of cognitive function, adverse events, cancer	Primary: Pravastatin therapy was associated with a significant 15% reduction in the risk of the primary end point compared to placebo (14.1% vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; *P*=0.014). Secondary: When the primary end point was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin therapy, but no apparent effect on cerebrovascular events (*P* value not reported). Pravastatin therapy was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1% vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94, *P*=0.006). When examining the rates of fatal or nonfatal stroke, there was no significant difference between pravastatin and placebo (HR, 1.03; 95% CI, 0.81 to 1.31, *P*=0.81). There was no significant difference in cognitive function between the pravastatin and the placebo groups (*P*>0.05). The rate of serious adverse events reported was similar between both pravastatin and placebo groups (56% vs 55%, respectively; *P* value not reported). There were no participants in either group with rhabdomyolysis or CK concentrations greater than 10 times the ULN (*P* value not reported). There were no significant differences in the rates of cancer development between groups (*P*>0.05).
Thompson et al[99] PACT	DB, MC, PC, RCT Patients aged 18-85	N=3,408 4 weeks	Primary: Composite of death from any cause, AMI,	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary end point compared with placebo (*P*=0.48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pravastatin 20-40 mg daily vs placebo daily	years with <24 hours onset of symptoms and diagnosis of AMI or unstable angina pectoris		or readmission to hospital with unstable angina pectoris during the first month following randomization Secondary: Incidence of individual causes of death, AMI other than the index event, readmission for angina in the first month, urgent or unscheduled revascularization procedure, other nonfatal cardiovascular events, adverse events	Secondary: There were no significant differences in the frequency of individual components of the primary end point in the 30 days after random assignment among patients assigned to pravastatin compared to placebo (*P*>0.05). The frequency of adverse events did not differ between the study groups (*P* value not reported).
Scandinavian Simvastatin Survival Study (4S) Group[100] Simvastatin 10 mg daily titrated up to 40 mg daily vs placebo daily	DB, PC, RCT Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Primary: Simvastatin therapy was associated with a 30% reduction in all-cause mortality compared with placebo (8% vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; *P*=0.0003). Secondary: Overall, more patients in the placebo group experienced at least one secondary event compared to the simvastatin group (28% vs 19%, respectively; *P* value not reported). There were 189 (8.5%) coronary deaths in the placebo group compared with 111 (5.0%) coronary deaths in the simvastatin group (RR, 0.58; 95% CI, 0.46 to 0.73; *P* value not reported). Definite AMI occurred in 270 (12.1%) patients in the placebo group compared with 164 (7.4%) patients in the simvastatin group. Definite or probable AMI occurred in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				418 (18.8%) patients in the placebo group compared with 279 (12.6%) patients in the simvastatin group. Silent MI occurred in 110 (4.9%) patients in the placebo group compared with 88 (4.0%) patients in the simvastatin group. Resuscitated cardiac arrest occurred in 1 patient who was in the simvastatin group. Additionally, a cerebrovascular event occurred in 95 (4.3%) patients in the placebo group compared with 61 (2.7%) patients in the simvastatin group. (RR, 95% CI, and *P* values were not reported for these end points.)
Chonchol et al[101] Scandinavian Simvastatin Survival Study (4S) Simvastatin 10 mg daily titrated up to 40 mg daily vs placebo daily	SA Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 mL/min/1.73 m^2 or <75 mL/min/1.73 m^2	N=4,444 (4,420 included in the subanalysis) 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Primary: Simvastatin therapy was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91; *P* value not reported). Secondary: Simvastatin therapy was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80; *P* value not reported). Simvastatin therapy was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79; *P* value not reported). Simvastatin therapy was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79; *P* value not reported). Simvastatin therapy was not associated with a significant reduction in the incidence of strokes among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36; *P* value not reported). There were no statistically significant differences in any of the outcome measures between patients with or without chronic renal insufficiency (*P*>0.44).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
de Lemos et al[102] A to Z trial Simvastatin 40 mg daily for 1 month, titrated up to 80 mg daily vs placebo daily for 4 months, then simvastatin 20 mg daily	DB, MC, PC Patients with either non–ST-elevation ACS or ST-elevation MI; median of 61 years of age	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation), and stroke Secondary: Individual components of the primary end point, revascularization due to documented ischemia, all-cause mortality, new-onset congestive heart failure (requiring admission or initiation of heart failure medications), and cardiovascular rehospitalization	Primary: Simvastatin 80-mg therapy was associated with a significant reduction in the risk of the primary end point compared to simvastatin 20-mg therapy (14.4% vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; *P*=0.14). Secondary: Simvastatin 80-mg therapy was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20-mg therapy (HR, 0.75; 95% CI, 0.57 to 1.00; *P*=0.05). There was no significant difference observed between treatment groups in the secondary end points of MI, readmission for ACS, revascularization due to documented ischemia, or stroke (*P*>0.05). Simvastatin 80-mg therapy was associated with a significant reduction in the risk of new onset congestive heart failure compared to simvastatin 20-mg therapy (3.7% vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; *P*=0.04).
Briel et al[103] Statins (pravastatin 10-40 mg, fluvastatin 80 mg, atorvastatin 20-80 mg, simvastatin 40-80 mg) vs placebo	MA Randomized, placebo-controlled trials in patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS, and with a follow-up ≥30 days; studies were excluded if they compared 2 different	N=13,024 (12 studies) ≥30 days	Primary: Composite end point of nonfatal MI, nonfatal stroke, and total death Secondary: Total death, total MI, total stroke, cardiovascular death, fatal/nonfatal MI, revascularization	Primary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in the primary end point between patients randomized to early statin therapy or placebo (*P*=0.39 and *P*=0.30, respectively). Secondary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in any of the secondary end points (except for unstable angina) between patients randomized to early statin therapy or placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	statins or included patients with a history of heart transplantation		procedures (CABG surgery, angioplasty), and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)	At 4 months of therapy, patients in the early statin group experienced moderate reduction in the incidence of unstable angina compared to the placebo group (*P*=0.05).
Mood et al[104] Statins (atorvastatin 20-40 mg daily, pravastatin 40 mg daily, fluvastatin 40 mg twice daily) vs placebo	MA Randomized controlled studies comparing statin therapy to placebo or usual care, initiated around the time of a PCI; studies evaluating patients right after an AMI or unstable angina were excluded	N=3,941 (6 studies) up to 45 months	Primary: Incidence of an MI Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous revascularization, or stroke	Primary: Compared to placebo, statin therapy was associated with a 43% reduction in the risk for MI (5.2% vs 3.0%; OR, 0.57; 95% CI, 0.42 to 0.78; *P*<0.0001). Secondary: Compared to placebo, statin therapy was associated with a 26% reduction in all-cause mortality (3% vs 2.3%; OR, 0.74; 95% CI, 0.50 to 1.1; *P*=0.14). Compared to placebo, statin therapy was associated with a 42% reduction in cardiovascular mortality (1.2% vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; *P*=0.10). Compared to placebo, statin therapy was associated with an 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9% vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; *P*=0.098). The incidence of stroke was higher in the statin group compared to the placebo arm (0.4% vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; *P*=0.18).
Afilalo, Duque et al[105] Moderate statin therapy (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 20-40 mg daily)	MA Randomized controlled trials with at least 6 months of follow-up evaluating ≥50 elderly patients with CHD randomized to a statin	N=19,569 (9 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, revascularization, nonfatal MI Secondary:	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared with placebo (15.6% vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89; *P* value not reported). Statin therapy was associated with a reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	or placebo		Not reported	0.70; 95% CI, 0.53 to 0.83), and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94). The calculated number needed to treat with statin therapy to save 1 life was 28 (95% CI, 15 to 56). Secondary: Not reported
Bushnell et al[106] Statins vs no statins	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes Secondary: Not reported	Primary: Patients reporting the use of statin therapy had lower rates of stroke at 90 days of follow-up (HR, 0.72; 95% CI, 0.53-0.97; *P* value not reported). Statin use was not associated with a significant reduction in stroke mortality (*P*=0.8). Women had an increased risk of experiencing a severe stroke compared with men (*P*=0.035). Statin use was not associated with a significant reduction in stroke severity among women (*P*=0.096). Secondary: Not reported
O'Regan et al[107] Statins (atorvastatin 10-80 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg, pravastatin 10-40 mg, lovastatin 20-73 mg) vs placebo	MA Randomized trials evaluating the effect of statin therapy on all-cause mortality, all-stroke incidence, fatal strokes, hemorrhagic, or ischemic strokes; studies were excluded if reported only surrogate outcomes (eg, LDL-C, HDL-C levels)	N=121,285 (41 primary prevention studies, 1 secondary prevention study) Up to 6 years	Primary All-cause mortality, all-stroke incidence Secondary Incidence of cardiovascular deaths, nonhemorrhagic cerebrovascular events, hemorrhagic strokes, fatal strokes	Primary Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91; *P* value not reported). Secondary: Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of nonhemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically nonsignificant reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21; *P* value not reported). A meta-regression analysis determined that every unit increase in LDL was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 0.1.0005 to 1.006; *P*=0.02).
LaRosa, Grundy, Waters et al[108] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT Patients between 35-75 years of age, with CHD (either previous MI, coronary revascu-larization, angina with objective evidence of coronary disease); patients were excluded if they had hypersensitivity to statin drugs, current liver disease, nephritic syndrome, pregnancy, uncontrolled CHD risk factors (diabetes, hypertension, etc.), CHD event or revascu-larization within a month, congestive heart	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 22% reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; *P*=0.021). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dl reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (*P*=0.002) and a 0.5% relative risk reduction in stroke (*P*=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	failure, unexplained creatine kinase elevation >6 times the ULN, life-threatening malignancy, immunosuppressive or lipid-lowering drug treatment.		event, side effects	group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; *P*=0.004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for heart failure (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no statistically significant difference between groups in the incidence of death from CHD (3.3% vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01). There was no statistically significant difference between groups in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; *P*=0.89). There was no statistically significant difference between groups in the incidence of peripheral artery disease (5.6% vs 5.5%; HR, 0.97; 95% CI, 0.83-1.15; *P*=0.76). There was no statistically significant difference between groups in the incidence of death from any cause (5.6% vs 5.7%; HR, 1.01; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.85 to 1.19; *P*=0.92). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; *P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; *P*<0.001).
Waters et al[109] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT Subanalysis of TNT study evaluating effects of high-dose atorvastatin on cerebrovascular events; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) (see above for exclusion criteria)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; *P*=0.021). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (*P*=0.002) and a 0.5% relative risk reduction in stroke (*P*=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; *P*=0.004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no statistically significant difference between groups in the incidence of transient ischemic attacks (*P*=0.099). There was no statistically significant difference between groups in the incidence of death from CHD (*P*=0.087). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; *P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; *P*<0.001).
Deedwania, Barter et al[110] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients with metabolic syndrome; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary	N=10,001 (subanalysis: N=5,584) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with metabolic syndrome Secondary: Any occurrence of a major coronary event,	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 29% reduction in the incidence of primary end point among patient with metabolic syndrome (13% vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; *P*<0.0001). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events among patients with metabolic syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; *P*=0.011). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disease) and metabolic syndrome (see above for exclusion criteria)		cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with metabolic syndrome	coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; *P*=0.0004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for congestive heart failure among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; *P*=0.027). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with metabolic syndrome (*P* value not reported).
Shepherd, Barter et al[111] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin in patients with diabetes; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for	N=10,001 (subanalysis: N=1,501) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with diabetes Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 25% reduction in the incidence of primary end point among patients with diabetes (17.9% vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; *P*=0.026). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the time to any cardiovascular events among patients with diabetes (HR, 0.85; 95% CI, 0.73 to 1.00; *P*=0.044). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 31% reduction in the incidence of time to the first cerebrovascular event among patients with diabetes (HR, 0.69; 95% CI, 0.48 to 0.98; *P*=0.037).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	exclusion criteria)		for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with diabetes	There was no statistically significant difference between groups in the incidence of cerebrovascular events among patients with diabetes (*P*=0.437). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; *P*=0.202). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; *P*=0.075). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; *P*=0.203). There was no statistically significant difference between groups in the incidence of major coronary events among patients with diabetes (*P*=0.922). There was no statistically significant difference between groups in the incidence of any coronary events among patients with diabetes (*P*=0.192). There was no statistically significant difference between groups in the incidence of any cardiovascular events among patients with diabetes (*P*=0.458). There was no statistically significant difference between groups in the incidence of major cardiovascular events among patients with diabetes (*P*=0.689). There was no statistically significant difference between groups in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				incidence of hospitalization with heart failure among patients with diabetes (*P*=0.277). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with diabetes (*P*=0.521). There was no statistically significant difference between groups in the incidence of PAD among patients with diabetes (*P*=0.789). There was no statistically significant difference between groups in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes (*P* value not reported).
Wenger et al[112] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients ≥65 years of age; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	N=10,001 (subanalysis: N=3,809) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients ≥65 years of age Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients ≥65 years of age	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 19% reduction in the incidence of primary end point among patients ≥65 years of age (12.6% vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; *P*=0.032). Consequently, in treating 35 patients with atorvastatin 80 mg versus atorvastatin 10 mg, one cardiovascular event could be prevented over a 5-year period. Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (*P*=0.010). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients ≥65 years of age (HR, 0.79; 95% CI, 0.60-1.03; *P*=0.084). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57-1.09; *P*=0.158). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group was not associated with a significant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to 1.29; *P*=0.59). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; *P*=0.70). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (*P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (*P*<0.001). Compared to atorvastatin 10 mg group, atorvastatin 80 mg group was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (*P*=0.008). There was no statistically significant difference between groups in the incidence of major coronary events among patients ≥65 years of age (*P*=0.128). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; *P*=0.55). Compared to the atorvastatin 10 mg group, more patients in the atorvastatin 80 mg group died from noncardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; *P*=0.129). More patients ≥65 years of age randomized to the atorvastatin 80 mg group experienced treatment-related adverse events compared to the atorvastatin 10 mg group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Khush et al[113] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin on hospitalization for heart failure; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	N=10,001 5 years	Primary: Hospitalization for heart failure among patients with and without a history of heart failure Secondary: Not reported	Primary: Prior history of heart failure is a significant risk factor for hospitalization from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the study period (*P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3% vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; *P*=0.008). Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15% vs 4.9%; *P*<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (*P*=0.007). Secondary: Not reported
LaRosa, Grundy, Kastelein et al[114] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of VLDL-C levels achieved with atorvastatin on cardiovascular end points and mortality; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary	N=10,001 (subanalysis: N=9,769) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and	Primary: Patients in the lowest quintiles were associated with the most reduction in the primary end point (*P*<0.0001). Secondary: Patients in the lowest quintiles were associated with the most reduction in the risk of death from CHD (*P*<0.01). Patients in the lowest quintiles were associated with the most reduction in the risk of nonfatal MIs (*P*<0.0001). Patients in the lowest quintiles were associated with the most reduction in the risk of stroke (*P*<0.05). There were no significant differences in the incidence of all-cause mortality across quintiles (*P*=0.104).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)		≥106 mg/dL (Quintile 5) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4, or 5 (from above)	There were no significant differences in the incidence of cardiovascular mortality across quintiles (*P*=0.060). There were no significant differences in the incidence of all-cause mortality across quintiles (*P*=0.653). There were no significant differences in the incidence of treatment-related adverse effects across quintiles (*P* value not reported).
Barter et al[115] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of HDL-C levels achieved with atorvastatin on cardiovascular end points; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria	N=10,001 (subanalysis: N=9,770) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48 to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5) Secondary:	Primary: Patients in the highest HDL-C quintiles were associated with the greatest reduction in the primary end point (*P*=0.04). Compared to patients in Quintile 1, patients classified as Quintile 5 had a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in the HDL-C reduces the risk of major cardiovascular events by 1.1% at 3 months (*P*=0.003). Patients with the lowest ratio of LDL-C to HDL-C were at a lower risk for major cardiovascular events (*P*=0.006). Patients with the lowest ratio of TC to HDL-C were at a lower risk for major cardiovascular events (*P* value not reported). Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C quintile were at the lowest risk for a major cardiovascular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	event (*P*=0.03). Secondary: Not reported
Shepherd, Kastelein et al[116] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Subanalysis of TNT study evaluating nephroprotective effects of atorvastatin; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	N=10,001 (subanalysis: N=9,770) 5 years	Primary: GFR Secondary: Not reported	Primary: Patients randomized to atorvastatin 80 mg daily experienced a significant increase in GFR from baseline over a 5-year study period compared with the atorvastatin 10 mg daily group (*P*<0.0001). Secondary: Not reported
Pedersen et al[117] IDEAL Atorvastatin 80 mg daily vs simvastatin 20 mg daily	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines; patients were excluded if they had liver enzyme elevation >2 times the ULN, pregnancy or breastfeeding, nephrotic syndrome, uncontrolled diabetes, uncontrolled hypothyroidism, plasma	N=8,888 ~4.8 years	Primary: Occurrence of a major coronary event (coronary death, confirmed nonfatal AMI, or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary revascularization	Primary: Atorvastatin therapy was associated with a nonsignificant reduction in the risk of a major coronary events compared with simvastatin therapy (9.3% vs 10.4%; HR, 0.89; *P*=0.07). Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of a nonfatal MI compared with simvastatin therapy (6% vs 7.2%; HR, 83; *P*=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of major cardiovascular events compared with simvastatin therapy (12% vs 13.7%; HR, 87; *P*=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of any cardiovascular events compared with simvastatin therapy (26.5% vs 30.8%; HR, 84; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	triglyceride levels >600 mg/dL, congestive heart failure, valvular heart disease, malabsorption condition, treatment with other drugs interfering with statin therapy, and treatment with other lipid-lowering drugs		procedure, or hospitalization for unstable angina), any cardiovascular events	Atorvastatin therapy was associated with a significant reduction in the risk of any CHD event compared with simvastatin therapy (20.2% vs 23.8%; HR, 84; *P*<0.001). Atorvastatin therapy was associated with a significant reduction in the risk of peripheral vascular disease compared with simvastatin therapy (2.9% vs 3.8%; HR, 76; *P*=0.02). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of death from noncardiovascular cause compared with simvastatin therapy (3.2% vs 3.5%; HR, 92; *P*=0.47). Atorvastatin therapy was associated with a nonsignificant reduction in the risk fatal/nonfatal stroke compared with simvastatin therapy (3.4% vs 3.9%; HR, 87; *P*=0.20). Atorvastatin therapy was associated with a nonsignificant reduction in the risk hospitalization for nonfatal heart failure compared with simvastatin therapy (2.2% vs 2.8%; HR, 81; *P*=0.11). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of all-cause mortality compared with simvastatin therapy (8.2% vs 8.4%; HR, 98; *P*=0.81). Atorvastatin therapy was associated with a higher rate of drug discontinuations due to adverse effects compared with simvastatin therapy (9.6% vs 4.2%; *P*<0.001). Atorvastatin therapy was associated with a higher rate of liver transaminase elevations compared with simvastatin therapy (*P*<0.001). There was no significant difference between treatment groups in the incidence of serious adverse events (*P*=0.42).
Cannon, Braunwald et al[118] PROVE IT–TIMI 22	DB, DD, MC, RCT Men and women ≥18	N=4,162 Up to 3 years	Primary Rates of composite death from any cause,	Primary The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization, and stroke at two years

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atorvastatin 80mg daily vs pravastatin 40mg daily	years of age (mean age 58.9 years), in stable condition after a hospitalization for an ACS with either an AMI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to six months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL	(mean 2 years)	MI, documented unstable angina requiring hospitalization, revascularization, and stroke Secondary Risk of death due to CHD, nonfatal MI, or revascularization and the risk of the individual components of the primary end points, discontinuation rates, tolerability and side effects	were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, representing a 16% reduction in the hazard ratio favoring atorvastatin (95% CI, 5% to 26%; *P*=0.005). Secondary The risk of death due to CHD, nonfatal MI, or revascularization was reduced by 14% in the atorvastatin group (*P*=0.029) with a two-year event rate of 19.7% compared with 22.3% in the pravastatin group. The risk of death, MI, or urgent revascularization was reduced by 25% in the atorvastatin group (*P*<0.001). Among the individual components of the primary end point, atorvastatin-treated patients had significant reduction of 14% for revascularization (*P*=0.04) and a 29% reduction in the risk of recurrent unstable angina (*P*=0.02) compared to the pravastatin group. There were nonsignificant reductions in the rates of death or MI (18%, *P*=0.06) and the rates of stroke (*P* value not reported) between the two groups. The discontinuation rates due to adverse events or for other reasons were 21.4% in the pravastatin group and 22.8% in the atorvastatin group at one year (*P*=0.30) and 33% and 30.4%, respectively at two years (*P*=0.11). Discontinuation rates due to myalgias or muscle aches or elevation in creatine kinase levels were 2.7% in the pravastatin group and 3.3% in the atorvastatin group (*P*=0.23). There were 1.1% of patients in the pravastatin group and 3.3% in the atorvastatin group who had elevations in ALT levels that were ≥3 times the ULN (*P*<0.001).
Ray, Cannon et al[119] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs	DB, RCT Subanalysis of PROVE IT-TIMI 22 study evaluating the timing of effects with statin therapy; patients, mean age 58.9 years, with an ACS within 10 days of	N=4,162 up to 3 years (mean 2 years)	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke	Primary: At 30 days, 3% of intensive regimen group experienced a primary end point compared with 4.2% in the standard treatment group (HR, 72; 95% CI, 0.52 to 0.99; *P*=0.046). From 6 months to the end of the study, 15.1% of intensive regimen group experienced a primary end point compared with 17.7% in the standard treatment group (HR, 82; 95% CI, 0.69 to 0.99; *P*=0.037).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pravastatin 40 mg daily (standard regimen)	randomization, stable for at least 24 hours (see above for exclusion criteria)		Secondary: A composite of death, MI, or unstable angina requiring hospitalization	Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of the triple composite end point compared with pravastatin therapy (15.7% vs 20%; HR, 76; 95% CI, 0.66 to 0.88; *P*=0.0002). At 30 days, patients randomized to the intensive statin regimen experienced a greater reduction in LDL-C and CRP level from baseline compared to the standard statin regimen group (*P*<0.001).
Ahmed et al[120] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients with diabetes; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours (see above for exclusion criteria)	N=4,162 Up to 3 years (mean 2 years)	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI, or CABG surgery occurring within 30 days after randomization, or stroke within 2 years after study onset Secondary: A composite of death, MI, or unstable angina requiring hospitalization, LDL-C <70 mg/dL goal, hsCRP <2 mg/L goal, MI, unstable angina requiring hospitalization	Primary: There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point among patients with diabetes (31.8% vs 28.4%; HR, 88; *P*=0.28). Secondary: Intensive atorvastatin therapy resulted in a significantly lower event rate for the secondary composite end point compared with the standard pravastatin regimen among patients with diabetes (21.1% vs 26.6%; HR, 0.75; *P*=0.03) and patients without diabetes (14% vs 18%; HR, 0.76; *P*=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with intensive statin regimen would prevent 55 and 40 events, respectively (*P* value not reported). Compared with nondiabetic patients, fewer patients with diabetes on the intensive statin regimen achieved the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L (37.6% vs 45.4%; *P*=0.004). Out of diabetic patients treated with intensive statin therapy, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L. Diabetic patients who reached the dual LDL-C/CRP goal had significantly lower rates of the secondary end point compared to patients who failed to reach the goal (17.7% vs 24.7%; *P*=0.021). In the diabetic population, among the individual components of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				primary and secondary composite end points, the only variable exhibiting a statistically significant reduction with intensive statin therapy compared with the standard regimen was unstable angina requiring hospitalization (3.1% vs 7.4%; *P*=0.003).
Scirica et al[121] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	DB, DD, RCT Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin on hospitalization for heart failure; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours, with TC <240 mg/dL (see above for exclusion criteria)	N=4,162 up to 3 years (mean 2 years)	Primary: Hospitalization for heart failure occurring at least 30 days after randomization Secondary: Not reported	Primary: Patients randomized to the intensive statin group experienced a statistically significant reduction in the rate of hospitalization for heart failure compared to the control group (1.6% vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; *P*=0.008). The benefit observed with the intensive statin therapy was independent on recurrent MI or prior history of heart failure. Higher B-type natriuretic peptide (BNP) was associated with an increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; *P*=0.016). Among patients with a high BNP level (>80 pg/mL), intensive statin therapy was associated with a lower incidence of heart failure compared to patients randomized to the standard statin regimen (HR, 0.32; 95% CI, 0.13 to 0.8; *P*=0.014). Secondary: Not reported
Ray, Bach et al[122] Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients ≥70 years of age. Patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours; patients were excluded if they had uncontrolled diabetes (fasting plasma	N=4,162 up to 3 years (mean 2 years)	Primary: Cardiac mortality, MI, unstable angina requiring hospitalization, relationship between NCEP goal and a composite primary end point of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke	Primary: At 30 days, a greater proportion of patients in both age groups randomized to atorvastatin therapy achieved the NCEP goals compared with pravastatin therapy (*P*<0.001). Among the elderly, the achievement of the NCEP LDL-C goal was associated with an 8% reduction in the risk of primary end point from baseline (*P*=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary end point from baseline (*P*=0.013). Younger patients were associated with a lower risk of the primary composite end point compared to the older age group (23% vs 30.4%; *P* <0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	glucose ≥230 mg/dL, an episode of hyperosmolar non-ketotic coma or ketoacidosis) within 6 months of study onset, stratified by age <70 and ≥70 years		Secondary: A composite of death, MI, or unstable angina requiring hospitalization	Younger patients were associated with a lower risk of all-cause mortality (*P*<0.0001), MIs (*P*<0.0001), unstable angina requiring hospitalization (*P*=0.01), or strokes (*P*=0.004) compared to the older age group**.** Secondary: The composite triple end point occurred more frequently in the elderly compared to the younger age group (20.1% vs 11%; HR, 1.93; 95% CI, 1.59 to 2.33; *P*<0.0001).
Deedwania, Stone et al[123] SAGE Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	DB, DD, MC, PG, RCT Ambulatory CAD patients, between 65 and 85 years of age, with ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48-hour ambulatory ECG at screening, and baseline LDL-C level between 100 mg/dL and 250 mg/dL; patients were excluded if they had atrial fibrillation or heart failure, NYHA stage III or IV	N=893 12 months	Primary: Absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 12 Secondary: Absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 3, the percent change in the total duration of myocardial ischemia from baseline to months 3 and 12, the absolute and percent change in the number of ischemic episodes from baseline to months 3 and 12, the percent change in ischemic burden, the proportion of patients	Primary: At 12 months, the total duration of ischemia was significantly reduced from baseline in both groups (*P*<0.001). There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point (*P*=0.88). Secondary: There were no statistically significant differences between the pravastatin and atorvastatin groups in any of the secondary end points assessing degree of ischemia at month 3 or 12 (*P* value not reported). Atorvastatin therapy was associated with a 77% reduction in all-cause mortality relative to pravastatin therapy over a 12-months period (HR, 0.33; 95% CI, 0.13 to 0.83; *P*=0.014). Compared with pravastatin, therapy with atorvastatin was associated with a significantly greater reductions in TC, LDL-C, TG, and apo B at months 3 and 12 (*P*<0.001). Compared with atorvastatin, therapy with pravastatin was associated with a significantly greater increase in the level of HDL cholesterol at months 3 (*P*<0.001) and 12 (*P*=0.009). Atorvastatin therapy was associated with a higher incidence of liver test abnormalities compared to pravastatin therapy (17.3% vs 13.9%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			free of ischemia at months 3 and 12, the percent change in the levels of TC, LDL-C, HDL, TG, and apo B	There were no statistically significant differences between the pravastatin and atorvastatin groups in treatment related adverse events (13.9% vs 17.3%; *P*=0.17).
Sakamoto et al[20] MUSASHI-AMI Lipophilic statins* (atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) within 96 hours of hospital admission with an AMI vs hydrophilic statin* (pravastatin 9.4 mg) within 96 hours of hospital admission with an AMI Pitavastatin is not commercially available in the Unites States. * Doses represent the mean daily doses evaluated in the study.	I, MC, RCT Patients, mean age 63.5 years, randomized to statin or no statin therapy within 96 hours of an AMI, with TC between 190 and 240 mg/dL	N=486 ~416 days	Primary: A composite end point of ACS events, such as cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, heart failure requiring emergent rehospitalization, new Q-wave appearance on the ECG	Primary: Hydrophilic statin therapy was associated with a lower incidence of ACS events compared to the lipophilic statin therapy (3.6% vs 9.9%; *P*=0.053). Secondary: Hydrophilic statin therapy was associated with a lower incidence of new Q-wave appearance on the ECG compared to the lipophilic statin therapy (75% vs 89%; *P*=0.0056). There was no statistically significant difference in any of the other secondary end points between the two groups (*P*=0.339).
Hulten et al[124] Intensive statin therapy (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 80 mg daily,	MA Randomized controlled trials in adults started on intensive statin therapy or control	N=17,963 (13 studies) Up to 2 years of follow-up	Primary: Composite end point of death, recurrent ischemia, and recurrent MI, death and cardiovascular	Primary: In patients with recent ACS, intensive statin therapy was associated with lower mortality and cardiovascular events over 24 months of follow-up (HR, 0.81; 95% CI, 0.77 to 0.87; *P*<0.001). In patients with recent ACS, intensive statin therapy was associated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 20 mg daily, atorvastatin 80 mg daily) vs placebo or lower-dosed statin therapy	within 14 days of hospitalization for ACS		events, cardiovascular death, ischemia, MI, LDL-C reduction, side effects Secondary: Not reported	with a lower risk of overall cardiovascular events over 24 months of follow-up (HR, 0.84; 95% CI, 0.76 to 0.94; *P* value not reported). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow-up (HR, 0.76; 95% CI, 0.66 to 0.87). In patients with recent ACS, intensive statin therapy was associated with lower ischemia over 24 months of follow-up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow-up (HR, 0.89; 95% CI, 0.60 to 1.33). Intensive statin therapy was associated with a greater reduction in LDL-C compared with controls (*P*<0.001). Adverse effects were similar with the intensive statin therapy and the controls (*P* value not reported). Secondary: Not reported
Afilalo, Majdan et al[125] Moderate statin therapy (pravastatin ≤40 mg daily, lovastatin ≤40 mg daily, fluvastatin ≤40 mg daily, simvastatin ≤20 mg daily, atorvastatin ≤10 mg daily, rosuvastatin ≤5 mg daily) vs intensive statin therapy (simvastatin 80 mg daily,	MA Randomized controlled trials with at least 6 months of follow-up evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 (6 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 80 mg daily, rosuvastatin 20-40 mg daily)				with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event. In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95% CI, 0.64-0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one patient to experience an adverse hepatic event. Secondary: Not reported
Cannon, Steinberg et al[126] Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily, atorvastatin 10 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 studies) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI, the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina, or revascularization), incidence of stroke, incidence of	Primary: Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4% vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; *P*<0.00001). Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3% vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; *P*<0.0000001). Intensive statin therapy was associated with a reduction in cardiovascular mortality of 12% compared to moderate statin therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			cardiovascular, non-cardiovascular, and all-cause mortality Secondary: Not reported	(3.8% vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; *P*=0.054). Intensive statin therapy was not associated with lower non-cardiovascular mortality compared to the moderate statin therapy (*P*=0.73). Intensive statin therapy was not associated with statistically significant reduction in all-cause mortality compared to the moderate statin therapy (6.2% vs 5.9%; *P*=0.20). Intensive statin therapy was associated with an overall significant odds reduction of 18% for stroke compared to moderate statin therapy (2.8% vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; *P*=0.012). Intensive statin therapy was associated with an overall significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; *P*<0.0001). Secondary: Not reported
Murphy et al[127] A to Z PROVE-IT–TIMI 22 Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS, clinically stable for 12-24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=8,658 (2 studies) Up to 2 years	Primary: Incidence of cardiovascular, non-cardiovascular, and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality, compared to moderate statin therapy (3.6% vs 4.9%; HR, 0.77; 95% CI, 0.63 to 0.95; *P*=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality, compared to moderate statin therapy (2.6% vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; *P*=0.025). Intensive statin therapy was not associated with a significant reduction in the risk of noncardiovascular mortality, compared to moderate statin therapy (1% vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; *P*=0.32). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Adverse Effects				
Silva, Swanson et al[128] Statins (atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	MA Randomized, prospective studies comparing statin therapy with placebo with a follow-up >6 weeks, reporting data on nonfatal adverse events	N=71,108 (18 studies) up to 317 weeks	Primary: Adverse events, cardiovascular events Secondary: Not reported	Primary: Statin therapy increased the risk of any adverse events by 39% compared with placebo (OR, 1.4; 95% CI, 1.09 to 1.80; *P*=0.008). Consequently, out of 197 patients treated with statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; *P* value not reported). Statin therapy was associated with a 26% reduction in the risk of a clinical cardiovascular event compared with placebo (OR, 0.74; 95% CI, 0.69 to 0.80; *P*<0.001). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular event was 27. Rosuvastatin studies were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin= simvastatin= lovastatin> fluvastatin. Secondary: Not reported
Kashani et al[129] Statins (atorvastatin 20-80 mg, fluvastatin 2.5-80 mg, lovastatin 10-80 mg, pravastatin 10-160 mg, rosuvastatin 1-80 mg, simvastatin 2.5-80 mg) vs placebo	MA Randomized, double-blinded studies comparing statin therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events; all studies were required to randomly allocate ≥100 patients to statin monotherapy vs placebo	N=74,102 (35 studies) up to 65 months	Primary: Adverse events (myalgia, CK elevation, rhabdomyolysis, transaminase elevation), discontinuation due to adverse event; results expressed in terms of the risk difference (RD) per 100 patients Secondary: Not reported	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (RD, 2.7; 95% CI, –3.2 to 8.7; *P*=0.37), CK elevation (RD, 0.2; 95% CI, –0.6 to 0.9; *P*=0.64), rhabdomyolysis (RD, 0.4; 95% CI, –0.1 to 0.9; *P*=0.13), or discontinuation due to adverse events (RD, –0.5; 95% CI, –4.3 to 3.3; *P*=0.80) compared with placebo. Statin therapy was associated with a statistically significant risk of transaminase elevations (RD, 4.2; 95% CI, 1.5 to 6.9; *P*<0.01) compared with placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a statistically significant increase in the risk of myalgias (*P*=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When individual statins were compared to placebo, fluvastatin (*P*<0.01) and lovastatin (*P*=0.05) were the only statins with a statistically significant increase in the risk of transaminase elevation. Secondary: Not reported
McClure et al[130] Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg daily lovastatin equivalent dose vs placebo	MA Randomized, controlled, double-blind studies comparing statin therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events	N=86,000 (119 studies) Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdomyolysis), discontinuations due to adverse events; results expressed in terms of Peto odds ratios (POR), in order to account for rare or zero events Secondary: Not reported	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (POR, 1.09; 95% CI, 0.97 to 1.23; *P*=0.471), rhabdomyolysis (POR, 1.59; 95% CI, 0.54 to 4.70; *P*=0.544), or myositis (POR, 2.56; 95% CI, 1.12 to 5.85; *P*=0.987) compared with placebo. Statin therapy was associated with a lower incidence of discontinuations due to adverse events (POR, 0.88; 95% CI, 0.84 to 0.93; *P*<0.001) compared with placebo. Secondary: Not reported
Newman et al[131] Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily vs placebo once daily	MA Studies evaluating adverse effects of atorvastatin administered to patients with various cardiovascular risks, LDL-C level ≥130 mg/dL and triglyceride level ≤600 mg/dL	N=14,236 (42 studies) Between 2 weeks and 52 months	Primary: Adverse effects Secondary: Not reported	Primary: Treatment-related side effects were similar across all study groups (*P* value not reported). Treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively (*P* value not reported). No cases of rhabdomyolysis were reported among the study groups (*P* value not reported). Elevations in hepatic transaminases >3 times the ULN were observed in 0.1%, 0.6%, and 0.2% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Shepherd, Hunninghake et al[132] Rosuvastatin 5-40 mg once daily vs atorvastatin 10-80 mg once daily vs simvastatin 10-80 mg once daily vs pravastatin 10-40 mg once daily vs placebo once daily	MA Randomized, controlled studies comparing statin therapy with placebo or comparator statins in patients with dyslipidemia; patients with secondary dyslipidemia or with a history of serious hypersensitivity reaction to statin therapy were excluded	N=16,876 (33 studies) 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-positive proteinuria, estimated glomerular rate Secondary: Not reported	Primary: The incidence of adverse events was similar in the rosuvastatin and the placebo groups (52.1% vs 51.8%, respectively; *P* value not reported). The incidence of adverse events was similar across all the active treatment groups (*P* value not reported). The incidence of elevation in transaminases, and CK, myopathy, dipstick-positive proteinuria, and estimated glomerular rate was similar across all the active treatment groups (*P* value not reported). Secondary: Not reported
Dale et al[133] Intensive-dose statin therapy including hydrophilic statins (atorvastatin 80 mg) and lipophilic statins (simvastatin 40-80 mg, lovastatin 76 mg) vs moderate-dose statin	MA Randomized, comparative studies comparing intensive- and moderate-dose statin therapies in at least 100 patients, with a follow-up ≥48 weeks, reporting data on the incidence of elevations in AST, ALT or CK	N=21,765 (9 studies) up to 5 years	Primary: Incidence of elevations in AST, ALT or CK Secondary: Not reported	Primary: Intensive statin therapy was associated with an increased risk of AST, or ALT elevation, compared to the moderate-dose statin therapy (1.5% vs 0.4%; RR, 3.10; 95% CI, 1.72 to 5.58; *P*=0.002). Intensive statin therapy was not associated with a statistically significant risk of CK elevation, compared to the moderate-dose statin therapy (0.1% vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; *P*=0.89). In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive-dose statin group, patients on lipophilic intensive-dose statin therapy experienced a non–statistically significant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy including hydrophilic statins (atorvastatin 10 mg, pravastatin 40 mg) and lipophilic statins (simvastatin 20-40 mg, lovastatin 4 mg)				27.35; *P*≥0.11). Secondary: Not reported
Silva, Matthews et al[134] Intensive-dose statin therapy (atorvastatin 80 mg, simvastatin 80 mg) vs moderate-dose statin therapy (atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg)	MA Randomized, comparative studies comparing intensive- and moderate-dose statin therapies for the reduction of secondary cardiovascular events in patients with ACS or stable CAD	N=27,548 (4 studies) ~3.4 years	Primary: CK ≥10 times the ULN, with or without myalgia, ALT or AST ≥3 times the ULN, rhabdomyolysis, drug-induced adverse effects requiring drug discontinuation, any drug-induced adverse event, all-cause mortality, cardiovascular death, nonfatal MI, and stroke Secondary: Not reported	Primary: Intensive statin therapy was associated with an increased risk of any adverse event compared with the moderate-dose statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; *P*<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; *P* value not reported). Intensive statin therapy was associated with an increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; *P*≤0.001). Intensive statin therapy was associated with an increased risk (absolute risk, 1.2%) of an elevation in AST/ALT ≥3 times the ULN (OR, 4.84; 95% CI, 3.27 to 6.16; *P*≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST/ALT ≥3 times the ULN (95% CI, 72 to 106; *P* value not reported). Intensive statin therapy was associated with an increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the ULN (OR, 9.97; 95% CI, 1.28 to 77.92; *P*=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the ULN (*P* value not reported). There was no statistically significant difference in the incidence of rhabdomyolysis between the study groups (*P* value not reported). Intensive statin therapy was not associated with a significant reduction in all-cause mortality compared to the moderate-dose statin therapy (*P*=0.185).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (*P*=0.031), nonfatal MI (*P*<0.001), and stroke (*P*=0.004). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular death, MI, or stroke was 229, 99, and 166, respectively. Secondary: Not reported
Law et al[135] Statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin); doses were not reported vs placebo	Systematic Review Cohort studies, randomized, placebo-controlled studies, voluntary adverse events notification to national regulatory authorities, and published individual case reports	2 cohort studies and 21 RCTs (N=not reported) Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal failure, elevated ALT, renal failure, proteinuria, peripheral neuropathy Secondary: Not reported	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and randomized, controlled studies was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years (*P* value not reported). The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years (*P* value not reported). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 4 times higher in patients receiving lovastatin, simvastatin, or atorvastatin compared with those on monotherapy with fluvastatin or pravastatin (*P*<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25) compared with those on statin monotherapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79; *P*<0.001). The incidence of myopathy associated with the use of statins in randomized, controlled studies was 5 (95% CI, –17 to 27) per 100,000 patient-years (*P* value not reported). The incidence of liver failure associated with the use of statins, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Statin use in patients with elevated ALT would lead to liver disease in <1 person (*P* value not reported). Statin use was not associated with a higher incidence of renal failure or proteinuria than with placebo (*P* value not reported). Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared with placebo (95% CI, 1.1 to 3.0; *P*<0.001). Secondary: Not reported

Study abbreviations: ARR=absolute risk reduction, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, FU=follow-up, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MN=multinational, I=international, OR=odds ratio, OL=open label, PC=placebo-controlled, PG=parallel group, POR=Peto odds ratio, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=risk ratio or relative risk, SB=single blind, SA=subanalysis
Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, ALT=alanine transaminase, AMI=acute myocardial infarction, apo AI=apoliprotein AI, apo B=apolipoprotein B, apo E=apoliprotein E, AST=aspartate aminotransferase, BMI=body mass index, BP=blood pressure, CABG=coronary artery bypass graft, CAC=coronary artery calcification, CAD=coronary artery disease, CCS=Canadian Cardiovascular Society, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CK=creatine kinase, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, CVD=cardiovascular disease, CVD=cerebrovascular disease, ECG=electrocardiogram, FBG=fasting blood glucose, FPG=fasting plasma glucose, FSG=fasting serum glucose, GFR=glomerular filtration rate, HbA_{1c}=hemoglobin A1c, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IMT= intima-medial thickness, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MACE=major adverse cardiac events, MI=myocardial infarction, NCEP=National Cholesterol Education Program, NCEP ATP III=National Cholesterol Education Program, Adult Treatment Panel III, NYHA=New York Heart Association , PAD=peripheral arterial disease, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, TAV=total atheroma volume, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

Additional Evidence

Dose Simplification:
Given that most of the body's cholesterol is synthesized at night and most of the statins have a short half-life, statins exhibit optimal lipid-lowering effects when administered in the evening. Atorvastatin, rosuvastatin, and the sustained-release fluvastatin may be taken at any time during the day due to their longer half-lives.[1, 2,136-138]

A study by Wongwiwatthananukit et al evaluated the difference in safety and efficacy between a once-daily rosuvastatin 10 mg dose and an every-other-day rosuvastatin 10 mg dose administered to 80 patients with primary hypercholesterolemia.[139] Patients were followed for 8 weeks. A significantly larger reduction in low-density lipoprotein cholesterol (LDL-C) levels was observed in the once-daily compared to the every-other-day rosuvastatin group (48% vs 39%, respectively; P=0.011). In addition, total cholesterol (TC) and triglyceride (TG) reduction was greater in the once-daily group (P<0.05). However, there was no statistically significant difference between the groups in the percentage of patients achieving their NCEP ATP III LDL-C goals (P=0.18).

An evidence-based medicine literature search did not reveal data on the effect of dosing schedules on adherence.

Stable Therapy:
A transition period is generally not necessary when transferring patients from one statin to another. The first agent may be discontinued abruptly and the other agent may be started at once.[1] However, liver function tests should be performed approximately three months after either an initiation of a new statin or an increase in dose, and semiannually thereafter.[1]

Cheetham et al evaluated the safety and efficacy of converting from the brand name simvastatin to generic lovastatin.[140] With more than 33,000 patients, this study demonstrated successful conversion of simvastatin to lovastatin with relatively few adverse effects, while maintaining efficacy. Patients switching to lovastatin therapy experienced a reduction in LDL-C, an increase in high-density lipoprotein cholesterol (HDL-C) and a decrease in TG. Rates of alanine aminotransferase and creatine kinase elevations were not found to be significantly different before and after conversion.

Usher-Smith et al examined the consequences of switching patients (N=65) from atorvastatin to simvastatin in a 2-year retrospective analysis.[141] Patients initially receiving atorvastatin 10 mg and 20 mg were converted to simvastatin 10-20 mg or 40 mg, respectively. The change in therapy was not associated with a statistically significant alteration in baseline total cholesterol level (P=0.06).

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Single Entity HMG-CoA Reductase Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
atorvastatin	tablet	Lipitor®	$$$	N/A
fluvastatin	capsule, sustained-release tablet	Lescol®, Lescol XL®	$$$	N/A
lovastatin	sustained-release tablet, tablets	Altoprev®, Mevacor®*	$$$$-$$$$$	$$$
pravastatin	tablet	Pravachol®*	$$$$	$$$
rosuvastatin	tablet	Crestor®	$$$	N/A
simvastatin	tablet	Zocor®*	$$$$	$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The single entity HMG-CoA reductase inhibitors (statins) are FDA approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[1,4-10] Atorvastatin, rosuvastatin, and simvastatin are also FDA approved for the treatment of homozygous familial hyperlipidemia in adjunction with other lipid-lowering treatments. Atorvastatin, lovastatin, pravastatin, and simvastatin are indicated for primary prevention of cardiovascular events in patients at risk but without clinically evident coronary heart disease (CHD). Atorvastatin, fluvastatin, pravastatin and simvastatin are also FDA approved for secondary prevention of cardiovascular events in patients with clinically evident CHD. To date, rosuvastatin has not been approved for the primary and/or secondary prevention of cardiovascular events but has been shown to reduce the rate of change in carotid intima-media thickness and atheroma volume.[1,9,25,26] Rosuvastatin is the only statin without an FDA indication for use in pediatric patients with heterozygous familial hypercholesterolemia. All these agents are formulated for once-daily oral administration, with lovastatin and fluvastatin available as sustained-release tablet formulations. Subsequent to their longer half-life, atorvastatin, rosuvastatin, and sustained-release fluvastatin may be taken at any time of the day, while the other statins should be administered in the evening. Lovastatin, pravastatin, and simvastatin are available generically.

The agents in this class have demonstrated a significant benefit in reducing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and modestly increasing high-density lipoprotein cholesterol (HDL-C).[1,2,4-11,27-122] With the exception of rosuvastatin, the statins have been shown to reduce the risk of all-cause mortality, cardiovascular mortality, and cardiovascular morbidity. All of the statins have demonstrated the ability to delay the progression of coronary atherosclerosis among patients with and without established CHD. Furthermore, numerous studies have demonstrated the added benefit of aggressive lipid-lowering with statin therapy in reaching NCEP ATP III LDL-C goals as well as prolonging CHD-free survival.[52-54,101-122]

All statins may cause an elevation in liver enzymes and creatinine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure. Consequently, liver function tests should be performed routinely with statin therapy. However, statins are generally well-tolerated and the common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. There are some differences among the statins with regards to drug interactions. Pravastatin is the only statin with low protein binding, leading to a lower risk of a drug interaction with warfarin. Pravastatin and rosuvastatin do not undergo extensive first-pass metabolism and are

therefore associated with a low risk for drug-drug interactions.[1,2,18] Atorvastatin, lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin is metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles as noted in Table 6. In patients with severe renal impairment, atorvastatin and fluvastatin are the only statins that do not require dosage adjustments.[1,2] All statins are contraindicated in patients with active liver disease.

The NCEP ATP III guidelines and the European Guidelines on Cardiovascular Disease Prevention designate statins as first-line agents for the treatment of patients with hypercholesterolemia, failing therapeutic lifestyle modification, at high risk for cardiovascular events as well as patients suffering from heterozygous familial hypercholesterolemia.[11,12] High-dose statin therapy is also recognized as moderately effective for patients with homozygous familial hypercholesterolemia.[12] The NCEP ATP III guidelines have established criteria for initiating lipid-lowering therapy. According to the criteria, the target LDL-C level <100 mg/dL is a therapeutic goal for patients with established CHD or CHD risk equivalent (ie, diabetes); however, an LDL-C goal of <70 mg/dL may be arbitrarily preferred for these high-risk patients. In addition, LDL-C goals of <130 mg/dL and <160 mg/dL are designated for patients at moderate and low risk for CHD, respectively. While the statins differ in their LDL-lowering potential as noted in Table 2, there are no clinical studies that have demonstrated that one statin is more efficacious than another with regards to clinical outcomes. If LDL-C goal is not reached after 6 weeks of therapy with a statin, either an elevation of dose or the addition of a second lipid-lowering agent is appropriate.[12]

At least one HMG-CoA reductase inhibitor (atorvastatin, lovastatin, pravastatin or simvastatin) that has demonstrated positive morbidity and mortality outcomes and at least one high-potency HMG Co-A reductase inhibitor (atorvastatin, rosuvastatin or simvastatin) should be available on the Alabama Medicaid Preferred Drug List (PDL). Lovastatin, pravastatin and simvastatin are available generically and are on the Alabama Medicaid PDL. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand single entity HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HMG-CoA Reductase Inhibitors
Combination Products
AHFS Class 240608
May 14, 2008

I. Overview

The combination hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") include fixed-dose combinations of atorvastatin with amlodipine, lovastatin with extended-release niacin, and simvastatin with ezetimibe. All agents are formulated for oral administration. HMG-CoA reductase inhibitors work by inhibiting HMG-CoA reductase.[1] HMG-CoA reductase is the rate-limiting enzyme in the hepatic cholesterol synthesis, which catalyzes the conversion of HMG-CoA to mevalonate, a cholesterol precursor. Cholesterol synthesis reduction leads to the up-regulation of hepatic low-density lipoprotein cholesterol (LDL-C) receptors and subsequently an enhanced clearance of circulating LDL-C.

Niacin (nicotinic acid) is a water-soluble, B complex vitamin.[2] The exact mechanism by which niacin lowers cholesterol and triglycerides is not completely understood but is independent of the drug's role as a vitamin. Reductions in LDL-C through reduced hepatic synthesis of very low-density lipoprotein cholesterol (VLDL-C) are primarily responsible for the antilipemic effect of niacin.[2,3] Niacin may decrease production of VLDL-C by partially inhibiting mobilization of free fatty acids from adipose tissue, decreasing delivery of free fatty acids to the liver, decreasing triglyceride synthesis and altering the hepatic production of apolipoprotein B. Niacin increases high-density lipoprotein cholesterol (HDL-C) by reducing its catabolism.

Ezetimibe, a cholesterol absorption inhibitor, blocks dietary and biliary cholesterol absorption from the small intestine, leading to a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately lower systemic cholesterol levels.[4-7] Ezetimibe differs chemically and pharmacologically from other antilipemic agents, and because of its different mechanism of action it has been investigated for possible additive effects on lipid levels.[4,5] Clinical studies documented in the product information for ezetimibe showed that when used alone, it reduced LDL-C by up to 18% while increasing HDL-C by up to 3%.[5] Product information for the simvastatin-ezetimibe combination cites LDL-C reductions of up to 60% with an increase in HDL-C levels of up to 10%.[7]

Amlodipine is a dihydropyridine calcium-channel blocking agent that is indicated for the treatment of hypertension, for the treatment of chronic stable angina or vasospastic angina, and to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).[8,9]

All combination sttains are FDA-approved for the treatment of primary hyperlipidemia.[7,10,11] Atorvastatin-amlodipine and lovastatin-niacin extended-release combination products are also indicated for the prevention of cardiovascular events.[10,11] Simvastatin-ezetimibe lacks the indication for primary and/or secondary prevention of cardiovascular events.[7] In general, combination statins are appropriate when both components of the formulation are indicated.[4,10,12]

At present, no combination statins are available generically. Some of their components, namely lovastatin, simvastatin, and amlodipine, are available generically[12]; the new generics for simvastatin and amlodipine have been approved since the last review of this class for Alabama Medicaid in February 2006.[12] In accordance with Preferred Drug Legislation for Alabama Medicaid, this review does not include information on Simcor®, a combination of simvastatin and extended-release niacin, because it has not been on the market for 6 months or more. This medication will be reviewed at a future time.

Combination HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Combination HMG-CoA Reductase Inhibitors Included in this Review

Generic Name*	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
atorvastatin and amlodipine	tablet	Caduet®	Caduet®
lovastatin and niacin	extended-release tablet	Advicor®	none
simvastatin and ezetimibe	tablet	Vytorin®	none

*No generic products are available in this class.

All statins lower cholesterol levels. However, the degree to which individual agents lower cholesterol level varies. The lipid-lowering effects with combination statins are noted in Table 2. Other drug products contained within these combinations offer added benefits for the indications noted in Tables 4-6.

Table 2. Combination HMG-CoA Reductase Inhibitors Effects on Cholesterol Levels[7,10,11]

Drug	Daily Dosage	TC ↓ (%)	LDL-C ↓ (%)	TG ↓ (%)	HDL-C ↑ (%)
atorvastatin-amlodipine	10 mg–80 mg*	↓ 29-45	↓ 39-60	↓ 19-37	↑ 5-6
lovastatin-niacin	20 mg/1,000 mg to 40 mg/2,000 mg†	Not reported	↓ 30-42	↓ 32-44	↑ 20-30
simvastatin-ezetimibe	10 mg/10 mg to 80 mg/10 mg	↓ 31-43	↓ 45-60	↓ 23-31	↑ 6-8

HDL-C=high-density lipoprotein cholesterol, LDL-C =low-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides
*The LDL-C lowering effect found in the atorvastatin-amlodipine package insert was attributed only to atorvastatin monotherapy; the figures for this combination are calculated from two studies of atorvastatin therapy in patients with primary hypercholesterolemia.
†Based on the package insert; the lower limit in these ranges is for patients titrated up to the 20 mg/1,000 mg dose over 12 weeks; the upper limit is for the same patients titrated up to the maximum dose of 40 mg/2,000 mg daily over 28 weeks.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate combination HMG-CoA reductase inhibitors (statins) are summarized in Table 3. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Combination HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[13]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid).

Clinical Guideline	Recommendation
	For the treatment of homozygous FH • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[14]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[15]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[16]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either

Clinical Guideline	Recommendation
	ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)[17]**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)[18]**	• Statins are considered first-line drugs for lowering LDL-C. • Statins are considered first-line drugs for lowering LDL cholesterol. • When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

All HMG-CoA reductase inhibitors (statins) should be used as adjuncts to a diet restricted in saturated fat and cholesterol for the reduction of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[1,19-22] Combination statins should not be used as initial therapy but have a role in the consolidation of therapy in patients already stabilized on the separate entities. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

As monotherapy, ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, and apolipoprotein (apo) B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.[5] Ezetimibe monotherapy is also indicated in patients with homozygous familial sitosterolemia.[5] FDA-approved indications for the simvastatin-ezetimibe combination product (Vytorin®) are noted in Table 4. Note that the effects of simvastatin-ezetimibe on cardiovascular morbidity/mortality end points have not yet been established.[7]

The atorvastatin-amlodipine combination product (Caduet®) is indicated in patients for whom treatment with both atorvastatin and amlodipine is appropriate.[10] Food and Drug Administration (FDA)-approved indications for atorvastatin are noted in Table 4, and those for amlodipine in Table 5.[10]

The lovastatin-niacin combination product (Advicor®) is indicated in patients for whom treatment with both lovastatin and extended-release niacin is appropriate.[11] FDA-approved indications for lovastatin are noted in Table 4, and those for extended-release niacin (Niaspan®) in Table 6.

Table 4. FDA-Approved Indications for Atorvastatin, Lovastatin, and Simvastatin-Ezetimibe[5,7,10,11,19-21]

Indication	Atorvastatin	Lovastatin	Simvastatin-Ezetimibe
Prevention of Cardiovascular Disease			
Primary prevention of cardiovascular events (patients without clinically evident coronary heart disease [CHD]); to reduce the risk of:	✔ *†	✔	
Angina	✔ *	✔ ‡ (Unstable)	
Myocardial infarction	✔ *†	✔ ‡	
Revascularization procedures	✔ *	✔ ‡ (Coronary)	

Indication	Atorvastatin	Lovastatin	Simvastatin-Ezetimibe
Stroke	✔ *†		
Secondary prevention of cardiovascular events (patients with clinically evident CHD) to reduce the risk of:	✔		
Angina	✔		
Hospitalization for congestive heart failure (CHF)	✔		
Myocardial infarction (nonfatal)	✔		
Revascularization procedures	✔		
Stroke (fatal and nonfatal)	✔		
Coronary atherosclerosis, slowing its progression in patients with CHD, as part of a treatment strategy to lower total and low-density lipoprotein cholesterol (LDL-C) to target levels		✔	
Treatment of Dyslipidemias			
Primary hypercholesterolemia (heterozygous familial and nonfamilial; Fredrickson Type IIa) and mixed dyslipidemia (Fredrickson Type IIb)	✔ §	✔ §	✔ §
To reduce:			
TC	✔	✔	✔
LDL-C	✔	✔	✔
Apo B	✔		✔
Triglyceride (TG)	✔		✔
Non– high-density lipoprotein cholesterol (HDL-C)			✔
To increase:			
HDL-C	✔		✔
Homozygous familial hyperlipidemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein [LDL] apheresis) or if such treatments are unavailable	✔		✔
To reduce:			
TC	✔		✔
LDL-C	✔		✔
Primary dysbetalipoproteinemia (Fredrickson Type III)	✔	‖	
Hypertriglyceridemia, elevated serum TG levels (Fredrickson Type IV)	✔	‖	
Elevated chylomicrons (Fredrickson Types I and V)	‖	‖	
Heterozygous familial hypercholesterolemia (HeFH) in pediatric patients, 10-17 years old, boys and postmenarchal girls¶	✔ §	#	

*In adult patients with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease
†In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension
‡In individuals with average to moderately elevated TC and LDL-C, and below average HDL-C
§As an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures
‖ Has not been studied for this condition.
¶To reduce TC, LDL-C and apolipoprotein B levels if after an adequate trial of diet therapy the following findings are present:
1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and either (a) there is a positive family history of premature cardiovascular disease or (b) 2 or more other CVD risk factors are present
#Single-entity lovastatin is indicated as an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures, for heterozygous familial hypercholesterolemia in boys and postmenarchal girls 10-17 years old; however, the combination lovastatin-niacin product (Advicor®) is not indicated in this population.

Table 5. FDA-Approved Indications for Amlodipine[9,10]

Indication	Amlodipine
For the treatment of hypertension, alone or in combination with other antihypertensive agents	✔
For the treatment of chronic stable angina, alone or in combination with other antianginal or other antihypertensive agents	✔
For the treatment of confirmed or suspected vasospastic angina (Prinzmetal's or variant angina), alone or in combination with other antianginal agents	✔

Indication	Amlodipine
In patients with recently documented coronary artery disease by angiography, without heart failure or an ejection fraction <40%, to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure	✔

Table 6. FDA-Approved Indications for Extended-Release Niacin (Niaspan®)[23]

Indication	Niacin, Extended-Release (Niaspan®)
Adjunct to diet for reduction of elevated TC, LDL-C, apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to an appropriate diet has been inadequate	✔
In combination with lovastatin, treatment of primary hypercholesterolemia and mixed dyslipidemia	✔
To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia	✔
Adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Fredrickson Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them	✔

*Unlike extended-release niacin (Niaspan®), the lovastatin-niacin combination product (Advicor®) is not indicated in combination with bile acid binding resins.

IV. Pharmacokinetics

The pharmacokinetic parameters for the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 7. Minor differences exist between the statins in regards to pharmacokinetic parameters. Half-life is one parameter that separates some statins from others. The pharmacokinetic parameters of the combination products are not significantly different from the pharmacokinetic parameters of the individual components.

Table 7. Pharmacokinetic Parameters of the Combination HMG-CoA Reductase Inhibitors[5-11,19-25]

Drug(s)	Absolute Bioavailability (%)	Protein Binding (%)	Lipid Solubility	Metabolism	Active Metabolites	Half-Life (hours)
Atorvastatin-amlodipine	14; 64-90	≥98; 93	Hydrophilic; not reported	Hepatic, CYP3A4	Yes, 2-hydroxy- and 4-hydroxy-atorvastatin acid; None	14-30; 30-50
Lovastatin-niacin	<5; 60-76	>95; 20	Lipophilic; not reported	Hepatic, CYP3A4; Hepatic	Yes, beta-hydroxyacid and 6-hydroxy derivatives; Yes, nicotinamide adenine dinucleotide	1.1-4.5; 0.3-0.8
Simvastatin-ezetimibe	5; Not reported	95; >90	Lipophilic; not reported	Hepatic, CYP3A4; Hepatic, glucuronide conjugation	Yes, beta-hydroxyacid of simvastatin; Yes, ezetimibe glucuronide	Not reported; 22

V. Drug Interactions

Significant drug interactions with the combination HMG-CoA reductase inhibitors (statins) are listed in Table 8. The drug interactions with the combination products are not significantly different from the drug interactions with the individual components.

Table 8. Significant Drug-Drug Interactions with the Combination HMG-CoA Reductase Inhibitors[6]

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Amiodarone	Amiodarone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic effects (ie, myositis, rhabdomyolysis) of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin, pravastatin, and rosuvastatin are not metabolized by CYP3A4 and may be safer alternatives.
HMG-CoA reductase inhibitors (all)	1	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their first-pass hepatic metabolism via CYP3A4/CYP2C9 isoenzymes resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Itraconazole is contraindicated with HMG-CoA reductase inhibitors metabolized by CYP3A4. If other azole antifungals are to be used, HMG-CoA reductase inhibitor dose should be decreased accordingly. Patients should be monitored for toxicity. Pravastatin may be a safer alternative since its levels are affected least by azole coadministration.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Cyclosporine	Cyclosporine may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism and resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity.
HMG-CoA reductase inhibitors (all)	1	Fibric acid derivatives (fenofibrate, gemfibrozil)	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis via an unknown mechanism. Decrease HMG-CoA reductase inhibitor dose accordingly; obtain creatine kinase levels and monitor for toxicity.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and ketolides (clarithromycin, erythromycin and telithromycin)	Macrolides may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, myopathy or rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Nefazodone	Nefazodone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentrations and increased pharmacologic and toxic (ie, rhabdomyolysis or myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin,	1	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine)	Delavirdine and nevirapine may inhibit the metabolism of HMG-CoA reductase inhibitors, via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis or myopathy) effects of HMG-CoA reductase inhibitors. In contrast, efavirenz may induce CYP3A4 metabolism, resulting in decreased concentration and consequently decreased

Drug(s)	Significance Level	Interaction	Mechanism
simvastatin)			pharmacologic effects of HMG-CoA reductase inhibitors. With concurrent administration, adjust HMG-CoA reductase inhibitor dose accordingly; monitor plasma low-density lipoprotein cholesterol (LDL-C) level, and adverse effects.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Grapefruit	Grapefruit may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of these HMG-CoA reductase inhibitors. Avoid concomitant administration of atorvastatin, lovastatin, and simvastatin with grapefruit products.
Lovastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of lovastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of lovastatin. Decrease lovastatin dose accordingly; monitor for toxicity. Lovastatin is contraindicated in patients receiving concomitant nelfinavir. In addition, lovastatin should not be coadministered with ritonavir, atazanavir, or darunavir.
Simvastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of simvastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of simvastatin. Simvastatin is contraindicated in patients receiving nelfinavir. In addition, coadministration of simvastatin with ritonavir or darunavir should be avoided.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Carbamazepine may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. Monitor patients for a decrease in clinical effect. Pravastatin and rosuvastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Diltiazem	Diltiazem may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Pravastatin may be a safer alternative.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their first-pass metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. The dose of the HMG-CoA reductase inhibitor may need to be increased. Pravastatin levels may be increased in some patients.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Verapamil	Verapamil may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	2	Warfarin	HMG-CoA reductase inhibitors may decrease the elimination of warfarin by inhibiting its hepatic metabolism resulting in increased anticoagulant effect of warfarin. Monitor patients' anticoagulant parameters when starting or discontinuing concurrent therapy with warfarin and HMG-CoA reductase inhibitors. Atorvastatin and pravastatin may be safer alternatives.
Atorvastatin	2	Protease inhibitors (amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of atorvastatin by inhibiting its first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of atorvastatin. Monitor patients receiving atorvastatin for toxicity, especially with ritonavir/saquinavir combination. Decrease atorvastatin dose accordingly; monitor for toxicity.
Ezetimibe	2	Cyclosporine	Coadministration of cyclosporine with ezetimibe may result in increased plasma concentration of both drugs via an unknown mechanism. Decrease ezetimibe dose accordingly; monitor for toxicity.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

All HMG-CoA reductase inhibitors (statins) may cause an elevation in liver enzymes and creatinine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure.[1,6] Niacin therapy is also associated with serum transaminase elevations, as well as hyperglycemia and elevation in uric acid levels.[2] As with the single entity statins, liver function tests should be performed routinely with combination statin therapy.

The most common adverse reactions reported with the combination statins are noted in Table 9. The adverse drug event profile of the combination products is not significantly different from the adverse reaction profile of the individual components.

Table 9. Adverse Drug Events (%) Reported with the Combination HMG-CoA Reductase Inhibitors [5-11,19-25]

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Cardiovascular						
Angina pectoris	<2	-	-	-	-	-
Arrhythmia	<2	<1	-	✔	-	-
Bradycardia	-	<1	-	-	-	-
Cardiac failure	-	≤0.1	-	-	-	-
Chest pain	≥2	<1	0.5-1	-	-	-
Hypertension	<2	-	-	-	-	-
Hypotension	-	<1	-	✔	-	-
Migraine	<2	≤0.1	-	✔	-	-
Phlebitis	<2	-	-	-	-	-
Palpitation	<2	≤4.5	-	✔	-	-
Peripheral ischemia	-	<1	-	-	-	-
Postural hypotension	<2	<1	-	✔	-	-
Vasodilatation	<2	-	-	-	-	-
Syncope	<2	<1	-	✔	-	-
Tachycardia	-	<1	-	✔	-	-
Central Nervous System/Neurological						
Abnormal dreams	<2	<1	-	-	-	-
Agitation	-	≤0.1	-	-	-	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Amnesia	<2	≤0.1	-	-	-	-
Anxiety	-	<1	✔	-	✔	-
Apathy	-	≤0.1	-	-	-	-
Chills	-	-	✔	-	-	-
Cranial nerve dysfunction	-	-	✔	-	✔	-
Depression	<2	<1	✔	-	✔	-
Dizziness	≥2	≤3.4	0.5-2.0	-	✔	✔
Emotional lability	<2	-	-	-	-	-
Facial paralysis	<2	-	-	-	-	-
Fever	<2	-	✔	-	✔	-
Flushing	-	≤4.5	✔	≥5	✔	-
Headache	2.5-16.7	7.8	2.1-8.0	≥5	3.5	6-7
Hyperkinesia	<2	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-
Hypesthesia	<2	<1	-	-	-	-
Incoordination	<2	-	-	-	-	-
Insomnia	≥2	<1	0.5-1	-	✔	-
Libido decreased	<2	-	✔	-	✔	-
Memory loss	-	-	✔	-	✔	-
Neck rigidity	<2	-	-	-	-	-
Paresthesia	<2	<1	0.5-1	-	✔	-
Peripheral nerve palsy	-	-	✔	-	✔	-
Peripheral neuropathy	<2	<1	✔	-	✔	-
Psychiatric disturbances	-	<1	✔	-	✔	-
Somnolence	<2	≤1.6	-	-	-	-
Torticollitis	<2	-	-	-	-	-
Tremor	-	<1	✔	-	✔	-
Vertigo	-	<1	✔	-	-	-
Dermatological						
Acanthosis nigricans	-	-	-	✔	-	-
Acne	<2	-	-	-	-	-
Alopecia	<2	≤0.1	0.5-1	-	✔	-
Contact dermatitis	<2	-	-	-	-	-
Dermatitis	-	≤0.1	-	-	-	-
Dry skin	<2	≤0.1	✔	-	-	-
Eczema	<2	-	-	-	0.8	-
Hyperpigmentation	-	-	-	✔	-	-
Pruritus	<2	<1	0.5-1	≥5	0.5	-
Rash	1.1-3.9	<1	0.8-1.3	≥5	0.6	✔
Seborrhea	<2	-	-	-	-	-
Skin ulcer	<2	-	-	-	-	-
Sweating	<2	1-2	-	✔	-	-
Urticaria	<2	≤0.1	✔	-	-	✔
Endocrine and Metabolic						
Gout	<2	-	-	-	-	-
Hyperglycemia	<2	1-2	-	≥5	-	-
Hypoglycemia	<2	-	-	-	-	-
Peripheral edema	≥2	≤14.6	-	✔	-	-
Thirst	-	1-2	-	-	-	-
Weight gain	<2	-	-	-	-	-
Gastrointestinal						
Abdominal pain	0-3.8	1.6	2.0-2.5	≥5	0.9-3.2	✔

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Acid regurgitation	-	-	0.5-1	-	-	-
Anorexia	<2	<1	✔	-	✔	-
Biliary pain	<2	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	-	✔	✔
Cirrhosis	-	-	✔	-	✔	-
Colitis	<2	-	-	-	-	-
Constipation	0-2.5	<1	2.0-3.5	-	2.3	-
Diarrhea	0-3.8	<1	2.2-2.6	≥5	0.5-1.9	✔
Dry mouth	<2	1-2	0.5-1	-	-	-
Duodenal ulcer	<2	-	-	-	-	-
Dyspepsia/heartburn	1.3-2.8	<1	1.0-1.6	≥5	0.6-1.1	-
Dysphagia	<2	<1	-	-	-	-
Enteritis	<2	-	-	-	-	-
Eructation	<2	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-
Flatulence	1.1-2.8	<1	3.7-4.5	-	0.9-1.9	-
Fulminant hepatic necrosis	-	-	✔	-	✔	-
Gastritis	<2	≤0.1	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-
Gingival hyperplasia	-	<1	-	-	-	-
Glossitis	<2	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-
Hepatitis	<2	-	✔	-	✔	✔
Hepatoma	-	-	✔	-	✔	-
Increased appetite	<2	≤0.1	-	-	-	-
Melena	<2	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-
Nausea	≥2	2.9	1.9-2.5	≥5	0.4-1.3	✔
Pancreatitis	<2	<1	✔	-	✔	✔
Rectal hemorrhage	<2	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-
Vomiting	<2	<1	0.5-1	≥5	✔	-
Genitourinary						
Abnormal ejaculation	<2	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-
Cystitis	<2	-	-	-	-	-
Dysuria	<2	≤0.1	-	-	-	-
Epididymitis	<2	-	-	-	-	-
Erectile dysfunction	-	-	✔	-	✔	-
Fibrocystic breast	<2	-	-	-	-	-
Gynecomastia	-	✔	✔	-	✔	-
Hematuria	≥2	-	-	-	-	-
Impotence	<2	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-
Nephritis	<2	-	-	-	-	-
Nocturia	<2	1-2	-	-	-	-
Sexual dysfunction	-	<1	-	-	-	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Urinary abnormality	-	1-2	-	-	-	-
Urinary frequency	<2	1-2	-	-	-	-
Urinary incontinence	<2	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-
Urinary tract infection	≥2	-	3.0	-	-	-
Urinary urgency	<2	-	-	-	-	-
Uterine hemorrhage	<2	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-
Hematologic						
Anemia	<2	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-
Eosinophilia	-	-	✔	-	✔	-
Hemolytic anemia	-	-	✔	-	✔	-
Leukopenia	-	1-2	✔	-	✔	-
Lymphadenopathy	<2	-	-	-	-	-
Petechia	<2	-	-	-	-	-
Purpura	-	1-2	✔	-	✔	-
Thrombocytopenia	<2	1-2	✔	-	✔	-
Vasculitis	-	<1	✔	-	✔	-
Laboratory Test Abnormalities						
Creatine phosphokinase increased	<2	-	-	-	✔	✔
Bilirubin elevation	-	-	✔	-	✔	-
Hematuria	-	-	-	-	-	-
Liver enzyme abnormalities	-	✔	✔	-	✔	✔
Proteinuria	-	-	-	-	-	-
Thyroid level abnormality	-	-	✔	-	✔	-
Musculoskeletal						
Arthritis	≥2	<1	0.5-6	-	✔	-
Arthralgia	-	<1	-	✔	✔	✔
Back pain	0-3.8	<1	5.0	≥5	-	✔
Bursitis	<2	-	-	-	-	-
Hypertonia	-	≤0.1	-	-	-	-
Leg cramps	<2	-	-	-	-	-
Muscle cramps	-	<1	0.6-1.1	-	✔	-
Myalgia	-	<1	1.8-3.0	≥5	1.2	2.3-4
Myopathy	-	-	-	✔	✔	✔
Myositis	<2	-	-	-	-	-
Myasthenia	<2	≤0.1	-	-	-	-
Polymyalgia rheumatica	-	-	✔	-	✔	-
Rhabdomyolysis	✔	-	✔	✔	✔	✔
Tendinous contracture	<2	-	-	-	-	-
Tendon rupture	✔	-	-	-	-	-
Tenesynovitis	<2	-	-	-	-	-
Respiratory						
Asthma	<2	-	-	-	-	-
Bronchitis	≥2	-	-	-	-	-
Cough	-	≤0.1	-	-	-	✔
Dyspnea	<2	<1	✔	-	✔	-
Epistaxis	<2	<1	-	-	-	-
Pharyngitis	0-2.5	-	-	-	-	✔
Pneumonia	<2	-	-	-	-	-
Rhinitis	≥2	≤0.1	-	✔	-	-

Adverse Event	Atorvastatin	Amlodipine	Lovastatin	Niacin ER	Simvastatin	Ezetimibe
Sinusitis	0-6.4	-	6.0	-	-	✔
Upper respiratory infection	-	-	-	-	2.1	5
Other						
Abnormal vision	-	1-2	0.9-1.2	-	-	-
Accidental injury	0-4.2	-	4	-	-	-
Allergic reaction	0-2.8	<1	-	-	-	-
Amblyopia	<2	-	-	-	-	-
Anaphylaxis	✔	-	✔	-	✔	✔
Angioedema	-	<1	✔	-	✔	✔
Angioneurotic edema	✔	-	-	-	-	-
Asthenia	0-3.8	<1	1.2-2.0	≥5	1.6	-
Cataracts	-	-	✔	-	0.5	-
Conjunctivitis	-	1-2	-	-	-	-
Dry eyes	<2	-	-	-	-	-
Erythema multiforme	<2	<1	✔	-	✔	-
Eye hemorrhage	<2	-	-	-	-	-
Eye irritation	-	-	0.5-1	✔	-	-
Facial/general edema	<2	-	-	✔	-	-
Fatigue	✔	4.5	-	-	-	✔
Flu syndrome	0-3.2	-	5.0	≥5	-	1-3
Glaucoma	<2	-	-	-	-	-
Hot flashes	-	<1	-	-	-	-
Hypersensitivity reaction	-	-	-	✔	-	✔
Infection	2.8-10.3	-	16	≥5	-	-
Lupus erythematosus-like syndrome	-	-	✔	-	✔	-
Malaise	<2	<1	✔	-	✔	-
Ophthalmoplegia	-	-	✔	-	✔	-
Parosmia	<2	≤0.1	-	-	-	-
Photosensitivity reaction	<2	-	✔	-	-	-
Refraction disorder	<2	-	-	-	-	-
Stevens-Johnson syndrome	✔	-	✔	-	✔	-
Taste disturbance	<2	≤0.1	-	-	-	-
Tinnitus	<2	1-2	-	-	-	-
Toxic epidermal necrolysis	✔	-	✔	-	✔	-
Visual disturbance	-	≤0.1	✔	-	-	-
Weight gain	-	<1	-	-	-	-

ER=extended-release
✔ Percent not specified
-Event not reported or incedance <1%

VII. Dosing and Administration

The usual dosing regimens for the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 10. The combination statins are dosed once daily in the evening. Atorvastatin is the exception; it can be administered at any time of the day. The dosing and administration schedule of the combination products is not significantly different from that of the individual components.

Table 10. Usual Dosing for the Combination HMG-CoA Reductase Inhibitors [5-11,19-25]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine/ atorvastatin*	Hypercholesterolemia; heterozygous familial/nonfamilial hypercholesterolemia; secondary prevention of cardiovascular	Heterozygous familial hypercholesterolemia (Adolescents 10-17 years old):	Tablets: 2.5/10 mg 2.5/20 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	events: Tablet: atorvastatin: initial, 10-20 mg once daily; maximum, 80 mg daily. For low-density lipoprotein cholesterol (LDL-C) reduction >45%, initiate at 40 mg once daily. Primary prevention of cardiovascular events: Tablet: atorvastatin: initial, 10 mg once daily Homozygous familial hypercholesterolemia: Tablet: atorvastatin: initial, 10 mg once daily; maximum, 80 mg daily Hypertriglyceridemia: Tablet: atorvastatin: initial, 10 mg once daily; maximum, 80 mg daily Hypertension/angina Tablet: amlodipine: initial, 2.5-5 mg once daily; maximum, 10 mg daily	Tablet: atorvastatin: initial, 10 mg once daily; maximum, 20 mg daily (doses greater than 20 mg have not been studied in this patient population) Safety and efficacy of atorvastatin in children younger than 10 years of age have not been established. Hypertension (Adolescents 6-17 years): Tablet: amlodipine, 2.5-5 mg once daily Safety and efficacy of doses above 5 mg daily of amlodipine have not been established in children. Note: there have been no studies conducted to determine the safety or effectiveness of Caduet® in pediatric populations.	2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg
Niacin ER/ lovastatin†	Tablet: initial, 500/20 mg once daily at bedtime; may titrate up by up to 500 mg daily every 4 weeks; maximum, 2,000/40 mg daily	Safety and efficacy in children have not been established.	Tablets: 500/20 mg 750/20 mg 1,000/20 mg 1,000/40 mg
Ezetimibe/ simvastatin‡	Primary hypercholesterolemia: Tablet: initial, 10/20 mg once daily at bedtime, or 10/10 mg in patients requiring less aggressive LDL-C lowering, or 10/40 mg in patients requiring LDL-C lowering >55% Homozygous familial hypercholesterolemia: Tablet: 10/40-10/80 mg once daily at bedtime	Safety and efficacy in children have not been established.	Tablets: 10/10 mg 10/20 mg 10/40 mg 10/80 mg

* Small, fragile or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg amlodipine daily.
† Equivalent doses of lovastatin-niacin can be substituted for Niaspan® but should not be substituted for other modified-release niacin products.
‡Product should not be started in those with severe renal insufficiency unless the patient has already tolerated treatment with simvastatin ≥5 mg.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the combination HMG-CoA reductase inhibitors (statins) are summarized in Table 11.

Table 11. Comparative Clinical Trials Using the Combination HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia, Primary				
Preston et al[26] RESPOND Atorvastatin-amlodipine 5 mg/10 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/10 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/40 mg once daily, separate entities	DB, RCT Patients 18-75 years of age with hypertension (HTN) and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and reduction of LDL-C Secondary: Augmentation of blood pressure-lowering with the addition of atorvastatin and augmentation of LDL-C-lowering with the addition of amlodipine, reduction in the Framingham risk scores, adverse effects	Primary: Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in SBP from baseline compared to atorvastatin alone ($P<0.001$). Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in LDL-C from baseline compared to amlodipine alone ($P<0.001$). Secondary: Regardless of dose, there was no significant difference in terms of SBP-lowering from baseline between patients taking atorvastatin and amlodipine and those on amlodipine monotherapy ($P>0.05$). Regardless of dose, there was no significant difference in terms of LDL-C-lowering from baseline between patients taking atorvastatin and amlodipine and those on atorvastatin monotherapy ($P>0.05$). Atorvastatin-amlodipine 5/10 mg once daily was more effective in reducing baseline LDL-C level compared to atorvastatin monotherapy ($P=0.007$). A maximal reduction in the Framingham risk scores was observed in the atorvastatin-amlodipine 5/80 mg and atorvastatin-amlodipine 10/80 mg treatment groups (*P* value not reported). The proportion of patients who discontinued therapy due to adverse effects was similar in the combination, amlodipine, and atorvastatin groups (5.6% vs 5.4% vs 4.1, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin-amlodipine 10 mg/40 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/80 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/80 mg once daily, separate entities vs amlodipine 5 mg or 10 mg once daily vs atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg once daily vs placebo				
Flack et al[27] CAPABLE Atorvastatin-amlodipine	MC, OL African-Americans 18-80 years of age with uncontrolled HTN and	N=489 20 weeks	Primary: Proportion of patients in 3 cardiovascular risk groups (group 1: patients without	Primary: More patients in groups 1 and 2 had reached both their JNC 7 and NCEP ATP III goals at end point compared to the group-3 patients (69.7%, 66.7%, and 28.2%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/20 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/40 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/80 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/20 mg daily, separate entities vs atorvastatin-amlodipine 10 mg/40 mg daily,	dyslipidemia; patients were excluded if their blood pressure was at goal or if they were receiving both amlodipine and atorvastatin, maximum-dose calcium channel blocker, or 80 mg of atorvastatin (with LDL-C ≥100 mg/dL), were pregnant/lactating, had impaired renal or hepatic function, MI within 6 months, coronary revascularization, atherosclerotic stroke, or transient ischemic attack within 3 months, a history of cardiomyopathy or chronic heart failure, secondary HTN or secondary dyslipidemia		additional risk factors; group 2: patients with >1 additional risk factors, excluding CHD and diabetes; group 3: patients with CHD or CHD risk equivalent) who reached both their JNC 7 and NCEP ATP III goals at end point Secondary: Change from baseline in SBP and DBP, LDL-C, total cholesterol, triglycerides, HDL-C, apolipoprotein B	Secondary: Atorvastatin-amlodipine therapy was associated with a 17.5 mm Hg and 10.1 mm Hg decrease in the SBP and DBP from baseline, respectively (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 23.6% reduction in LDL-C from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 17% reduction in total cholesterol from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 2.2% increase in HDL-C from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 6.9% reduction in TG from baseline (*P* value not reported). Atorvastatin-amlodipine therapy was associated with a 19.3% reduction in apo B from baseline (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination entity vs atorvastatin-amlodipine 10 mg/80 mg daily, combination entity				
Messerli et al[28] AVALON Amlodipine 5 mg daily for 8 weeks, followed by the addition of atorvastatin 10 mg for another 8 weeks, followed by a 12-week open-label treatment vs atorvastatin 10 mg daily for 8 weeks, followed by the addition of amlodipine 5 mg for another 8 weeks, followed by a 12-week open-label treatment vs atorvastatin-amlodipine 5 mg/10 mg daily for 16 weeks, followed by a 12-week open-label treatment vs placebo daily for 16 weeks,	DD, MC, OL, RCT Patients with HTN and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached both their JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	Primary: More patients in the combination group reached both their JNC 7 and NCEP ATP III LDL-C goals at 8 weeks compared to patients receiving amlodipine or atorvastatin as monotherapy (45%, 8.3%, and 28.6%, respectively; $P<0.001$). The incidence of side effects was similar across all treatment groups (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by a 12-week open-label treatment				
Sharma et al[29] Niacin ER/lovastatin 1,500 mg/20 mg daily, combination entity, titrated up to LDL-C goal	MC, I, OL Patients living in India with HTN and dyslipidemia	N=131 24 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, TG, total cholesterol Secondary: Not reported	Primary: Niacin ER/lovastatin therapy was associated with a statistically significant reduction from baseline in LDL-C (38%), TG (21%), and total cholesterol (25.2%) at week 24 of therapy ($P<0.01$). Niacin ER/lovastatin therapy was associated with a statistically significant increase from baseline in HDL-C at week 24 of therapy (18.2%; $P<0.01$). Secondary: Not reported
Advicor Package Insert Study[8] Niacin ER/lovastatin (Advicor®) 2,000 mg/40 mg daily, combination entity vs niacin ER (Niaspan®) daily vs lovastatin 40 mg daily	DB, MC, RCT Patients with type IIa and IIb hyperlipidemia	N=179 28 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean percent change from baseline in HDL-C, TG	Primary: At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant reduction in LDL-C from baseline compared with niacin ER and lovastatin 40 mg monotherapy groups (42%, 14%, and 32%, respectively; $P<0.0001$). Secondary: At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant increase in HDL-C from baseline compared with niacin ER and lovastatin 40 mg monotherapy groups (30%, 24%, and 6%, respectively; *P* value not reported). At 28 weeks, niacin ER/lovastatin combination therapy arm was associated with a significant reduction in TG from baseline compared with niacin ER and lovastatin 40 mg monotherapy groups (44%, 31%, and 20%, respectively; *P* value not reported).
Bays, Du jovne et al[30] ADVOCATE Niacin ER/lovastatin 1,000 mg/40 mg daily, combination entity	MC, OL, R Patients 18-70 years old, with 2 consecutive LDL-C ≥160 mg/dL (if no CAD), or ≥130 mg/dL (with CAD), TG <300 mg/dL, and	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline in total	Primary: Atorvastatin was associated with a statistically significant 49% reduction in LDL-C from baseline at week-16 of therapy, compared with a 39%, 42%, and 39% reduction observed with niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups, respectively ($P\leq0.05$). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs niacin ER/lovastatin 2,000 mg/40 mg daily, combination entity vs simvastatin 40 mg daily vs atorvastatin 40 mg daily	HDL-C <45 mg/dL (men) or <50 mg/dL (women); patients were excluded if they had an allergy to any of the study drugs, a history of substance abuse or dependence within 12 months, consumption of >14 alcoholic drinks/week, uncontrolled psychiatric disease, active gallbladder disease, uncontrolled HTN, renal insufficiency, hepatic dysfunction, heart failure NYHA class III/IV, active gout symptoms or uric acid >1.3 times the ULN, active peptic ulcer disease, type 1 or 2 diabetes, fibromyalgia, cancer within the previous 5 years, unstable angina, MI, CABG, stroke, or percutaneous coronary angioplasty within 6 months		cholesterol, apo B, apo AI, HDL subfractions, HDL_2 and HDL_3 and median percent change in TG and lipoprotein(a)	associated with a statistically significant increase in HDL-C from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (17%, 32%, 6%, and 7%, respectively; $P \leq 0.05$). Secondary: Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and atorvastatin groups experienced a statistically significant reduction in TG from baseline at week 16 of therapy, compared with the simvastatin group (29%, 49%, 31%, and 19%, respectively; $P \leq 0.05$). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were associated with a statistically significant reduction in lipoprotein(a) from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (19%, 21%, 0%, and 2%, respectively; $P \leq 0.05$). Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups were associated with a statistically significant increase in apo AI from baseline at week-16 of therapy, compared with the atorvastatin group (7%, 14%, 6%, and 2%, respectively; $P<0.05$). Niacin ER/lovastatin 2,000/40 mg and atorvastatin were associated with a statistically significant reduction in lipoprotein B from baseline at week 16 of therapy, compared with the niacin ER/lovastatin 2,000/40 and simvastatin groups (38%, 40%, 33%, and 31%, respectively; $P<0.05$). Niacin ER/lovastatin 1,000/40 mg, and niacin ER/lovastatin 2,000/40 mg were associated with a statistically significant increase in HDL_2 and HDL_3 from baseline at week 16 of therapy, compared with the atorvastatin and simvastatin groups ($P<0.05$).
McKenney et al[31] COMPELL Atorvastatin 20 mg for the	MC, OL, PG, RCT Adult patients ≥21 years of age with hypercholesterolemia	N=292 12 weeks	Primary: LDL-C level at week 12 Secondary:	Primary: Patients randomized to atorvastatin/niacin ER, rosuvastatin/niacin ER, simvastatin/ezetimibe, and rosuvastatin therapies experienced similar reductions in LDL-C from baseline at week 12 of the study (56%, 51%, 57%, and 53%, respectively; $P=0.093$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to niacin ER 500 mg for the first 4 weeks, titrated up to 1,000 mg on weeks 5-8, and 2,000 mg on weeks 9-12 vs simvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to ezetimibe 10 mg for 12 weeks vs rosuvastatin 10 mg for the first 8 weeks, titrated up to 20 mg on weeks 9-12, in addition to niacin ER 500 mg for the first 4 weeks, titrated up to 1,000 mg on weeks 5-12 vs rosuvastatin 10 mg for the first 4 weeks, titrated up to 20 mg on weeks 5-8, and 40 mg on weeks 9-12	eligible for treatment based on the NCEP ATP III guidelines, with two consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL; patients were excluded if they had secondary dyslipidemia, known hypersensitivity to the study drugs, major organ system disease, severe HTN, diabetes, major cardiovascular event within 12 months, severe heart failure, history of myopathy, active gout, life expectancy <2 years, had active liver disease, creatinine clearance <30 ml/min, or uric acid > three times the ULN		HDL-C level at week 12, non–HDL-C, total cholesterol, TG, lipoprotein(a), apo B	Secondary: Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in apo B from baseline at week 12 of the study compared to the rosuvastatin group (43% vs 39%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant increase in HDL-C from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (22%, 10%, and 7%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in TG from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (47%, 33%, and 25%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin ER experienced a statistically significant reduction in lipoprotein(a) from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (14%, –7%, and –18%, respectively; *P*≤0.05). Side effects were similar across treatment groups (*P* value not reported). There were no cases of myopathy or hepatotoxicity reported during the study period.
Rodney et al[32] Ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 12	DB, MC, PG, RCT African-American patients with LDL-C ≥145 mg/dL but ≤250	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, total cholesterol, TG, HDL-C, non–	Primary: Patients on the combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (45.6% vs 28.3%; *P*≤0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs simvastatin 20 mg, in addition to placebo, separate entities, for 12 weeks	mg/dL, TG ≤350 mg/dL		HDL-C, apo B Secondary: Not reported	Patients on the combination therapy experienced a statistically significant reduction in total cholesterol from baseline compared to the simvastatin monotherapy group (33% vs 21%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant triglyceride reduction from baseline compared to the simvastatin monotherapy group (22% vs 15%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant non–HDL-C reduction from baseline compared to the simvastatin monotherapy group (42% vs 26%; *P*≤0.01). Patients on the combination therapy experienced a statistically significant apo B reduction from baseline compared to the simvastatin monotherapy group (38% vs 25%; *P*≤0.01). There was no difference in the change of HDL level from baseline between the two groups (~1-2% increase in each group; *P* value not reported). There was no statistically significant difference in side effects between the combination therapy and simvastatin groups (*P* value not reported). Secondary: Not reported
Patel et al[33] Ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 6 weeks vs simvastatin 20 mg, in addition to placebo, separate	DB, MC, PG, RCT Patients 18-75 years of age with primary hypercholesterolemia and CHD (at least 3 month prior to baseline), not on lipid management therapy; patients were excluded if they were women on	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/L) at 6 weeks Secondary: Change in serum cholesterol, TG, HDL	Primary: Patients on the combination therapy experienced an additional LDL-C reduction of 14.6% compared to the simvastatin monotherapy group (95% CI, 10.1 to 19.1; *P*<0.0001). A significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (93% vs 75%, respectively; *P*<0.001). Patients on combination therapy were 5.1 times more likely to reach target LDL-C levels compared to patients on simvastatin alone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
entities, for 6 weeks	hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset, had ALT/AST or CK >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled HTN, or body mass index ≥30 kg/m^2			(95% CI, 1.8 to 15.0; *P*=0.003). Secondary: Patients on the combination therapy experienced an additional total cholesterol reduction of 0.69 mmol/L compared to the simvastatin group (95% CI, 0.48 to 0.90; *P*<0.0001). Significantly greater proportion of patients in the combination therapy group reached total cholesterol target (<4 mmol/l) compared to simvastatin group (*P*<0.001). Greater reduction in TG was observed in the combination therapy group compared to the simvastatin group (20.4% vs 12.4%; *P*=0.06). There was no difference in the change of HDL level from baseline between the two groups (~6% increase in each group; *P* value not reported). There was no statistically significant difference in treatment emergent adverse events between the combination therapy and simvastatin groups (40% vs 25%; *P*=0.07).
Masana et al[34] Ezetimibe 10 mg daily, in addition to simvastatin 10 mg titrated up to 80 mg daily, separate entities vs simvastatin 10 mg titrated up to 80 mg daily, in addition to placebo, separate entities	DB, ES, MC, RCT Patients with primary hypercholesterolemia ≥18 years of age, currently taking a stable daily dose of a statin ≥6 weeks, with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL; patients were excluded if they had heart failure, uncontrolled	N=355 48 weeks	Primary: Percent change from baseline in LDL-C between the study groups at week 12 Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, non–HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C at 12 weeks	Primary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant 27% reduction in LDL-C compared to patients on simvastatin monotherapy (*P*<0.001). The benefit was maintained up to week 48 of the study (*P* value not reported). Secondary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant reduction in total cholesterol, TG, non–HDL-C, ratios of LDL-C:HDL-C, and TC:HDL-C, compared to patients on simvastatin monotherapy (*P*<0.001). At week 12, simvastatin-ezetimibe groups experienced a non-significant 2.6% increase in HDL-C compared to patients on simvastatin monotherapy (*P*=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cardiac arrhythmias, MI, CABG, coronary angioplasty, or severe peripheral artery disease within the past 3 months, unstable angina pectoris, poorly controlled or newly diagnosed diabetes, uncontrolled endocrine or metabolic disease, impaired renal function, active or chronic liver or hepatobiliary disease, ALT or AST >2 times the ULN, creatine phosphokinase >1.5 times the ULN, and cancer (other than basal cell carcinoma) within the past 5 years			Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe groups (17% and 19%, respectively; *P* value not reported). There were no cases of rhabdomyolysis or myopathy during the study.
Denke et al[35] EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	DB, MC, PG, RCT Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet; patients were excluded if within 3 months of study entry	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target, change in serum cholesterol, TG, HDL in patients with diabetes, metabolic syndrome or neither Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional LDL-C reduction of 24.8% (diabetic patients), 21.4% (metabolic syndrome patients), and 22.4% (neither) from baseline (*P*<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional triglyceride reduction of 12.3% (diabetic patients), 10.7% (metabolic syndrome patients), and 11% (neither) from baseline (*P*<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	had an acute coronary insufficiency, MI, stroke, surgical coronary intervention, or other major vascular surgery procedures, untreated hypothyroidism or hyperthyroidism, untreated uncontrolled HTN, impaired renal function, active liver disease, a history of statin-induced myopathy, uncontrolled diabetes, or were taking lipid-altering medications,other than statins, or oral corticosteroids			with an additional increase in HDL cholesterol among diabetic patients (*P*<0.001) and patients with metabolic syndrome (*P*=0.002) from baseline. The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional non-HDL cholesterol reduction of 21.8% (diabetic patients), 19.5% (metabolic syndrome patients), and 20.3% (neither) from baseline (*P*<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in total cholesterol of 16% (diabetic patients), 14.8% (metabolic syndrome patients), and 15% (neither) from baseline (*P*<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in apo B to apo AI ratio of 17.7% (diabetic patients), 16.6% (metabolic syndrome patients), and 15.1% (neither) from baseline (*P*<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction from baseline in CRP of 14.8% and 9.7% among diabetic patients (*P*<0.001) and patients with metabolic syndrome (*P*=0.027), respectively. A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP-ATP LDL-C goals compared to the control group (*P*<0.001). Side effects were similar across all treatment groups (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pearson et al[36] EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	DB, MC, PG, RCT Subanalysis of the EASE study; patients > 65 years old with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet (for above for exclusion criteria)	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target across different races and ethnicities, change in serum cholesterol, TG, HDL at 6 weeks Secondary: Not reported	Primary: Compared to placebo, patients on the ezetimibe combination therapy experienced an LDL-C reduction of 23% (white patients), 23% (African American patients), and 21% (Hispanic patients) from baseline (*P*<0.001). The difference in LDL-C lowering among the three races studied was not statistically significant (*P*>0.5). A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP ATP LDL-C goal compared to the control group (*P*<0.001). Patients on the ezetimibe combination therapy experienced a total cholesterol reduction of 15.3 mg/dL from baseline compared to the control group (*P*<0.001). Patients on the ezetimibe combination therapy experienced a triglyceride reduction of 11.5 mg/dL from baseline compared to the control group (*P*<0.001). Patients on the ezetimibe combination therapy experienced an increase in HDL of 2.1 mg/dL from baseline when compared to the control group (*P*<0.001). Side effects were similar across treatment groups and races (*P* value not reported). Secondary: Not reported
Chenot et al[37] Simvastatin 40 mg daily vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities	RCT Patients admitted for an AMI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission; patients	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL Secondary: Not reported	Primary: Patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (27%, 41%, and 51%, respectively; *P*<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (15%, 27%, and 25%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no lipid-lowering therapy	were excluded if they had a thyroid disorder, inflammatory disease, neoplasia, serious hepatic disease, creatinine level >1.7 mg/dL, creatinine clearance <30 mL/min, CK >3 times the ULN, LDL-C <90 mg/dL, or were receiving potent 3A4 inhibitors			There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group ($P \geq 0.09$). Patients on the simvastatin-ezetimibe combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day 4 (P=0.03) and day 7 (P=0.002) of the study. A greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day 4 and day 7 (45% vs 5%, and 55% vs 10%, respectively; P value not reported). Secondary: Not reported
Sampalis et al[38] Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	SA Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals on statin therapy	N=825 6 weeks	Primary: Reduction in the 10-year risk of CAD after 6 weeks Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy was associated with a 25.3% reduction in the 10-year risk of CAD (P<0.001). Secondary: Not reported
Gaudiani et al[39] Simvastatin 20 mg daily for 6 weeks, followed by the addition of ezetimibe 10 mg daily for another 24 weeks, separate entities vs	DB, MC, PG, RCT Patients 30-75 years of age with type 2 diabetes (hemoglobin A_{1C} ≤9%), treated with a stable dose of pioglitazone (15-45 mg daily) or rosiglitazone (2-8 mg daily) for at	N=214 30 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20.8% vs 0.3%; P<0.001). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.5% vs 1.5%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 20 mg daily for 6 weeks, titrated up to 40 mg daily for another 24 weeks, separate entities	least 3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy); patients were excluded if they had type 1 diabetes, type I or type V hyperlipidaemia, homozygous familial hypercholesterolemia, a history of active liver disease, uncontrolled HTN, renal dysfunction, hyperlipidemic pancreatitis, or hypercholesterolemia secondary to hypothyroidism, MI, percutaneous coronary angioplasty, stent insertion, CABG, or stroke within 3 months, and liver transaminase levels >30% above the ULN, CK >50% above the ULN, fasting plasma C-peptide ≤0.5 ng/mL, or if they were taking warfarin, cyclical sex hormones, or any potent inhibitors of CYP3A4		TC:HDL-C, non–HDL-C, apo B, apo AI	Non–HDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20% vs 1.7%; *P*<0.001). Apo B was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.1% vs 1.8%; *P*<0.001). The ratios of LDL-C:HDL-C, TC:HDL-C, and apo B to apo AI were reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (*P*<0.001). The reduction in HDL-C was similar in the simvastatin 40 mg and simvastatin-ezetimibe 10/20 mg groups (*P*=948). The incidence of treatment-related adverse effects was lower in the simvastatin 40 mg group than in the simvastatin-ezetimibe 10/20 mg group (10% and 18.3%, respectively; *P* value not reported).
Feldman, Koren et al[40] Simvastatin 10 mg daily, in	DB, MC, RCT Patients 18-80 years of	N=710 23 weeks	Primary: LDL-C <100 mg/dL at week 5	Primary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily for 23 weeks	age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL, not pregnant, liver transaminase and CK ≤50% above the ULN, off all lipid-lowering agents ≥6 weeks		Secondary: LDL-C <100 mg/dL at study end	level <100 mg/dL at week 5, compared with patients receiving simvastatin 20 mg monotherapy (*P*<0.001). Secondary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 23, compared with patients receiving simvastatin 20 mg monotherapy (*P*<0.001). At week 5, there was a statistically significant reduction in total cholesterol, non–HDL-C, apo B, ratios of TC:HDL-C, and LDL-C:HDL-C among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (*P*<0.001). HDL-C was significantly increased only in the simvastatin-ezetimibe 10/20 mg group from baseline, compared with simvastatin monotherapy (*P*<0.05). At week 5, there was a statistically significant reduction in TG among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (*P*<0.05). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe 10/10 mg, 10/20 mg, 10/40 mg groups (7.5%, 9.6%, 14%, and 10%, respectively; *P* value not reported).
Bays, Ose et al[41] Simvastatin-ezetimibe 10 mg/10 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg daily for 12	DB, MC, RCT Patients aged 18 to 80 years with primary hypercholes-terolemia, LDL-C >145 mg/dL but ≤150 mg/dL and TG ≤350 mg/dL; patients were excluded if they had an	N=1,528 24 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/simvastatin vs simvastatin or ezetimibe monotherapy Secondary:	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53% vs 39%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (53% vs 18.9%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12	active liver disease and CK >1.5 times the ULN		Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and C-reactive protein (CRP), proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks	Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (*P*<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks, compared with simvastatin (92.2%, 78.6%, 38.7% vs 79.2%, 45.9%, and 7.0%, respectively; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (*P*=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, simvastatin-ezetimibe, and ezetimibe groups, but were more frequent than placebo (14.8%, 15.1%, 12.8%, 8.1%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs placebo daily for 12 weeks				
Goldberg, Sapre et al[42] Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the ULN, no active liver disease, CK ≤1.5 times the ULN; patients were excluded if they had heart failure, uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease, MI, CABG, uncontrolled, newly diagnosed diabetes, or change in antidiabetic therapy within 3 month, renal dysfunction, coagulation disorder, uncontrolled HTN, were taking non-statin lipid-lowering drugs, immunosuppressants, corticosteroids, other potent inhibitors of P450 3A4 isoenzyme	N= 887 20 weeks	Primary: Mean percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/ simvastatin vs simvastatin alone Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP, proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant 14.8% reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53.2% vs 38.5%; *P*<0.001). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (*P*<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (*P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks, compared with simvastatin (92% and 82% vs 82% and 43%, respectively; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (*P*=0.53).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				Treatment-related adverse effects were similar in the pooled simvastatin and simvastatin-ezetimibe, but were more frequent than in the ezetimibe and placebo groups (13%, 14%, 9%, and 9%, respectively; *P* value not reported).
Ose et al[43] Ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for 14 weeks vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 14 weeks	DB, MC, RCT Patients with primary hypercholesterolemia (LDL-C between 145 mg/dL and 250 mg/dL and TG <350 mg/dL)	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, total cholesterol, non-HDL, CRP, LDL:HDL cholesterol ratio, TC:HDL ratio, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL) Secondary:	Primary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (53.7% vs 38.8%; *P*<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant reduction from baseline in TG, total cholesterol, non-HDL, CRP, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the simvastatin monotherapy group (*P*<0.001). A significantly greater proportion of patients randomized to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ezetimibe 10 mg once daily for 14 weeks vs placebo once daily for 14 weeks			Not reported	simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2% vs 47.9%; *P*<0.001). A greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4% vs 7%; *P*<0.001). The incidence of drug-related adverse effects was similar in the simvastatin-ezetimibe and simvastatin monotherapy groups (7.4% vs 5.5%, respectively; *P* value not reported). Secondary: Not reported
Davidson et al[44] Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia; patients were excluded if they had heart failure, uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease, MI, or CABG within 6 months, uncontrolled, newly diagnosed diabetes, or change in antidiabetic therapy within 1 month, active liver disease, renal dysfunction, coagulation disorder, unstable endocrine disease	N=668 20 week	Primary: Mean percent change in LDL-C from baseline to the end of treatment period Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (49.9% vs 36.1%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (49.9% vs 18.1%; *P*<0.001). Patients randomized to either simvastatin-ezetimibe 10/10 mg or simvastatin 80 mg monotherapy experienced a 44% reduction in LDL-C from baseline at 12 weeks (*P* value not reported). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (*P*<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with simvastatin monotherapy (*P*<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with simvastatin monotherapy (*P*=0.03). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with ezetimibe monotherapy (*P*<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with ezetimibe monotherapy (*P*=0.02). A significantly greater proportion of patients on simvastatin-ezetimibe therapy experienced a reduction in LDL-C >50% from baseline, compared with the simvastatin monotherapy group (*P* value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and simvastatin-ezetimibe groups (72% and 69%, respectively; *P* value not reported).
Feldman, Davidson et al[45] Simvastatin-ezetimibe 10 mg/10 mg daily for 12	MA Post hoc analysis of three randomized,	N=3,083 (3 studies) 28 weeks	Primary: Percent change in LDL-C, TG, non–HDL-C, apo B, and	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C, TG, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs	double-blind, placebo controlled studies among patients with primary hypercholesterolemia		CRP from baseline, achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	with simvastatin monotherapy (*P*<0.001). These affects did not differ between the older and younger patients (*P* value not reported). Treatment with simvastatin-ezetimibe and simvastatin monotherapy resulted in comparable increases in HDL-C from baseline (8% vs 7%, respectively; *P* value not reported). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (79% vs 42%; *P*<0.001). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <70 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (37% vs 6%; *P*<0.001). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe combination therapy groups, regardless of dose used and age group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				
Ballantyne, Blazing et al[46] Simvastatin-ezetimibe 10 mg/20 mg, combination product, daily for weeks 1-6, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 7-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs simvastatin-ezetimibe 10 mg/10 mg, combination product, daily for weeks 1-6, titrated to simvastatin-ezetimibe 10 mg/20 mg for weeks 7-12, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 12-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs	DB, MC, RCT Patients ≥18 years with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10-year risk of >20% for CHD, and with LDL cholesterol ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10-year risk of <20% for CHD, and with LDL-C ≥160 mg/dL, and no CHD or its risk equivalent with <2 risk factors and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the	N=788 24 weeks	Primary: Mean percent change in LDL-C from baseline to end of treatment period Secondary: Percent change in LDL-C and HDL-C from baseline to the ends of the second and fourth (final) 6-week treatment periods	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline, compared with atorvastatin monotherapy (52.4% vs 45.1%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline, compared with atorvastatin monotherapy (12.3% vs 6.5%; *P*<0.001). Secondary: At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/20 mg and 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (50.2%, 54.3%, and 44.3%, respectively; *P*≤0.05). At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (12.4% vs 6.9%; *P*≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 80 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 10 mg daily for weeks 1-6, titrated to atorvastatin 20 mg for weeks 7-12, titrated to atorvastatin 40 mg for weeks 12-18, titrated to atorvastatin 80 mg for weeks 19-24	ULN, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the ULN, and a hemoglobin A_{1C} <9% in patients with diabetes			monotherapy group (59.4% vs 52.5%, respectively; *P*≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 80 mg monotherapy group (12.3% vs 6.5%; *P*≤0.05). The safety of simvastatin-ezetimibe was observed to be similar to that of atorvastatin monotherapy (*P* value not reported).
Goldberg, Guyton et al[47] VYTAL Simvastatin-ezetimibe 10 mg/20 mg daily for 6 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 6 weeks, combination product vs atorvastatin 10 mg daily for 6 weeks vs atorvastatin 20 mg daily for 6 weeks vs atorvastatin 40 mg daily for 6 weeks	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with hemoglobin A_{1c} ≤8.5%, LDL-C >100 mg/dL and a triglyceride level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week 6 Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non–HDL-C, total cholesterol, TG, and CRP	Primary: Patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy experienced greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 10 mg or 20 mg daily (53.6%, 38.3%, and 44.6%, respectively; *P*<0.001). Patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy experienced greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 40 mg daily (57.6% and 50.9%, respectively; *P*<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (59.7%, 21.5%, and 35%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 40 mg daily (74.4% and 55.2%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (90.3%, 70%, and 82.1%, respectively; *P*=0.007). A greater proportion of patients randomized to simvastatin 40

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 40 mg daily (93.4% and 88.8%, respectively; *P*=0.07). Patients randomized to simvastatin-ezetimibe combination therapy, at all doses, experienced a significant increase in HDL level (*P*≤0.001), a greater reduction in total cholesterol, and non-HDL cholesterol (*P*<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and triglyceride level compared to patients receiving atorvastatin (*P*=0.02). Side effects were similar in the simvastatin-ezetimibe and atorvastatin groups (19.85 vs 22.7%; *P* value not reported).
Ballantyne, Abate et al[48] VYVA Simvastatin-ezetimibe 10 mg/10 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/20 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/40 mg daily,	DB, MC, PG, RCT Adult patients with hypercholesterolemia, between 18 and 79 years of age, with an LDL-C level at or above drug treatment thresholds established by NCEP ATP III, with established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≤20% with an LDL-C ≥130	N=1,902 10 weeks	Primary: Mean percent change from baseline in LDL-C at 6 weeks Secondary: Percent change from baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, percentage of subjects that reached NCEP ATP III LDL-C goal	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin (53.4% vs 45.3%; *P*<0.001). Secondary: Simvastatin-ezetimibe 10/20 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 10 mg (50.6% vs 36.1%; *P*<0.001), and atorvastatin 20 mg therapy (50.6% vs 43.7%; *P*<0.001). Simvastatin-ezetimibe 10/40 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 40 mg (57.4% vs 48.3%; *P*<0.001). Simvastatin-ezetimibe 10/80 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/80 mg daily, combination product for 6 weeks vs atorvastatin 10 mg daily for 6 weeks vs atorvastatin 20 mg daily for 6 weeks vs atorvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks	mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with ≥2 risk factors, and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT, AST, or CK level ≤1.5 times the ULN, serum creatinine ≤1.5 mg/dL, and hemoglobin A_{1C} <9.0% in patients with diabetes			weeks, compared with atorvastatin 80 mg (58.6% vs 52.9%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline at 6 weeks, compared with atorvastatin (7.9% vs 4.3%; *P*<0.001). A greater proportion of patients reached their NCEP ATP III LDL-C goal at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (89.7% vs 81.1%; *P*<0.001). A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <100 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (85.4% vs 70%; *P*<0.001). A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <70 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (45.3% vs 20.5%; *P*<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in the risk of ALT/AST elevation >3 times the ULN, compared with atorvastatin therapy (*P*=0.006).
Constance et al[49] Atorvastatin 20 mg daily for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, hemoglobin A_{1C} ≤10%, ALT/AST levels <1.5 times the ULN, CK <1.5 times	N=661 6 weeks	Primary: Change from baseline in LDL-C at 6 weeks Secondary: Change from baseline in total cholesterol, HDL-C, TG, non–	Primary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin 20 mg monotherapy group (*P*≤0.001). Secondary: Across all doses, patients on the simvastatin-ezetimibe combination

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ezetimibe 10 mg daily added to simvastatin 20 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period	the ULN; patients were excluded if they had congestive heart failure NYHA classes III- IV, MI, CABG or angioplasty within 3 months, uncontrolled HTN or endocrine/metabolic disease, renal dysfunction or nephrotic syndrome, alcohol consumption >14 drinks per week and treatment with excluded concomitant medications		HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	therapy experienced a statistically significant reduction from baseline in total cholesterol, non-HDL, apo B, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the atorvastatin 20 mg monotherapy group ($P \leq 0.001$). Patients on the simvastatin-ezetimibe 10/40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared with the atorvastatin 20 mg monotherapy group (P=0.006). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe 10/20 mg and 10/40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5%, 87%, and 70.4%, respectively; $P \leq 0.001$). The incidence of drug-related adverse effects was similar in the simvastatin-ezetimibe 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5%, 0.5%, and 2.3%, respectively; P value not reported).
Pearson, et al[50] Ezetimibe 10 mg daily for 12 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks, separate entities vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks	MA Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to simvastatin-ezetimibe or atorvastatin for 6 weeks	N=4,373 (4 studies) Up to 12 weeks	Primary: Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (52.5% vs 38%; P<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin monotherapy group (53.4% vs 45.3%; P<0.001). Across all doses, patients on the simvastatin-ezetimibe combination therapy experienced a statistically significant CRP reduction from baseline compared with the simvastatin monotherapy group (31% vs 14.3%; P<0.001). Patients on the simvastatin-ezetimibe combination therapy experienced a similar CRP reduction from baseline compared with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs placebo				the atorvastatin monotherapy group (25.1% vs 24.8%; *P* value not reported). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9% vs 43.1%; *P*<0.001). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37% vs 5.7%; *P*<0.001). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8% vs 61.9%; *P*<0.001). Significantly greater proportion of patients randomized to the simvastatin-ezetimibe combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2% vs 16.8%; *P*<0.001). Secondary: Not reported
Piorkowski et al[51] Atorvastatin 10 mg daily in addition to ezetimibe 10 mg daily, separate entities vs atorvastatin 40 mg	RCT Patients between 18 and 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10-20 mg daily, receiving aspirin and clopidogrel; patients were excluded	N=56 4 weeks	Primary: Reduction in LDL-C, TG, change in liver transaminases, CK, HDL from baseline, percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL in either group (*P* value not reported). Both groups exhibited a statistically significant reduction in LDL-C from baseline (*P*<0.005). There was no statistically significant difference between the two groups in the percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) (*P* value not reported). There was no statistically significant difference between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	if they had a history of an MI or CK elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal insufficiency, active liver disease, liver cirrhosis, unexplained transaminase elevation, recent antibiotic therapy, or known alcohol abuse			groups in degree of LDL-C reduction from baseline (*P* value not reported). Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in triglyceride level from baseline (*P*<0.005 and *P*<0.05, respectively). Secondary: Not reported
Ballantyne, Weiss et al[52] EXPLORER Ezetimibe 10 mg, in addition to rosuvastatin 40 mg daily, separate entities, for 6 weeks vs rosuvastatin 40 mg daily for 6 weeks	MC, OL, PG, RCT Patients ≥18 years of age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%), and mean LDL-C between 160 mg/dL and 250 mg/dL with the two last measurements within 15% of each other, and TG <400 mg/dL; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral	N=469 6 weeks	Primary: Percentage of patients achieving the ATP III LDL-C goal (<100 mg/dL) at 6 weeks Secondary: Change from baseline in LDL-C, total cholesterol, TG, HDL, non-HDL cholesterol, LDL:HDL cholesterol, TC:HDL, non-HDL:HDL, apo B, apo AI, CRP	Primary: Significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (94% vs 79.1%; *P*<0.001). Secondary: Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL-C compared to the monotherapy group (70% vs 57%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in total cholesterol compared to the monotherapy group (51% vs 42%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL cholesterol compared to the monotherapy group (65% vs 52%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TG compared to the monotherapy group (35% vs 25%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL:HDL cholesterol compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or CK >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled HTN, or body mass index ≥30 kg/m^2			to the monotherapy group (72% vs 60%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC:HDL cholesterol compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL/HDL cholesterol compared to the monotherapy group (67% vs 55%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in apo B compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in CRP compared to the monotherapy group (46% vs 29%; *P*<0.001). There was no statistically significant difference in HDL cholesterol increase (*P*=0.151) or apo AI reduction (*P*=0.202) between the combination therapy and rosuvastatin monotherapy groups. The frequency and types of adverse events were similar across the combination and monotherapy groups (31.5% and 33.5%, respectively; *P* value not reported).
Farnier et al[53] Simvastatin-ezetimibe 10 mg/20 mg for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg, combination product, in addition to fenofibrate 160 mg for 12	DB, I, MC, PG, RCT Patients ≥18 years of age with mixed hypercholesterolemia, no CHD or a CHD risk equivalent disease (except for diabetes), or 10-year CHD risk score >20% according to the NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in total cholesterol, TG, HDL, non-HDL cholesterol, LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B	Primary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction in LDL-C from baseline compared with the fenofibrate monotherapy group (45.8% vs 15.7%; *P*<0.05). There was no significant difference between LDL-C reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (45.8% vs 47.1%; *P*>0.2). Secondary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction from baseline in non-HDL cholesterol, TG, and apo B

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs fenofibrate 160 mg for 12 weeks vs placebo for 12 weeks				compared with the other treatment groups (*P*<0.01). There was no significant difference between total cholesterol reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (38.7% vs 35.4%; *P*>0.05). Simvastatin-ezetimibe/fenofibrate group exhibited significant increase from baseline in HDL cholesterol compared with the simvastatin-ezetimibe group (18.7% vs 9.3%; *P*<0.01). Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction from baseline in LDL:HDL cholesterol, TC:HDL compared with the simvastatin-ezetimibe group (*P*=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (88.5% vs 92.9%; *P* value not reported).
Kastelein et al[54] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH,	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events		IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs 8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Homozygous Familial Hypercholesterolemia (HoFH)				
Gagné et al[55] Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg daily for another 12 weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition of ezetimibe 10 mg daily for another 12 weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with HoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day); patients were excluded if they had liver disease, ALT or AST >2 times the ULN, significant renal disease, unstable coronary syndromes or advanced congestive heart failure, or ongoing treatment with fibric acid derivatives	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7% vs 6.7%; *P*=0.007). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7% vs 5.3%; *P*<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Statins used in the study included simvastatin and atorvastatin.				

Study abbreviations: CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, ER=extended release, ES=extension study, FU=follow-up, HR=hazard ratio, I=international, MA=meta-analysis, MC=multicenter, OR=odds ratio, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RR=risk ratio, SB=single blind, SA=subanalysis

Miscellaneous abbreviations: ALT=alanine transaminase, ACS=acute coronary syndrome, AMI=acute myocardial infarction, AST=aspartate transaminase, DBP=diastolic blood pressure, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, CVD=cerebrovascular disease, FBG=fasting blood glucose, HDL-C=high density lipoprotein cholesterol, HTN=hypertension, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NCEP ATP =National Cholesterol Education Program Adult Treatment Panel, NYHA=New York Heart Association, PCI=percutaneous intervention, TC=total cholesterol, TG=triglycerides, upper limit of normal

Additional Evidence

Dose Simplification:
All combination HMG-CoA reductase inhibitors (statins) are administered once daily. Their only advantage over individual components is that they allow therapy consolidation, offering patients the opportunity to decrease their pill burden.

A study by LaFleur et al evaluated the differences in adherence and persistence with (1) a fixed-dose combination product containing lovastatin and extended-release niacin, (2) statin monotherapy, (3) extended-release niacin monotherapy, and (4) extended-release niacin taken with lovastatin as separate formulations.[56] A total of 2,389 patients met the eligibility criteria and were followed for one year. All groups exhibited an adherence rate >80%. Patients receiving extended-release niacin and lovastatin taken separately demonstrated higher adherence rates compared to those on the fixed-dose product (90% vs 88%; P=0.033). In addition, patients were less adherent to statin monotherapy than to either the fixed-dose combination product or niacin monotherapy (81%, 90%, and 89%, respectively; P<0.05). At 12 months, all treatment groups had a persistence rate of <20%. At 9 months, patients randomized to niacin monotherapy exhibited a significantly lower rate of persistence compared to the rest of the groups (P<0.05). Since this was an adherence study only, based on an evaluation of pharmacy claims, the study did not measure the impact of adherence on low-density lipoprotein cholesterol (LDL-C) or other cholesterol goals.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Combination HMG-CoA Reductase Inhibitors

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
atorvastatin and amlodipine	tablet	Caduet®	$$$$	N/A
lovastatin and niacin	extended-release tablet	Advicor®	$$$	N/A
simvastatin and ezetimibe	tablet	Vytorin®	$$$	N/A

No generic products are available in this class.
N/A=not available.

X. Conclusions

The combination HMG-CoA reductase inhibitors (statins) are FDA-approved for the treatment of primary hypercholesterolemia.[7,10,11] Atorvastatin-amlodipine and lovastatin-niacin combination products are also indicated for the prevention of cardiovascular events.[9,10] Simvastatin-ezetimibe is not FDA-approved for either primary or secondary prevention of cardiovascular events.[6] All products are formulated for once-daily oral administration. None of the products in this class are available generically. In general, the pharmacokinetic, pharmacologic, drug-interaction, and side-effect parameters with the combination statins are similar to their separate constituents.

The combination statins have demonstrated a significant benefit in reducing total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and increasing high-density lipoprotein cholesterol (HDL-C).[1,2,4] Statins are used as first-line agents for the treatment of hypercholesterolemia and prevention of cardiovascular events.[1] Niacin may increase HDL-C and lower triglycerides to a greater degree compared to statin monotherapy.[2,11,30,31] When used in combination with statin therapy, patients evaluated in clinical studies were able to achieve greater LDL-C reduction compared to either niacin or statin monotherapy. Ezetimibe may be used as adjunctive therapy to statins in helping patients reach their NCEP ATP III targets for lipid levels.[4,5]

Although studies have shown that the combination of ezetimibe and a statin is more efficacious in improving lipid parameters than monotherapy with either agent, the recently published results of the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) did not show that these reductions led to better clinical outomes.[54] The ENHANCE trial consisted of 720 patients with familial hypercholesterolemia with a primary end point of mean change in the intima-media thickness measured at three sites in the carotid artery. No significant difference was found in this primary end point between the treatment groups (simvastatin-ezetimibe 80/10 mg compared to patients treated with simvastatin 80 mg alone) during the two-year study period. Combination therapy with ezetimibe and simvastatin significantly lowered LDL-C by 16.5% compared to simvastatin alone. Additional studies are necessary to determine if the combination of ezetimibe plus a statin results in better clinical outcomes since no trial has yet demonstrated a reduction of cardiovascular outcomes with either ezetimibe alone or in combination therapy with a statin.[57,58]

The NCEP ATP III guidelines designate statins as first-line agents for the treatment of patients with hypercholesterolemia, failing therapeutic lifestyle modification, at high risk for cardiovascular events as well as patients suffering from heterozygous familial hypercholesterolemia.[13,14] Therapy should be adjusted to the recommended LDL-C goal <100 mg/dL in high-risk patients; however, an LDL-C goal of <70 mg/dL can be a therapeutic option for patients with coronary heart disease or those at very high risk. If LDL-C goal is not reached after 6 weeks of statin therapy, either an elevation of dose or the addition of a second agent, such as ezetimibe or niacin, is (according to current guidelines)appropriate. Furthermore, niacin may be preferred among patients with high triglycerides or low HDL-C levels. The European Guidelines on Cardiovascular Disease Prevention suggest that ezetimibe can be used in patients with active liver disease.[18] Otherwise, ezetimibe's primary beneficial effect is add-on therapy to statins. The guidelines do not directly address the role of statin fixed-dose combination products.

Therefore, all brand products within the class reviewed are comparable to each other with regards to lipid parameters and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use. In general, HMG-CoA reductase inhibitor combination products do not offer any significant clinical advantage over administration of their individual components.

XI. Recommendations

No brand combination HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous Antilipemic Agents
AHFS Class 240692
May 14, 2008

I. Overview

Niacin and omega-3 acid ethyl esters are the only two agents classified as miscellaneous antilipemic agents by the American Hospital Formulary Service (AHFS).[1] Both agents are available as over-the-counter (OTC) and brand name prescription formulations.[1-5] Prescription niacin and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) as adjunctive agents for the treatment of hypertriglyceridemia.[2,3,5] Prescription niacin has several other FDA indications which are to manage hypercholesterolemia and mixed dyslipidemias, to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, and to slow progression or promote regression of atherosclerotic disease in combination with bile acid binding resins in patients with a history of coronary artery disease and hypercholesterolemia.[3]

Niacin (nicotinic acid) is a water-soluble, B complex vitamin.[1] The exact mechanism by which niacin lowers cholesterol and triglycerides is not completely understood but is independent of the drug's role as a vitamin. Reductions in low-density lipoprotein cholesterol (LDL-C) through reduced hepatic synthesis of very low-density lipoprotein cholesterol (VLDL-C) are primarily responsible for the antilipemic effect of niacin.[1,6] Niacin may decrease production of VLDL-C by partially inhibiting mobilization of free fatty acids from adipose tissue, decreasing delivery of free fatty acids to the liver, decreasing triglyceride synthesis and altering the hepatic production of apolipoprotein B. Niacin increases high-density lipoprotein cholesterol (HDL-C) by reducing its catabolism.

Lovaza® (formerly known as Omacor®) is the only FDA-approved prescription omega-3 fatty acid product and it was first approved in 2004.[7] Each 1-g capsule contains at least 900 mg of the ethyl esters of omega-3 fatty acids, which are predominantly eicosapentaenoic acid (EPA-approximately 465 mg) and docosahexaenoic acid (DHA-approximately 375 mg).[5] The omega-3 fatty acids in this formulation are derived from a natural marine origin (eg, herring, mackerel, salmon) and through an FDA-monitored process the oil expressed from the fish carcass is purified and refined.[7] The mechanism(s) by which omega-3 fatty acids lower triglyceride levels is not completely understood but may be related to a reduction in triglyceride production and/or increase in triglyceride clearance.

OTC niacin and omega-3 acid ethyl esters are labeled as "dietary supplements" and as such, the production and marketing are not strictly regulated by the FDA in the same way as it oversees prescription products.[7,8] While dietary supplements are "generally recognized as safe", the FDA does not examine the efficacy and safety of these products or inspect or regulate manufacturing processes.[7] In addition, the FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease" (only FDA-approved drugs can legally make such claims). Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[8] The American Heart Association (AHA) states that OTC "dietary supplement niacin must not be used as a substitute for prescription niacin" and "it should not be used for lowering cholesterol because of potential very serious side effects".[9] OTC omega-3 fatty acid products may also contain widely variable amounts and ratios of the active ingredients EPA and DHA.[1] The most common fish-oil capsule provides approximately 180 mg EPA and 120 mg DHA per capsule. The total EPA and DHA dose recommended for triglyceride lowering is approximately 2-4 g per day.[7] The AHA advises that therapy with EPA and DHA to lower very high triglyceride levels should be used only under a physician's care. In addition, the FDA has recommended that the dosage of EPA and DHA as a dietary supplement not exceed 2 g per day.

The miscellaneous antilipemic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic legend products in this class. Niacin is available as OTC and prescription brand name immediate-release and sustained-release formulations; the OTC products are

included on the Alabama Medicaid Preferred Drug List (PDL). While omega-3 acid ethyl esters are also available OTC and by prescription, the OTC products are not covered by Alabama Medicaid.

Table 1. Miscellaneous Antilipemic Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
niacin	sustained-release capsule, sustained-release tablet, tablet	Niacor®, Niaspan®, Slo-Niacin®†	niacin†, Niacor®, Niaspan®
omega-3 acid ethyl esters	capsule	Lovaza®‡,	none

†Product is available over-the-counter.
‡Omacor was renamed to Lovaza in August 2007.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the miscellaneous antilipemic agents are summarized in Table 2. The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[10] The NCEP guidelines focus primarily on attaining goal LDL-C levels, since LDL-C is the major atherogenic lipid component. In general for every 1% reduction in LDL-C there is a 1% reduction in coronary heart disease (CHD) event rates.[6] Although LDL-C is the primary treatment target, very elevated triglycerides should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C even if the LDL-C goal has already been achieved.[10] Elevations of HDL-C by 1% result in a reduction of approximately 2% in CHD events.[6] For a more comprehensive overview of the treatment of dyslipidemias, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Miscellaneous Antilipemic Agents

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[10]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • In high-risk patients with high triglyceride (TG) or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins). The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. • The use of omega-3 acid ethyl esters was not addressed in this guideline.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[11]**	<u>General Recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Nicotinic Acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk persons with

Clinical Guideline	Recommendation
	atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Omega-3 Fatty Acids</u> • Omega-3 fatty acids (linolenic acid, DHA, EPA) have 2 potential uses. • In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3-12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent clinical trials also suggest that relatively high intakes of omega-3 fatty acids (1-2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive clinical trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1-2 g/day) for either primary or secondary prevention.
American Heart Association (AHA)/ American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[12]	<u>All Patients With Coronary and Other Atherosclerotic Vascular Disease</u> • In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction. <u>Lipid Management</u> • Therapeutic options to reduce non–HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy. • Dietary supplement niacin must not be used as a substitute for prescription niacin.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[13]	• Lifestyle modifications may include fish oil (EPA and DHA). • Dietary and nondietary intake of omega-3 polyunsaturated fatty acids may reduce overall mortality and sudden death in patients with stable coronary artery disease (CAD). The guideline notes that the AHA recommends omega-3 fatty acids in patients with stable CAD and the recommended daily amount is 1 g of EPA/DHA by capsule supplement, the equivalent amount in alpha-linolenic acid (ALA) from vegetable sources or by eating at least two servings of fatty fish per week. • Statins are considered the drugs of choice for lowering LDL-C. • If patients are unable to take a statin, then bile acid sequestrants, ezetimibe, fibric acid derivatives and niacin are available. • Niacin and omega-3 fatty acids are considered treatment options after therapeutic lifestyle changes, in patients with increased LDL-C and triglycerides. • Niacin is considered a treatment option after therapeutic lifestyle changes, in patients with increased LDL-C with or without a low HDL-C. • Niacin is considered a treatment option after therapeutic lifestyle changes, in patients with normal LDL-C and HDL-C <40 mg/dL.

Clinical Guideline	Recommendation
	• Niacin and omega-3 fatty acids are considered treatment options after therapeutic lifestyle changes, in patients with increased triglycerides. • The guidelines note that niacin can elevate glucose in patients with diabetes.
American Heart Association (AHA): Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: **A Scientific Statement From the American Heart Association (2007)**[14]	• Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[15]	• Statins are first-line drugs for lowering LDL-C. • Niacin is considered an effective lipid-lowering agent but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When triglycerides are between ~450-900 mg/dL, either fibrates or statins may be used as first-line drugs, and niacin is considered a good drug for selected patients. • Fish oils are also triglyceride-lowering agents and might be useful as a third-line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other triglyceride-lowering drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antilipemic agents are summarized in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Antilipemic Agents

Indications	Niacin, Extended-Release* (Niaspan®)	Niacin, Immediate-Release† (Niacor®)	Omega-3 Acid Ethyl Esters
Adjunct to diet for reduction of elevated TC, LDL-C, apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to an appropriate diet has been inadequate	✔		
Adjunct to diet for reduction of elevated TC and LDL-C in patients with primary hypercholesterolemia when response to an appropriate diet and nonpharmacologic measures alone have been inadequate		✔	
In combination with lovastatin, treatment of primary hypercholesterolemia and mixed dyslipidemia	✔		
To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia	✔		
In combination with a bile acid binding resin, to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hypercholesterolemia	✔		

Indications	Niacin, Extended-Release* (Niaspan®)	Niacin, Immediate-Release† (Niacor®)	Omega-3 Acid Ethyl Esters
In combination with a bile acid binding resin as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia, when the response to an appropriate diet or diet plus monotherapy has been inadequate	✔	✔	
Adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Fredrickson Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them	✔	✔	
Adjunct to diet to reduce triglyceride levels in adult patients with very high (>500 mg/dL) triglyceride levels			✔

apo B=apolipoprotein B, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides
*Slo-Niacin, an over-the-counter extended-release niacin tablet, is "suggested as a dietary supplement". [4]
†Over-the-counter immediate-release niacin is a dietary supplement.[3]

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous antilipemic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Antilipemic Agents[1-5,16]

Drug	Bioavailability (%)	Time to Peak	Protein Binding (%)	Elimination	Active Metabolites	Serum Half-Life
Niacin, extended-release (Niaspan®)	60-76*	4-5 hours	Not reported	Rapidly metabolized and undergoes extensive first-pass metabolism; 60%-76% eliminated by the kidneys as unchanged drug and metabolites; up to 12% recovered as unchanged niacin after multiple dosing	Several metabolites whose activity is unknown	20-60 minutes (niacin)
Niacin, immediate-release tablet (Niacor®)	Rapid absorption from the gastrointestinal tract (% not reported)	30-60 minutes	Not reported	Rapidly metabolized and undergoes extensive first-pass metabolism; 88% eliminated by kidneys as unchanged drug and nicotinuric acid, the primary metabolite (inactive)	Unknown	20-45 minutes
Omega-3 acid ethyl esters (Lovaza®)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

*Single-dose bioavailability studies have demonstrated that the 500 mg and 1,000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablets are not dosage form equivalent.

V. Drug Interactions

Drug interactions of major (Level 1) and/or moderate (Level 2) severity for niacin or omega-3 acid ethyl esters have not been reported.[17] Rare cases of rhabdomyolysis have been linked to concomitant administration of niacin (doses ≥1 g/day) and hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins). In clinical studies with a combination tablet of niacin and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1,079 patients who were treated with doses up to 2,000 mg of niacin and 40 mg of lovastatin daily for periods up to 2 years. When selecting combination therapy with niacin and HMG-CoA

reductase inhibitors, prescribers should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.[2,3]

VI. Adverse Drug Events

The most common adverse events with the miscellaneous antilipemic agents are noted in Table 5. At usual antilipemic dosages, niacin is generally well tolerated and side effects have been mild and transient.[1] The most common adverse effects with niacin are gastrointestinal upset, flushing (especially of the face and neck) and pruritus. Flushing is more common with the immediate-release formulation and may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin (325 mg) or ibuprofen (200 mg).[1,18] The frequency and severity of adverse hepatic effects appear to be dose related and may be increased with the sustained-release preparations.[1] Sustained-release preparations have been hepatotoxic in doses ≥2 g per day. Although uncommon, cases of severe hepatotoxicity have occurred in patients who have substituted sustained-release niacin for equivalent doses of immediate-release niacin. Therefore, different formulations should not be used interchangeably.

The American Heart Association has issued the following statement regarding niacin:

> "Niacin comes in prescription form and as 'dietary supplements.' Dietary supplement niacin must *not* be used as a substitute for prescription niacin. It should *not* be used for lowering cholesterol because of potential very serious side effects. Dietary supplement niacin is not regulated by the United States (US) Food and Drug Administration (FDA) the same way that prescription niacin is. It may contain widely variable amounts of niacin—from *none* to much more than the label states. The amount of niacin may even vary from lot to lot of the same brand."[9]

Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters (Lovaza®) are safe and well tolerated.[7] The most common adverse events were eructation, infection, flu-like syndrome, dyspepsia and taste perversion. Omega-3 acid ethyl esters should be used with caution in patients with known hypersensitivity to fish or shellfish.[1]

Table 5. Adverse Drug Events (%) Reported with the Miscellaneous Antilipemic Agents[2-5]

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Cardiovascular			
Angina pectoris	-	-	1.3
Arrhythmia (including atrial fibrillation)	✔	✔	✔
Bypass surgery	-	-	✔
Cardiac arrest	-	-	✔
Chest pain	-	-	✔
Hyperlipidemia	-	-	✔
Hypertension	-	-	✔
Hypotension	✔	✔	-
Migraine	✔	-	✔
Myocardial infarction/ischemia/occlusion	-	-	✔
Orthostasis	✔	✔	-
Palpitations	✔	-	-
Peripheral vascular disorder	-	-	✔
Syncope	✔	-	✔
Tachycardia	✔	-	✔
Central Nervous System			
Depression	-	-	✔
Dizziness	✔	-	✔
Emotional lability	-	-	✔
Facial paralysis	-	-	✔

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Headache	5-11	✔	-
Insomnia	✔	-	✔
Nervousness	✔	-	-
Paresthesia	✔	-	-
Vasodilatation	-	-	✔
Vertigo	-	-	✔
Dermatologic			
Acanthosis nigricans	✔	✔	-
Alopecia	-	-	✔
Dry skin	✔	✔	-
Eczema	-	-	✔
Hyperpigmentation	✔	✔	-
Mild-to-severe cutaneous flushing	✔	✔	-
Pruritus	≤6	✔	✔
Rash	0-5	-	1.8
Urticaria	✔	-	-
Sweating	✔	-	✔
Endocrine/Metabolic			
Abnormal liver function tests	✔	✔	✔
Decreased glucose tolerance	✔	✔	-
Edema (generalized)	✔	-	✔
Face edema	✔	-	-
Gout	✔	✔	-
Hyperglycemia	✔	-	✔
Hyperuricemia	✔	✔	-
Increased amylase	✔	-	-
Increased lactate dehydrogenase	✔	-	-
Peripheral edema	✔	-	-
Reductions in phosphorus	✔	-	-
Gastrointestinal			
Abdomen enlarged	-	-	✔
Abdominal pain	2-5	-	-
Anorexia	-	-	✔
Colitis	-	-	✔
Constipation	-	-	✔
Diarrhea	6-8	✔	-
Dry mouth	-	-	✔
Dyspepsia	2-5	✔	3.1
Dysphagia	-	-	✔
Eructation	✔	-	4.9
Fecal incontinence	-	-	✔
Flatulence	✔	-	-
Gastritis	-	-	✔
Gastroenteritis	-	-	✔
Hepatotoxicity	-	✔	-
Increased appetite	-	-	✔
Intestinal obstruction	-	-	✔
Jaundice	✔	✔	-
Nausea	2-8	-	-
Pancreatitis	-	-	✔
Peptic ulceration	✔	✔	-
Tenesmus	-	-	✔

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Vomiting	0-8	✔	✔
Hematologic/Lymphatic			
Lymphadenopathy	-	-	✔
Prolongation prothrombin time	✔	-	-
Slight reduction platelet count	✔	-	-
Musculoskeletal			
Arthralgia	-	-	✔
Arthritis	-	-	✔
Asthenia	✔	-	✔
Back pain	-	-	2.2
Fracture	-	-	✔
Leg cramps	✔	-	-
Malaise	-	-	✔
Myalgia	✔	-	✔
Myasthenia	✔	-	-
Neck pain	-	-	✔
Pain	1-5	-	1.8
Rhabdomyolysis	-	✔	-
Rheumatoid arthritis	-	-	✔
Tendon rupture	-	-	✔
Respiratory			
Asthma	-	-	✔
Bronchitis	-	-	✔
Cough increased	-	-	✔
Dyspnea	✔	-	✔
Epistaxis	-	-	✔
Laryngitis	-	-	✔
Pharyngitis	-	-	✔
Pneumonia	-	-	✔
Rhinitis	2-5	-	✔
Sinusitis	-	-	✔
Urogenital			
Cervix disorder	-	-	✔
Endometrial carcinoma	-	-	✔
Epididymitis	-	-	✔
Impotence	-	-	✔
Other			
Body odor	-	-	✔
Cataract	-	-	✔
Chills	✔	-	✔
Cystoid macular edema	✔	✔	-
Fever	-	-	✔
Flu symptoms	-	-	3.5
Hypersensitivity reactions	✔	-	-
Infection	-	-	4.4
Neoplasm	-	-	✔
Sudden death	-	-	✔
Suicide	-	-	✔
Taste perversion	-	-	2.7
Toxoid amblyopia	✔	✔	-

- Event not reported or incidence <1%
✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antilipemic agents are summarized in Table 6. Both immediate-release and sustained-release niacin should be initiated at a low dose and titrated slowly according to patient tolerance and response.

Table 6. Usual Dosing for the Miscellaneous Antilipemic Agents[2-5,16]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Niacin	Hyperlipidemia: Immediate-release tablet (Niacor®): initial, 250 mg once daily following an evening meal; increase frequency and/or dose every 4-7 days to desired response or first-level therapeutic dose (1.5-2 g/day in 2 to 3 divided doses); after 2 months, may increase at 2- to 4-week intervals to 3 g/day (1 g 3 times per day); maximum: in patients with marked lipid abnormalities, a higher dose is occasionally required but generally should not exceed 6 g/day Sustained-release capsule or tablet (Niaspan®): initial, 500 mg at bedtime for 4 weeks, then 1 g at bedtime for 4 weeks; after week 8, titrate to patient response and tolerance; can increase to a maximum of 2 g/day, but only at 500 mg/day at 4-week intervals Niacin deficiency: Oral: 10-20 mg/day; maximum: 100 mg/day Note: sustained-release niacin preparations should not be substituted for equivalent doses of immediate-release niacin.	Safety and effectiveness in children have not been established.	Sustained-release capsule: 125 mg 250 mg 400 mg 500 mg Sustained-release tablet: 250 mg 500 mg 750 mg 1,000 mg Tablet: 50 mg 100 mg 250 mg 500 mg
Omega-3 acid ethyl esters	Oral: 4 g per day taken as a single 4 g dose or as two 2 g doses (2 capsules given twice daily)	Safety and effectiveness in pediatric patients <18 years of age have not been established.	Capsule: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antilipemic agents are summarized in Table 7.

Table 7. Clinical Efficacy Studies Using the Miscellaneous Antilipemic Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Niacin Cardiovascular Outcome Trials				
CDP Research Group (1975)[19] IR niacin 3 g per day vs clofibrate 1.8 g per day vs placebo Treatment arms also included estrogens and dextrothyroxine.	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 (N=1,119 for niacin, N=2,789 for placebo) 5 years	Primary: Total mortality Secondary: Cause-specific mortality (eg, coronary mortality and sudden death), nonfatal cardiovascular events	Primary: The incidence of total mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (all *P*=NS). Secondary: Five-year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (all *P*=NS). Major cardiovascular events were reduced with niacin: CHD events by 13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin treatment significantly reduced the incidence of nonfatal MI compared to placebo (8.9% vs 12.2%; *P*<0.004). There was no evidence of significant efficacy of clofibrate with regard to total mortality and cause-specific mortality. Treatment with niacin for 5 years lowered TC by 10% and TG levels by 26%. Treatment with clofibrate lowered TC by 7% and TG levels by 22%.
CDP Research Group (1986) [20] IR niacin 3 g per day	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 (N=1,119 for niacin, N=2,789 for placebo) 9 years	Primary: Total mortality Secondary: Cause-specific mortality (eg, coronary mortality and sudden death)	Primary: A follow-up of subjects 9 years after completion of the CDP study (total mean follow-up of 15 years) showed that niacin reduced the risk of all-cause mortality by 11% (52.0% for niacin and 58.2% for placebo; *P*=0.0004). Secondary: The survival benefit in the niacin group was primarily evident for death caused by CHD (36.5% for niacin vs 41.3% for placebo; *P*<0.05).
HATS[21] Niacin (mean dose 2.4±2.0 g per day) plus simvastatin	DB, PC Patients with clinical coronary disease (defined	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change	Primary: The mean levels of LDL-C, HDL-C and TG were significantly changed by –42% (*P*<0.001), +26% (*P*<0.001) and –36% (*P*<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(mean dose 13±6 mg per day) vs antioxidants (total daily dose of 800 IU vitamin E, 1,000 mg vitamin C, 25 mg beta carotene and 100 µg selenium) vs niacin plus simvastatin plus antioxidants vs placebos Note: niacin was initiated as SR niacin (Slo-Niacin®) 250 mg BID and increased to 1,000 mg BID at 4 weeks. Patients whose HDL-C had not increased by 5 mg/dL at 3 months, 8 mg/dL at 8 months and 10 mg/dL at 12 months were switched to IR niacin (Niacor®) up to a maximum of 4 g per	as previous MI, coronary interventions or confirmed angina) and with at least 3 stenoses of at least 30% of the luminal diameter or 1 stenosis of at least 50%, low HDL-C, normal LDL-C		in coronary stenosis (% stenosis caused by most severe lesion in each of 9 proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or revascularization) Secondary: Mean change in % stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	simvastatin. The protective increase in HDL2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (+65%) was attenuated by concurrent therapy with antioxidants (+28%; *P*=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (*P*=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (*P*=0.004) and regressed by 0.4% with niacin plus simvastatin (*P*<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo (*P*=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group (*P* values not reported). Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
day. Niacin "placebo" tablets contained immediate-release niacin and delivered 50 mg BID.				
Zhao et al[22] Niacin (mean dose 2.4±2.0 g per day) plus simvastatin (mean dose 13±6 mg per day) vs antioxidants (total daily dose of 800 IU vitamin E, 1,000 mg vitamin C, 25 mg beta carotene and 100 µg selenium) vs niacin plus simvastatin plus antioxidants vs placebo	ES of HATS[21] (see above) Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to question "Overall, how difficult is it to take the study medication?" Secondary: Not reported	Primary: Patients who had received niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo: any degree of flushing (30% vs 23%; *P*=NS), symptoms of fatigue, nausea and/or muscle aches (9% vs 5%; *P*=NS), AST ≥3 times ULN (3% vs 1%; *P*=NS), CPK ≥2 times ULN (3% vs 4%; *P*=NS), new onset of uric acid ≥7.5 mg/dL (18% vs 15%; *P*=NS), and homocysteine ≥15 µmol/L (9% vs 4%; *P*=NS). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly in the niacin plus simvastatin group but returned to pretreatment levels at 8 months and remained stable for the rest of the study. The niacin plus simvastatin combination regimen was repeatedly described by 91% of treated patients and 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported
ARBITER 2[23] SR niacin (Niaspan®) 1,000 mg QD	DB, PC, RCT Patients mean age 67 years (91% men) with known	N=167 1 year	Primary: Change in mean common CIMT after 1 year	Primary: After 12 months, mean CIMT increased significantly in the placebo group (0.044±0.100 mm; *P*<0.001) and was unchanged in the niacin group (0.014±0.104 mm; *P*=0.23). The overall difference in CIMT progression between the groups was not statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients received background statin therapy (specific statin not described).	coronary heart disease and low levels of HDL-C (<45 mg/dL)		Secondary: Changes in lipid concentrations, composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death), adverse events	significant (*P*=0.08); however, a post hoc analysis showed that niacin significantly reduced the rate of CIMT progression in subjects without insulin resistance (*P*=0.026). Secondary: HDL-C increased 21% in the niacin group but did not change in the placebo group (*P*<0.003). Clinical cardiovascular events occurred in 3 patients treated with niacin (3.8%) and 7 patients treated with placebo (9.6%; *P*=0.20). Adherence to study medication based on pill counts ranged from 90.3% to 94.5% and was not statistically different between the placebo and niacin groups (*P* value not reported). No patient experienced significant (3 times the ULN) elevations of liver enzymes or developed myositis. At the end of the study, skin flushing was reported to have occurred in 69.2% of patients receiving niacin compared to 12.7% of patients receiving placebo (*P*<0.001).
Niacin Clinical Trials				
ADMIT[24] IR niacin (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week double-blind)	Primary: Change in lipid profile, glucose, HbA_{1c}, ALT, uric acid; hypoglycemic drug use, compliance, adverse events Secondary: Not reported	Primary: Niacin use significantly increased HDL-C by 29% and 29% and decreased TG by 23% and 28% and LDL-C by 8% and 9%, respectively, in participants with and without diabetes compared to baseline (*P*<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; *P*=0.04 and *P*<0.001) in participants with and without diabetes, respectively. HbA_{1c} levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA_{1c} decreased by 0.3% (*P*=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ADVENT[25] SR niacin (Niaspan®) 1,000 mg per day vs SR niacin (Niaspan®) 1,500 mg per day vs placebo	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, HbA_{1c} Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13% to 19% for the 1,000 mg dose and 22% to 24% for the 1,500 mg dose; both *P*<0.05 vs placebo) and reductions in TG levels (–15% to –20% for the 1,000 mg dose; *P*=NS, and –28% to –36% for the 1,500 mg dose; *P*<0.05) were observed. Changes in HbA_{1c} levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28% and 7.35%; *P*=0.16) and placebo (7.13% and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2% and 7.5%; *P*=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (*P*<0.05). The mean changes from baseline at 16 weeks were +9%, +5% and –7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of +4% in both the placebo and niacin 1,000 mg groups and a decrease of –6% in the SR niacin 1,500 mg group (*P* values not reported). In both the niacin groups, an initial rise in FBG was observed between weeks 4 and 8 which returned to baseline by week 16. Four patients in the niacin group (3 patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving SR niacin and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.
Kuvin et al[26] SR niacin (Niaspan®) initially 500 mg HS for 2 weeks then	PC, RCT Patients with stable coronary artery disease and	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and	Primary: Six patients did not complete the protocol, 2 discontinued treatment due to flushing and 4 were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,000 mg HS vs placebo	LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)		inflammatory markers Secondary: Not reported	compared to baseline (*P*<0.005 for both), whereas TC and LDL-C remained unchanged. Compared with baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (*P*<0.001) and an 8% decrease in small-particle HDL (*P*=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (*P*=0.09) and a 12% decrease in small-particle LDL (*P*=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20% and 15%, respectively, compared to baseline (*P*<0.05 for both). No significant changes from baseline were seen in any tested parameter in subjects who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group. Secondary: Not reported
Capuzzi et al[27] SR niacin (Niaspan®) initiated at 375 mg HS for 1 week, then 500 mg HS for 1 week, then 1,000 mg HS for 1 week; dosages were titrated to 1,000 mg to 3,000 mg per day for weeks 4-96 based on clinical response and adverse events Concomitant therapy with a statin, bile acid	ES, MC, OL Patients (mean age 54 years) with primary hypercholesterol-emia who were previously enrolled in a randomized short-term study or in a placebo-only qualification clinical trial	N=517 Up to 96 weeks	Primary: Changes in LDL-C and apo B Secondary: Changes in TC, HDL-C, TC:HDL-C ratio, Lp(a) and TG; adverse events	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (*P*<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12% and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third (all *P*<0.001). TG and Lp(a) levels were decreased by 27% and 30%, respectively, at week 48, and by 28% and 40%, respectively, at week 96 (all *P*<0.001). SR niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of SR niacin.				≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to SR niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (all *P*<0.001). These changes were considered small and not likely to be biologically or clinically significant since the majority of the changes occurred within the reference values for these analytes. Six patients had AST levels >2 times the ULN and 2 patients had AST levels >3 times the ULN on niacin monotherapy. Five patients had ALT levels >2 times ULN and no patient had ALT levels >3 times ULN. Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy (all *P*<0.0001).
Guyton et al[28] SR niacin (Niaspan®) initiated at 375 mg HS for 1 week, then 500 mg HS for 1 week, then 1,000 mg HS for 1 week; dosages were titrated to 1,000 mg to 3,000 mg per day for weeks 4-96 based on clinical response and adverse events Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve	ES, MC, OL Patients (mean age 53 years) with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification clinical trial	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3 months (safety data)	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety Secondary: Not reported	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%) and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26% and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (*P*<0.01 for all values). At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%) and TG (32%) and increased HDL-C (25%) (*P*<0.01 for all values). Apo B (26%; *P*<0.01) and Lp(a) (19%; *P*=NS) were also reduced at 48 weeks but values for these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%) and increased HDL-C (31%) (*P*<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; *P*=NS). Apo B and Lp(a) were significantly reduced by 19% and 24% (*P*<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of SR niacin.				Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue SR niacin. (Combining all of the data, 7.3% of patients discontinued SR niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, 9 of 499 (2.6%) patients experienced an ALT or AST elevation >2 times ULN. Five of these patients were on combination therapy, including 4 with a statin and 1 with a bile acid sequestrant. In 5 of the 9 cases, the transaminase elevation resolved while SR niacin was continued without reduction in dose. Three cases led to SR niacin dosage reduction. One patient discontinued SR niacin because of transaminase elevations. Leg aches and myalgias with normal creatine kinase levels were described in 1 patient taking niacin with simvastatin. Secondary: Not reported
Gray et al[29] SR niacin (Slo-Niacin®) average maintenance dose of 1.67 g per day	RETRO cohort study Male veterans (mean age 61.7 years) treated for dyslipoprotein-emia with SR niacin between October 1988 and October 1991	N=969 1-36 months (mean 13.0 months)	Primary: Changes in lipid profile, alterations in hepatic enzymes and blood chemistry tests, hepatotoxicity Secondary: Not reported	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC –19.1%, LDL-C –24.0%, HDL-C +5.7%, and TG –32.5% (all $P \leq 0.0035$). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST +29%, ALT +23%, alkaline phosphatase +25%, and glucose +7%; $P=0.0001$). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic control led to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for “probable” and for “possible or probable” niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				concurrent oral sulfonylurea therapy. Secondary: Not reported
Knopp et al[30] IR niacin (brand not specified) TID titrated up to 1.5 g per day for weeks 4 to 8, and 3.0 g per day for weeks 9 to 16 vs SR niacin (Niaspan®) titrated up to 1.5 g HS by week 4 vs placebo	DB, MC, PG, RCT Patients with hypercholesterol-emia, average age 54 years	N=223 25 weeks (9 week lead-in period)	Primary: Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL subfractions, apo B, apo AI, apo E, and Lp(a)	Primary: LDL-C was significantly reduced by 12%, 12% and 22%, respectively, by SR niacin 1.5 g HS, IR niacin 1.5 g/day, and IR niacin 3.0 g/day, respectively, compared to placebo ($P \leq 0.05$). At equal doses of 1.5 g/day of SR niacin versus IR niacin, AST increased 5.0% vs 4.8% (P=NS), FPG increased 4.8% vs 4.5% (P=NS), and uric acid concentration increased 6% vs 16% (P=0.0001), respectively. Flushing events were more frequent with IR niacin versus SR niacin (1,905 vs 575; $P<0.001$). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary: Compared with placebo at 8 weeks, SR niacin 1.5 g HS vs IR niacin 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI ($P \leq 0.05$ in all instances). IR niacin 3.0 g/day produced significantly greater changes in the above lipid parameters compared to IR niacin 1.5 g/day and SR niacin 1.5 g HS ($P \leq 0.05$).
McKenney et al[31] IR niacin (generic by Rugby) administered BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks vs SR niacin (generic by	DB, PG, RCT Patients with LDL-C >160 mg/dL after 1 month on an NCEP ATP III - Step 1 diet	N=46 36 weeks	Primary: LCL-C, HDL-C, TG, adverse events (especially hepatotoxicity) Secondary: Not reported	Primary: SR niacin lowered LDL-C significantly more than IR niacin at the dosage of 1,500 mg/day and above ($P<0.04$ to $P<0.001$). IR niacin increased HDL-C levels significantly more than SR niacin at all dosage levels ($P<0.04$ to $P<0.001$). The reduction in TG levels was similar (P=NS) between IR and SR niacin at all dosages except for the 1,000 mg dose where the IR formulation led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) in the IR niacin group withdrew before completing the 3,000 mg daily dose. Four patients withdrew at the 1,000 mg dose, 1 patient at the 1,500 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Goldline) administered BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks				dose, 3 patients at the 2,000 mg dose and 1 patient at the 3,000 mg dose. The most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen of 23 patients (78%) in the SR niacin group withdrew before completing the 3,000 mg daily dose. Two patients withdrew at the 1,000 mg dose, 2 patients at the 1,500 mg dose, 7 patients at the 2,000 mg dose and 7 patients at the 3,000 mg dose. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatotoxic effects, while 12 patients (52%) receiving SR niacin did. Secondary: Not reported
Superko et al[32] IR niacin (brand not specified) 3,000 mg per day vs SR niacin (Niaspan®) 1,500 mg per day vs placebo In addition, results of 38 subjects receiving SR niacin 3,000 mg from a previous study were utilized.	PC, RCT Patients with hypercholesterol-emia	N=180 plus 38 subjects from a previous trial 14 weeks	Primary: Changes in lipid profile and lipoprotein subclass distribution Secondary: Not reported	Primary: IR and SR niacin significantly decreased TG, LDL-C, apo B, and Lp(a) and significantly increased HDL-C (all $P \leq 0.0001$). Both niacin products significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb (all $P<0.05$ with the exception of LDL I where $P=0.12$ for SR niacin 1,500 mg). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared with those with LDL pattern A (predominance of buoyant LDL). Compared to the IR 3,000 mg group, SR niacin 3,000 mg produced a smaller decrease in TG (–27% vs –47%; $P<0.001$) but had similar changes in LDL-C (–20% vs –22%; *P* value not reported), apo B (–22% vs –21%; *P* value not reported), HDL-C (27% vs 28%; *P* value not reported) and LDL peak particle diameter (0.90 mm vs 0.76 mm; *P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Guyton et al[33] SR niacin (Niaspan®) titrated up to 1,000 mg HS for 4 weeks, 1,500 mg HS for 4 weeks and 2,000 mg HS for 8 weeks vs gemfibrozil 600 mg BID	DB, MC, PC, RCT Patients between the ages of 21 and 75 years with an HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease, TG ≤400 mg/dL	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: SR niacin 1,500 mg and 2,000 mg raised HDL-C by 21% and 26%, respectively, vs 13% with gemfibrozil (*P*<0.02). Secondary: SR niacin 1,500 mg and 2,000 mg vs gemfibrozil significantly raised apo AI (9% and 11% vs 4%), reduced TC:HDL-C ratio (–17% and –22% vs –12%), reduced Lp(a) level (–7% and –20% vs no change), and had no adverse effect on LDL-C (2% and 0% change vs 9% increase; *P* values ranged from *P*<0.001 to *P*<0.02.). Triglycerides decreased by 40% with gemfibrozil vs 16% with SR niacin 1,000 mg (*P*<0.001) and 29% with niacin 2,000 mg (*P*<0.06). Effects on plasma fibrinogen levels were significantly favorable for SR niacin compared with gemfibrozil (–1% to –6% vs 5% to 9%, respectively; *P*<0.02). Flushing was significantly more frequent with SR niacin (78% of patients) compared with gemfibrozil (10% of patients) at every point (*P* values not reported). Flu syndrome occurred more frequently with SR niacin vs gemfibrozil group (*P*=0.006). Dyspepsia was a more frequent occurrence with gemfibrozil (*P*=0.009).
Omega-3 Acid Ethyl Esters Cardiovascular Outcome Trials				
GISSI-Prevenzione Investigators[34] Omega-3 PUFA 1 g daily (specific product not named but provided 850-882 mg EPA and DHA as ethyl esters in the average ratio of 1:2) vs vitamin E 300 mg daily	MC, OL, RCT Patients surviving a recent (≤3 months) MI	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; cumulative rate of CV death, nonfatal MI and nonfatal stroke Secondary: Analyses of components of primary end points and main causes of	Primary: Treatment with omega-3 PUFA, but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI and nonfatal stroke (RR, 10%; 95% CI, 1% to 18%; *P*=0.048 by 2-way analysis and RR, 15%; 95% CI, 2% to 26%; *P*=0.023 by 4-way analysis). Treatment with omega-3 PUFA decreased the risk of the composite of CV death, nonfatal MI and nonfatal stroke (RR 11%; 95% CI, 1% to 20%; *P*=0.053 by 2-way analysis and RR, 20%; 95% CI, 5% to 32%; *P*=0.008 by 4-way analysis). The effect of the combined treatment with omega-3 PUFA and vitamin E was similar to that for omega-3 PUFA for the primary end point (RR, 14%; 95% CI, 1% to 26%) and for fatal events (RR, 20%; 95% CI, 5% to 33%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs omega-3 PUFA and vitamin E vs no treatment			death, adverse events	Analyses of the individual components of the main end point showed that the decrease in mortality (20% for total deaths [*P* value not reported], 30% for cardiovascular deaths [*P*=0.0242], and 45% for sudden deaths [*P*=0.010]) which was obtained with omega-3 PUFA accounted for all of the benefit seen in the combined end point. There was no difference across the treatment groups for nonfatal cardiovascular events. At 1 year and at the end of the study, 11.6% and 28.5% of patients receiving omega-3 PUFA and 7.3% and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Side effects were reported as a reason for discontinuing therapy for 3.8% of patients in the omega-3 PUFA groups and 2.1% of those in the vitamin E groups. Overall, gastrointestinal disturbances and nausea were the most frequently reported side effects (4.9% and 1.4% of omega-3 PUFA recipients and 2.9% and 0.4% of vitamin E recipients, respectively; no *P* values were reported.).
Omega-3 Acid Ethyl Esters Clinical Trials				
Pownall et al[35] Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, PG, RCT Patients with severe hypertrigycer-idemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks (6 week run-in period)	Primary: Effect on TG, lipid profile, and lipid composition Secondary: Not reported	Primary: Median TG levels were reduced 38.9% from baseline in the omega-3 acid ethyl ester group compared to 7.8% with placebo (*P*=0.001). Omega-3 acid ethyl esters also significantly reduced TC (–9.9%; *P*=0.004) and VLDL-C (–29.2%; *P*=0.001) and significantly increased LDL-C (16.7%; *P*=0.007) from baseline. HDL-C increased in patients receiving omega-3 acid ethyl esters (5.9%; *P*=0.057 vs baseline and *P*=0.023 vs placebo) and decreased in patients receiving placebo (–5.9%; *P*=NS vs baseline). Secondary: Not reported
McKeone et al[36] Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertrigyceride mia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks (6 week run-in period)	Primary: Effect on TG and serum phospha-tidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3 acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase for placebo (*P* values not reported). Incorporation of eicosapentaenoic and docosahexaenoic acid into the serum phosphatidylcholine occurred within 6 weeks and was usually accompanied by a reduction in plasma TG. Secondary: Omega-3 acid ethyl esters also significantly reduced VLDL-C (28%) and TC (11%),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and increased HDL-C (14%) (*P* values not reported). None of these parameters significantly changed in the placebo group (*P* values not reported).
Calabresi et al[37] (2000) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks then crossed over to placebo vs placebo for 8 weeks then crossed over to omega-3 acid ethyl esters	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks (4 week run-in period and 6 week follow-up period after treatment)	Primary: Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Primary: Omega-3 acid ethyl esters significantly lowered plasma TG and VLDL-C by 27% and 18%, respectively (both $P<0.05$) compared to baseline. TC and HDL-C did not change but LDL-C and apo B increased by 21% ($P=0.05$) and 6% compared to baseline ($P<0.05$). Omega-3 acid ethyl esters treatment caused a redistribution of LDL-C subclasses towards less dense lipoprotein particles (possibly indicative of a less atherogenic LDL-C profile); however, the average LDL-C size did not change. Secondary: Omega-3 acid ethyl esters were well tolerated with no reports of drug-related adverse events or negative safety parameters (eg, glucose, uric acid, liver enzymes, kidney function, and platelet count).
Calabresi et al[38] (2004) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks then crossed over to placebo vs placebo for 8 weeks then crossed over to omega-3 acid ethyl esters	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 20 weeks (4 week run-in period)	Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution Secondary: Not reported	Primary: Plasma TG were 44% lower and LDL-C and apo B were 25% and 7% higher after omega-3 acid ethyl esters than placebo (all $P<0.05$). HDL-C was higher (8%) after omega-3 acid ethyl esters than placebo but this difference did not reach statistical significance ($P>0.05$). Omega-3 acid ethyl esters caused a selective increase of the more buoyant HDL2-C subfraction; plasma HDL2-C and total mass increased by 40% ($P<0.05$) and 26% (no *P* value reported), respectively, whereas HDL3-C and total mass decreased by 4% ($P>0.05$) and 6% (no P value reported). The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% after omega-3 acid ethyl esters ($P<0.05$). Secondary: Not reported
Davidson et al[39] Omega-3 acid ethyl	DB, MC, PC, PG, RCT	N=254 16 weeks	Primary: Change in non–HDL-C	Primary: At the end of treatment, the median percent change in non–HDL-C was significantly greater in the omega-3 acid ethyl ester plus simvastatin group than placebo plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ester (Lovaza®) 4 g per day plus simvastatin 40 mg per day vs placebo plus simvastatin 40 mg per day	Adults (mean age 59.8 years) who had received ≥8 weeks of stable statin therapy and had mean fasting TG ≥200 mg/dL and <500 mg/dL and mean LDL-C below or within 10% NCEP ATP III goal	(8 weeks OL treatment with simva-statin)	Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC, and apo B; adverse events	simvastatin group (–9.0% vs –2.2%; *P*<0.001). Secondary: Treatment with omega-3 acid ethyl esters plus simvastatin was associated with significant reductions in TG (2.9% vs 6.3%) and VLDL-C (27.5% vs 7.2%), a significant increase in HDL-C (3.4% vs –1.2%) and a significant reduction in TC:HDL-C ratio (9.6% vs 0.7%) (all *P*<0.001). Adverse events reported by ≥1% of patients in the omega-3 acid ethyl esters group that occurred with a higher frequency than in simvastatin monotherapy group were nasopharyngitis (3.3%), upper respiratory tract infection (3.3%), diarrhea (2.5%) and dyspepsia (2.5%). There was no significant difference in the frequency of adverse events between groups and no serious adverse events were considered treatment related.
Stalenhoef et al[40] Omega-3 acid ethyl esters (Omacor*) 4 g per day vs gemfibrozil 1,200 mg per day	DB, DD, RCT Patients with primary hypertriglycer-idemia	N=28 12 weeks (treatment duration)	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported Results regarding in vitro data on oxidation were not included since their clinical relevance is not known.	Primary: Both omega-3 acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (*P*=0.05 to *P*<0.001 from baseline and *P*=0.29 to *P*=1.00 between groups). Both therapies resulted in a more buoyant LDL-C subfraction profile (*P*=0.05 for omega-3 acid ethyl esters, *P*<0.01 for gemfibrozil and *P*=0.09 between groups in favor of gemfibrozil). Secondary: Not reported

*Omacor was renamed to Lovaza in August 2007.
Drug regimen abbreviations: BID=twice daily, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, HS=bedtime, IR=immediate release, IU=international units, PUFA=polyunsaturated fatty acids, QD=once daily, SR=sustained release, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover
Miscellaneous abbreviations: ADMIT=Arterial Disease Multiple Intervention Trial, ADVENT=Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial, ALT=alaninine aminotransferase, apo AI=apoliprotein AI, apo B=apolipoprotein B, apo E=apoliprotein E, ARBITER=ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol, AST=aspartate aminotransferase, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, FBG=fasting blood glucose, GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, HATS=HDL-Atherosclerosis Treatment Study, HbA_{1c}=hemoglobin A1c, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.
Cases of severe hepatotoxicity have occurred in patients who have substituted sustained-release niacin for equivalent doses of immediate-release niacin.[1] Therefore, different formulations should not be used interchangeable, and dietary supplement niacin preparations should not be used for cholesterol lowering or as substitutes for prescription-only niacin preparations.

Impact on Physician Visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Miscellaneous Antilipemic Agents

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
niacin	sustained-release capsule, sustained-release tablet, tablet	Niacor®, Niaspan®, Slo-Niacin®†	$-$$$	$
omega-3 acid ethyl esters	capsule	Lovaza®‡	$$$$	N/A

† Product is available over-the-counter.
‡ Omacor was renamed to Lovaza in August 2007.
N/A=not available.

X. Conclusions

Niacin and omega-3 acid ethyl esters are the only two agents classified by the American Hospital Formulary Service as miscellaneous antilipemic agents.[1] Niacin is available over the counter (OTC) in immediate-release and sustained-release formulations, which are currently on the Alabama Medicaid Preferred Drug List (PDL). Niacin is also available by prescription only as immediate-release (Niacor®) and sustained-release (Niaspan®) formulations.

Omega-3 acid ethyl esters are also available OTC and by prescription only; however, the OTC products are not covered by Alabama Medicaid. There are no generic formulations for either legend niacin or omega-3 acid ethyl esters.

Prescription sustained-release niacin and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) as adjunctive therapy for the treatment of adult patients with very high triglyceride levels (>500 mg/dL).[3,5] Clinical trials have shown that both niacin and omega-3 acid ethyl esters are effective in managing hypertriglyceridemia, reducing triglyceride levels by 20%-35% and 20%-50%, respectively.[18] There are no trials comparing the safety and efficacy of niacin to omega-3 acid ethyl esters. Omega-3 acid ethyl esters may be an alternative to the fibric acid derivatives for combination use with a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor ("statin") because it does not increase the risk of rhabdomyolysis.[18] While established coronary and vascular disease is not an FDA-approved indication for omega-3 acid ethyl esters, for patients with these conditions the American Heart Association (AHA) encourages increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day).[12]

Prescription niacin has obtained additional indications since it has been shown to have favorable effects on all plasma lipoproteins and lipids. Niacin increases HDL-C by 15%-35% and decreases TC and LDL-C by 5%-25%, changing small, dense LDL particles to large, buoyant forms. Niacin has been shown to lower the incidence of nonfatal myocardial infarction and overall mortality rates, and to slow progression or promote regression of atherosclerotic disease in combination with other antilipemic agents in patients with a history of coronary artery disease and hypercholesterolemia.[18] While statins are considered the drugs of choice for lowering LDL-C, niacin is primarily used for the management of mixed hyperlipidemia, or as a second-line agent in combination therapy for hypercholesterolemia.[10-15] There are limited head-to-head studies comparing the safety and efficacy of immediate-release to sustained-release niacin, but overall, these agents appear to be comparable in efficacy.[30-32] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release products and may be diminished by starting with a low dose, taking after meals and by pretreating with aspirin (325 mg) or ibuprofen (200 mg). Hepatotoxicity has been reported with sustained-release preparations in doses ≥2 g per day and in situations where equivalent doses of the sustained-release product were substituted for the immediate-release formulation. Therefore, different formulations should not be used interchangeably. Due to significant safety concerns with regarding OTC niacin products, the AHA stresses that OTC dietary supplement niacin must not be used as a substitute for prescription niacin, because these agents are not regulated by the FDA in the same manner as prescription niacin, thus the amount of niacin may vary from product to product and within lots of the same brand.[9] Furthermore, the AHA states that OTC niacin should not be used for cholesterol lowering because of the potential for very serious side effects.

Therefore, the prescription immediate-release and sustained-release niacin products are comparable to each other but do offer significant clinical advantages over other brand and OTC products within the class reviewed. Given its limited FDA-approved indication and potential for off-label use, prescription omega-3 acid ethyl esters should be available for patients with very high (≥500 mg/dL) triglyceride levels through the medical justification portion of the prior-authorization process.

XI. Recommendations

Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Nitrates and Nitrites
AHFS Class 241208
May 14, 2008

I. Overview

The nitrates and nitrites are a class of vasodilating agents primarily indicated for the acute treatment, prophylaxis and management of angina pectoris due to coronary artery disease. Myocardial ischemia develops when there is an imbalance between myocardial oxygen supply and demand which can lead to symptoms such as angina pectoris. Nitrates and nitrites effectively reduce myocardial oxygen demand by increasing blood flow. On the other hand, vasodilation can also lead to side effects, such as headache and flushing. Various formulations are available that differ in both onset and duration of action, which dictates their role in treatment of acute, stable and unstable angina.[1-2]

The nitrates, isosorbide dinitrate in combination with hydralazine in particular, also serve a role in the management of heart failure as an adjunct to standard treatment.[8-10] Furthermore, nitroglycerin administered intravenously is indicated for blood pressure control during cardiovascular procedures while either intravenous or sublingual nitroglycerin is beneficial in the management of patients with acute myocardial infarction.[2]

Frequently repeated or continuous exposure to organic nitrates leads to a decrease in their pharmacological effects. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route of administration. Nitrate-free interval dosing can limit the degree of tolerance associated with chronic use.[1]

The nitrates and nitrites that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Nitrates and Nitrites Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amyl nitrite	inhalant	N/A*	amyl nitrite
isosorbide dinitrate	sublingual tablet, sustained-release capsule, sustained-release tablet, tablet	Dilatrate-SR®, Isordil®*	isosorbide dinitrate, Isordil®*
isosorbide mononitrate	sustained-release tablet, tablet	Imdur®*, Ismo®*, Monoket®*	isosorbide mononitrate
nitroglycerin	injection, ointment, sublingual tablet, sustained-release capsule, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®, Nitro-Dur®*, Nitroglyn®*, Nitrolingual®, Nitrostat®*	nitroglycerin, Nitro-Bid®, Nitrostat®*

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the nitrates and nitrites are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nitrates and Nitrites

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines:	• Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina. • Long-acting calcium-channel blocking agents (CCB) or long-acting nitrates may be used if β-blockers are contraindicated. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is

Clinical Guideline	Recommendation(s)
Guideline Update for the Management of Patients with Chronic Stable Angina (2002)[3]	not successful. • In 2007 an update to this guidline was published but it did not address the use of the nitrates and nitrites.[4]
American College of Cardiology (ACC)/American Heart Association (AHA): **ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) (2007)[5]**	<u>Clinical Assessment</u> • Patients with suspected acute coronary syndrome should be instructed to take no more than 1 dose of sublingual NTG for chest pain or discomfort. If additional doses are required for persistent or worsening pain, emergency medical attention should be sought. Additional NTG may be taken every 5 minutes for a total of 3 doses while awaiting an ambulance. • Patients with chronic stable angina should be instructed that if symptoms are significantly improved after the first dose of sublingual NTG, doses can be repeated every 5 minutes if needed for a total of 3 doses. If pain does not completely resolve after 3 doses, immediate medical attention should be sought. • Instructions for sublingual NTG administration may be individualized for patients who are known to have frequent angina episodes. The frequency and characteristics of symptoms, as well as the typical response time should be evaluated to determine an appropriate plan. <u>Immediate Management</u> • Low-risk patients that are referred to outpatient stress testing should be given medications such as sublingual NTG, aspirin and/or β-blockers as a preventative measure prior to receiving test results. <u>Anti-Ischemic Therapy</u> • Sublingual NTG (0.4 mg) should be given to patients with UA/NSTEMI and continuing angina every 5 minutes as needed for up to 3 doses. An evaluation of the need for intravenous (IV) NTG, if not contraindicated, should then be performed. • An evaluation as to whether to administer IV NTG should be performed after alternative mortality-reducing interventions with agents such as β-blockers or angiotensin-converting enzyme inhibitors (ACEI) have been utilized. • IV NTG is indicated during the first 48 hours after UA/NSTEMI and continuing ischemia, heart failure (HF) or hypertension. • The recommended starting dose of IV NTG is 10 μg/min and then titrated by 10 μg/min every 3-5 minutes until patient is either nonsymptomatic or a response in blood pressure is seen. • Once the dose has reached 20 μg/min and no response has been noted, an increase of 10 μg/min and then 20 μg/min may be used. • In the absence of relief of symptoms, the goal is to achieve a response in blood pressure. Once this is reached, the dose of IV NTG should then be decreased and the dosing intervals should be extended. • The maximum dose of IV NTG has not been established although it is generally considered to be 200 μg/min. • Topically or orally administered nitrates are considered options for patients without persistent refractory ischemic symptoms but who require additional treatment for angina. • Once patients have been symptom-free for 12-24 hours IV NTG doses should be decreased and converted to oral or topical nitrates. • Nitrates should not be given under the following circumstances: in patients with UA/NSTEMI with systolic blood pressure <90 mm HG or ≥30 mm Hg below baseline, in cases of severe bradycardia [<50 beats per minute (bpm)], in patients with tachycardia (>100 bpm) in nonsymptomatic HF or right ventricular infarction. • Nitrates are also contraindicated within 24 hours of receiving sildenafil or 48 hours of taking tadalafil. The appropriate time between vardenafil utilization and nitrate administration has not been established. • Nitrate-free intervals are recommended in patients on oral or topical nitrates and decreases in IV doses should be attempted whenever possible to avoid tolerance.

Clinical Guideline	Recommendation(s)
	Post-UA/NSTEMI • All patients post-UA/NSTEMI should be given sublingual or spray NTG. • Sublingual NTG should be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. If symptoms persist or worsen after 5 minutes emergency medical services should be contacted. Doses can be repeated every 5 minutes if needed for 3 total doses while patient is lying down or sitting. Long-Term Medical Therapy and Secondary Prevention • NTG is recommended to treat ischemic symptoms.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (STEMI)–Pharmacological Management (2004)**[6]	Initial Emergency Department Management • Sublingual NTG 0.4 mg should be given to patients with ongoing ischemic discomfort every 5 minutes for 3 total doses. After 3 doses, assess need for IV NTG. • IV NTG is indicated for relief of ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion. Hospital Management–Medication Assessment • IV NTG is indicated during the first 48 hours for treatment of persistent ischemia, hypertension or congestive heart failure (CHF), provided that therapy does not preclude treatment with β-blockers or ACEI. • NTG after 48 hours can be useful for recurrent angina or persistent CHF provided that therapy does not preclude treatment with β-blockers or ACEI. • In 2007 an update to this guidline was published but it did not address the use of the nitrates and nitrites.[7]
American College of Physicians: **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease (2004)**[8]	• Sublingual NTG or NTG spray should be given for immediate angina symptomatic relief. • Long-acting nitrates or long-acting CCBs may be used for symptomatic chronic stable angina if β-blockers are contraindicated. • Long-acting nitrates or long-acting CCBs may be used with β-blockers if monotherapy is not successful in treating symptomatic chronic stable angina. • Nitrates have not demonstrated any reduction in mortality in either post-myocardial infarction (MI) patients or in patients with coronary artery disease (CAD).
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris (2006)**[9]	• Short-acting NTG may be used for prompt relief or prevention of angina, and should be offered to all patients with stable angina. • Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated or inadequately controlling symptoms. A nitrate-free regimen should be implemented to avoid tolerance. • If CCBs alone or in combination with β-blockers, do not adequately relieve symptoms, long-acting nitrates should be considered. • Continuous transdermal NTG therapy is ineffective and it is recommended that patches be removed for a portion of the day. • Long-acting nitrates have shown no clinical benefit over either β-blockers or CCBs.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)**[10]	• IV nitrates may be considered in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who require hospitalization. Once symptoms are controlled, a non-parenteral alternative should be used at intermittent dosing intervals to avoid tolerance. • Nitrates administered IV or orally are effective in treating acute symptoms of angina. • Patients with NSTE-ACS should be initiated on sublingual or IV NTG with caution given to those with systolic blood pressure <90 mm Hg.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in**	Recommended Routine Prophylactic Therapies in the Acute Phase • Routine use of nitrates in the initial phase of MI has not shown to be of convincing value and is not recommended.

Clinical Guideline	Recommendation(s)
Patients Presenting with ST-segment Elevation (2003)[11]	Secondary Prevention • Nitrates should be used only in the presence of angina pectoris.
National Institute for Health and Clinical Excellence (NICE): **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[12]	Patients With Prior Myocardial Infarction Without Heart Failure • CCBs, nitrates, and potassium channel activators (not currently available in the U.S.) have no effect on premature mortality and can be used for management of risk factors such as hypertension in patients intolerant to a β-blocker and an ACEI.
American College of Cardiology (ACC)/American Heart Association (AHA) Task Force for Practice Guidlines: **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)**[13]	• The addition of a combination of hydralazine and a nitrate is reasonable for patients with HF who are already taking an ACEI and β-blocker for symptomatic HF, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF) who cannot be given an ACEI or an angiotensin II receptor blocker (ARB) because of drug intolerance, hypotension, or renal insufficiency. • Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACEI for African Americans with New York Heart Association (NYHA) functional class III or IV HF. Any potential benefit in other patients has yet to be evaluated. • Patients with HF should be given nitrates and β-blockers for the treatment of angina.
Heart Failure Society of America (HFSA): **Comprehensive Heart Failure Practice Guidelines (2006)** [14]	• Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACEI for African Americans with left ventricular systolic dysfunction. • May be considered in non–African American patients with left ventricular dysfunction (LVD) who remain symptomatic despite optimized standard therapy and in patients who do not tolerate ARB therapy.
European Society of Cardiology (ESC): **Guideline for the Diagnosis and Treatment of Chronic Heart Failure (2005)**[15]	• Patients should be counseled on the possible role of nitrates in sublingual or spray formulation as they may be used as temporary treatment at the onset, or in some cases prophylactically, for dyspnea. • Nitrates may be used as adjunctive therapy for angina or relief of dyspnea. • Nitrates in combination with hydralazine may be considered for the management of HF in cases of intolerance to ACEI and ARBs. Caution should be used because of the risk of developing hypotension. • The addition of long-acting nitrates is recommended in patients with symptomatic systolic LVD and comorbid angina or hypertension.
European Society of Cardiology (ESC): **Guideline on the Diagnosis and Treatment of Acute Heart Failure (2005)**[16]	• In most patients with acute HF as first line therapy, if hypoperfusion is associated with and adequate blood pressure and signs of congestion with low diuresis, to open the peripheral circulation and to lower pre-load; vasodilators are indicated. • In acute MI nitrates may be given orally, however IV formulations are also well tolerated.
National Institute for Health and Clinical Excellence (NICE): **Management of Chronic Heart Failure in Adults in Primary and Secondary Care (2003)**[17]	• An isosorbide/hydralizine combination may be used in patients with HF who are intolerant to ACEI or ARB's.
Joint National Committee (JNC):	• IV NTG, at a rate of 5-100 µg/min, is among the treatment options for the management of hypertensive emergencies, particularly in the setting of coronary ischemia. Intravenous

Clinical Guideline	Recommendation(s)
The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (2003)[18]	NTG's onset and duration of action are 2-5 minutes and 5-10 minutes, respectively.

III. Indications

FDA-approved indications for the nitrates and nitrites are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Nitrates and Nitrites [19-31]

Indication	Amyl Nitrite	Isosorbide Dinitrate*†	Isosorbide Mono-nitrate†	Nitroglycerin		
				Sublingual Tablet/Spray	Injection	Capsule SR, Trans-dermal†
Acute angina pectoris due to coronary artery disease	✔			✔		
Acute prophylaxis of angina pectoris due to coronary artery disease				✔		
Control of congestive heart failure in the setting of acute myocardial infarction					✔	
Induction of intraoperative hypotension					✔	
Prevention of angina pectoris due to coronary artery disease		✔	✔			✔
Treatment of angina pectoris due to coronary artery disease		✔	✔ ‡			
Treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers					✔	
Treatment of perioperative hypertension					✔	

*Because the onset of action of sublingual isosorbide dinitrate is significantly slower than that of sublingual nitroglycerin, sublingual isosorbide dinitrate is not the drug of first choice for aborting an acute anginal episode.
†The onset of action of oral isosorbide dinitrate (immediate or sustained-release), oral isosorbide mononitrate, oral nitroglycerin capsules, or transdermal nitroglycerin is not sufficiently rapid for these products to be useful in aborting an acute anginal episode.
‡Monoket and equivalents

IV. Pharmacokinetics

The pharmacokinetic parameters for the nitrates and nitrites are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Nitrates and Nitrites[19-35]

Drug	Bioavailability (%)	Onset (minutes)	Duration	Active Metabolites	Half-Life
Amyl nitrite	Not reported	0.5	3-15 min	Not reported	Not reported
Isosorbide dinitrate sublingual tablet	40-50	2-10	1-2 hours	2-mononitrate, 5-mononitrate	1-4 hours

Drug	Bioavailability (%)	Onset (minutes)	Duration	Active Metabolites	Half-Life
Isosorbide dinitrate sustained-release capsule/tablet	Not reported	60	Up to 8 hours	2-mononitrate, 5-mononitrate	1-4 hours
Isosorbide dinitrate tablet	10-90	45-60	4-6 hours	2-mononitrate, 5-mononitrate	1-4 hours
Isosorbide mononitrate sustained–release tablet	100	30-60	12 hours	None	4 hours
Isosorbide mononitrate tablet	100	30-60	12 hours	None	4 hours
Nitroglycerin injection	Not reported	Immediate	3-5 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin ointment	Not reported	15-60	2-12 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin sublingual tablet	40	1-3	30-60 min	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin sustained-release capsule	Not reported	20-45	4-8 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin transdermal patch	Not reported	40-60	18-24 hours	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes
Nitroglycerin translingual spray	Not reported	2	30-60 minutes	1,2- dinitroglycerols, 1,3-dinitroglycerols	1-4 minutes

V. Drug Interactions

Significant drug interactions with the nitrates and nitrites are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Nitrates and Nitrites[36]

Drug(s)	Significance Level	Interaction	Mechanism
Nitrates and nitrites	1	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Nitrates and nitrites	2	Dihydro-ergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse reactions reported with the nitrates and nitrites are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Nitrates and Nitrites[19-31]

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Cardiovascular					
Abnormal heart sound	-	-	≤5	-	-
Aggravated angina pectoris	-	-	≤5	-	-
Angina pectoris	-	-	-	<1	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Arrhythmia	-	-	≤5	<1	-
Atrial fibrillation	-	-	≤5	<1	-
Bradycardia	-	-	≤5	-	-
Bundle branch block	-	-	≤5	-	-
Cardiac failure	-	-	≤5	-	-
Crescendo angina	-	✔	-	-	✔
Extrasystole	-	-	≤5	-	-
Flushing	✔	-	≤5	-	✔
Heart murmur	-	-	≤5	-	-
Hypertension	-	-	≤5	-	-
Hypotension	✔	✔	≤5	<1	✔
Migraine	-	-	≤5	-	-
Myocardial infarction	-	-	≤5	-	-
Palpitation	-	-	≤5	<1	✔
Postural hypotension	-	-	-	<1	✔
Premature ventricular contraction	-	-	-	<1	-
Q wave abnormality	-	-	≤5	-	-
Rebound hypertension	-	✔	-	-	✔
Supraventricular tachycardia	-	-	-	<1	-
Syncope	✔	✔	✔	<1	✔
Tachyarrhythmia	✔	-	-	-	-
Tachycardia	-	-	≤5	-	-
Ventricular tachycardia	-	-	≤5	-	-
Central Nervous System					
Anxiety	-	-	≤5	<1	-
Confusion	-	-	≤5	<1	-
Decreased libido	-	-	≤5	-	-
Depression	-	-	≤5	-	-
Dizziness	-	✔	8-11	3-5	✔
Headache	✔	✔	38-57	19-38	✔
Impotence	-	-	≤5	<1	-
Insomnia	-	-	≤5	<1	-
Lightheadedness	✔	-	-	-	✔
Nervousness	-	-	≤5	<1	-
Neuritis	-	-	≤5	-	-
Paresis	-	-	≤5	-	-
Paresthesia	-	-	≤5	-	-
Purpura	-	-	≤5	-	-
Somnolence	-	-	≤5	-	-
Vertigo	-	-	≤5	-	✔
Dermatological					
Acne	-	-	≤5	-	-
Anaphylactoid reactions	-	-	-	-	✔
Contact dermatitis	-	-	-	-	✔ *
Exfoliative dermatitis	-	-	-	-	✔
Photophobia	-	-	≤5	-	-
Pruritus	-	-	≤5	<1	-
Rash	✔	-	≤5	<1	✔
Skin nodule	-	-	≤5	-	-
Endocrine and Metabolic					
Edema	-	-	≤5	<1	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Gastrointestinal					
Abdominal pain	-	-	≤5	<1	-
Constipation	-	-	≤5	-	-
Diarrhea	-	-	≤5	<1	-
Dyspepsia	-	-	≤5	<1	-
Flatulence	-	-	≤5	-	-
Gastric ulcer	-	-	≤5	-	-
Gastritis	-	-	≤5	-	-
Hemorrhagic gastric ulcer	-	-	≤5	-	-
Loose stools	-	-	≤5	-	-
Nausea	✔	-	≤5	2-4	✔
Vomiting	✔	-	≤5	2-4	✔
Genitourinary					
Dysuria	-	-	-	<1	-
Polyuria	-	-	≤5	-	-
Renal calculus	-	-	≤5	-	-
Urinary tract infection	-	-	≤5	-	-
Hematologic					
Hemolytic anemia	✔	-	-	-	-
Hypochromic anemia	-	-	≤5	-	-
Methemoglobulinemia	✔	✔	✔	✔	✔
Thrombocytopenia	-	-	≤5	-	-
Laboratory Test Abnormalities					
Elevated SGOT	-	-	≤5	-	-
Elevated SGPT	-	-	≤5	-	-
Musculoskeletal					
Arthralgia	-	-	≤5	<1	-
Asthenia	✔	-	≤5	<1	-
Muscle weakness	-	-	≤5	-	-
Musculoskeletal pain	-	-	≤5	-	-
Myalgia	-	-	≤5	-	-
Respiratory					
Bronchitis	-	-	≤5	<1	-
Bronchospasm	-	-	≤5	-	-
Coughing	-	-	≤5	-	-
Dyspnea	✔	-	≤5	-	-
Increased sputum	-	-	≤5	-	-
Nasal congestion	-	-	≤5	-	-
Pharyngitis	-	-	≤5	-	-
Pneumonia	-	-	≤5	<1	-
Pulmonary infiltration	-	-	≤5	-	-
Rales	-	-	≤5	-	-
Rhinitis	-	-	≤5	-	-
Sinusitis	-	-	≤5	-	-
Upper-respiratory tract infection	-	-	-	<1	-
Other					
Abnormal hair texture	-	-	≤5	-	-
Abnormal vision	-	-	≤5	-	-
Agitation	-	-	-	<1	-
Atrophic vaginitis	-	-	≤5	-	-
Back pain	-	-	≤5	-	-
Bacterial infection	-	-	≤5	-	-

Adverse Event(s)	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate	Nitroglycerin
Blurred vision	-	-	-	<1	-
Breast pain	-	-	≤5	-	-
Chest pain	-	-	≤5	-	-
Cold sweat	-	-	-	<1	-
Collapse	-	-	-	-	✔
Conjunctivitis	-	-	≤5	-	-
Diplopia	-	-	-	<1	-
Dry mouth	-	-	≤5	-	-
Dyscoordination	-	-	-	<1	-
Earache	-	-	≤5	-	-
Fatigue	-	-	≤5	-	-
Fever	-	-	≤5	-	-
Flu-like symptoms	-	-	≤5	-	-
Frozen shoulder	-	-	≤5	-	-
Glossitis	-	-	≤5	-	-
Hemorrhoids	-	-	≤5	-	-
Hot flashes	-	-	≤5	-	-
Hyperuricemia	-	-	≤5	-	-
Hypoesthesia	-	-	≤5	<1	-
Hypokalemia	-	-	≤5	-	-
Hypokinesia	-	-	-	<1	-
Impaired concentration	-	-	≤5	-	-
Increased appetite	-	-	-	<1	-
Increased sweating	-	-	≤5	-	-
Intermittent claudication	-	-	≤5	-	-
Leg ulcer	-	-	≤5	-	-
Malaise	-	-	≤5	<1	-
Melena	-	-	≤5	-	-
Moniliasis	-	-	≤5	-	-
Myositis	-	-	≤5	-	-
Nightmares	-	-	-	<1	-
Pallor	-	-	-	-	✔
Paroniria	-	-	≤5	-	-
Ptosis	-	-	≤5	-	-
Restlessness	✔	-	-	-	✔
Rigors	-	-	≤5	<1	-
Tendon disorder	-	-	≤5	-	-
Tenesmus	-	-	-	<1	-
Tinnitus	-	-	≤5	-	-
Tooth disorder	-	-	-	<1	-
Tremor	-	-	≤5	-	-
Tympanic membrane perforation	-	-	≤5	-	-
Varicose veins	-	-	≤5	-	-
Viral infection	-	-	≤5	-	-
Weakness	-	-	-	-	✔

SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, SR=sustained-release
*Topical formulations only
✔ Percent not specified
- Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the nitrates and nitrites are summarized in Table 7.

Table 7. Usual Dosing for the Nitrates and Nitrites[19-31, 35]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amyl nitrite	Inhalant: 2-6 inhalations holding capsule under nose, repeat in 3-5 minutes as needed	Safety and efficacy in children have not been established.	Inhalant
Isosorbide dinitrate sublingual tablet	Sublingual tablet: 2.5-5 mg 15 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 2.5 mg 5 mg
Isosorbide dinitrate sustained-release capsule/tablet	Sustained-release capsule/tablet: 40 mg every 8-12 hours; maximum: 160 mg daily	Safety and efficacy in children have not been established.	Sustained-release capsule: 40 mg Sustained-release tablet: 40 mg
Isosorbide dinitrate tablet	Tablet: initial, 5-20 mg 2-3 times daily; maintenance, 10-40 mg 2-3 times daily; A daily dose-free interval of at least 14 hours is advisable to minimize tolerance	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 30 mg 40 mg
Isosorbide mononitrate sustained-release tablet	Sustained-release tablet: initial, 30-60 mg once daily may increase to 120 mg once daily; Rarely, 240 mg once daily may be required	Safety and efficacy in children have not been established.	Sustained-release tablet: 30 mg 60 mg 120 mg
Isosorbide mononitrate tablet	Tablet: 20 mg twice daily given 7 hours apart	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Nitroglycerin injection	Injection: 5 µg/min, increase by 5 µg/min every 3-5 minutes to 20 µg/min. If no response at 20 µg/min increase by 10 µg/min every 3-5 minutes, up to 200 µg/min	Safety and efficacy in children have not been established.	Vial: 0.1 mg/mL 0.2 mg/mL 0.4 mg/mL 5 mg/mL
Nitroglycerin ointment	Ointment: initial, 1/2 inch (7.5 mg) twice daily, 2nd dose applied 6 hours later; dose may be doubled then doubled again	Safety and efficacy in children have not been established.	Ointment: 2%
Nitroglycerin sublingual tablet	<u>Acute relief of anginal attack</u> Sublingual tablet: One tablet dissolved under tongue or in the buccal pouch at the first sign of an acute angina attack, may repeat every 5 minutes up to 3 doses in a 15-minute period <u>Prophylaxis of an angina attack</u> Sublingual tablet: One tablet 5-10 minutes prior to activity	Safety and efficacy in children have not been established.	Sublingual tablet: 0.3 mg 0.4 mg 0.6 mg
Nitroglycerin sustained-release capsule	Sustained-release capsule: 2.5-6.5 mg 3-4 times daily	Safety and efficacy in children have not been established.	Sustained-release capsule: 2.5 mg 6.5 mg 9 mg

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Nitroglycerin transdermal patch	Transdermal patch: initial, 0.2-0.4 mg/hour up to 0.8 mg/hour with a patch-off period of 10-12 hours	Safety and efficacy in children have not been established.	Transdermal patch: 0.1 mg/hr 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr 0.6 mg/hr 0.8 mg/hr
Nitroglycerin translingual spray	Translingual spray: 1-2 sprays onto or under tongue no more than 3 sprays in a 15-minute period, 5-10 minutes prior to activity	Safety and efficacy in children have not been established.	Translingual spray: 400 µg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the nitrates and nitrites are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Nitrates and Nitrites

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Stable Angina				
Parker et al[37] ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina Secondary: Not reported	Primary: Patients underwent testing prior to exercise as well as 2 and 7 hours after each dose on days 1 and 14. Additionally, on days 7 and 21, testing was performed 2 hours after the first dose. ISMN, at all doses, showed improvement over placebo at 2 and 7 hours after the morning dose and 2 hours after the second dose on day 1. Active treatment prolonged exercise duration over placebo at 2 hours postdose for each of the 2 daily doses. ISMN 20 mg was the only strength which demonstrated increased exercise duration 7 hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group (*P* values not reported). Secondary: Not reported
Thadani et al[38] ISMN 20 mg BID vs placebo Patients were allowed to continue β-blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: Magnitude of ST-segment depression, heart rate, systolic and diastolic blood pressure, number of anginal attacks, number of nitroglycerin doses	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo ($P<0.01$). Secondary: The magnitude of ST-segment depression was comparable in both the isosorbide-5-mononitrate and placebo groups (1.2±0.1 mm vs 1.2±0.2 mm; $P>0.2$). Heart rate and systolic blood pressure, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chrysant et al[39] ISMN ER 30 mg QAM vs ISMN ER 60 mg QAM vs ISMN ER 120 mg QAM vs ISMN ER 240 mg QAM vs placebo	DB, RCT Patients with stable effort-induced angina	N=313 6 weeks	Primary: Mean change from baseline in total exercise time (serial exercise testing immediately prior to and 4 and 2 hours after administration, on days 1, 7, 14, 28 and 42) Secondary: Adverse effect	Primary: A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active-treatment groups compared to placebo at 4 and 12 hours postdose ($P<0.01$). The mean changes from baseline in total exercise time in patients on ISMN ER 120 mg or 240 mg surpassed placebo by about 50 to 60 seconds at 4 hours postdose ($P<0.01$), and by 30 to 35 seconds 12 hours after dosing ($P\leq0.05$). There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina. Secondary: The most common adverse effect among active treatment groups was transient headache.
Bray et al[40] NTG administered buccally vs NTG administered sublingually	DB, MC Patients with proven chronic stable exercise-induced angina	N=Not reported Duration not reported	Primary: Efficacy Secondary: Not reported	Primary: The two formulations had comparable effects on acute attacks of angina pectoris. Secondary: Not reported
Ryden et al[41] NTG administered buccally vs NTG administered	MC, XO Patients with stable angina pectoris	N=126 2 weeks	Primary: Efficacy Secondary: Ease of use, patient preference	Primary: Buccal nitroglycerin resulted in 31% less acute anginal attacks compared to the sublingual formulation ($P<0.001$). Prophylaxis was effective in 74% of patients taking buccal NTG compared to 66% of sublingual-treated patients ($P<0.05$). Secondary: There was no difference in ease of use reported in 67% of patients, whereas 19% indicated that sublingual NTG was easier and 14% buccal NTG. Overall,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sublingually				65% of patients preferred buccal NTG and 19% preferred sublingual NTG (*P*<0.05). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual use (4%; *P*<0.05).
Demots et al[42] NTG 0.2 mg/hour or 0.4 mg/hour TD for 12 hours (Group A) vs NTG 0.6 mg/hour or 0.8mg/hour TD for 12 hours (Group B) vs placebo The concurrent use of β-blockers was greater in Group A.	DB, RCT Patients with chronic stable angina	N=206 4 weeks	Primary: Effectiveness in chronic stable angina (serial treadmill testing performed 0, 4, 8 and 12 hours after patch application at baseline and on days 1, 15 and 29) Secondary: Adverse reaction	Primary: Improved walking times were observed in both Group A and Group B over placebo at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at 4, 8 and 12 hours (*P* values not reported). At weeks 2 and 4, walking times were again greater in Group B over placebo at all testing points with the 4 hour test time at week 2 and the 8 hour test time at week 2 and 4 reaching statistical significance (*P* values not reported). Group A did not demonstrate increased duration in walking time long-term. Secondary: Active therapy was generally tolerated well. An increase in nonexertional angina during the patch-off interval was reported in 9 patients.
Unstable Angina				
Dellborg et al[43] NTG IV for 24 hours vs NTG administered buccally every 4 hours	RCT Patients admitted to the coronary care unit due to unstable angina	N=29 24 hours	Primary: Efficacy Secondary: Adverse effects	Primary: Efficacy was comparable in the two groups Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal nitroglycerin than IV although the differences were not significant.
Kaplan et al[44] NTG IV 10 µg/min increased by 10 µg/min	OL, OS Patients with angina at rest	N=35 24 hours	Primary: Clinical response Secondary:	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual NTG from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (*P*<0.001 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 5 minutes to 50 µg/min then increased by 50 µg/min per each episode of angina	unresponsive to standard therapy including oral or topical nitrates and β-blockers		Not reported	all). Complete response, defined as no rest angina, was achieved in 25 patients, while 8 patients experienced greater than a 50% reduction in episodes and 2 patients where nonresponders. Secondary: Not reported
Karlberg et al[45] NTG IV titrated from 1.5 mL/hour in <1 hour to a maximum of 12 mL/hour vs placebo	DB, PC, RCT Patients with recent onset of chest pain, suggestive of myocardial ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying coronary artery disease	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia [more than 2 angina attacks responding to 1-3 sublingual NTG tablets and lasting <20 minutes (AP1), or 1 angina attack lasting >20 minutes, despite 3 sublingual NTG tablets (AP2)], leukocyte activation, inhibition of platelet aggregation Secondary: Adverse effects	Primary: Treatment with NTG IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1 + AP2) than placebo (25; $P<0.03$). There were significantly less patients on active treatment that required >2 sublingual NTG tablets compared to placebo (12 vs 22; $P<0.005$). There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in 7 patients compared to 0 in the placebo group ($P<0.001$). Five patients terminated therapy prematurely because of headache while 2 patients stopped because of a decrease in blood pressure and bradycardia.
Heart Failure				
Cohn et al[46] V-HeFT I ISDN 160 mg daily plus hydralazine 300 mg daily vs prazosin 20 mg daily	AC, DB, PC, RCT Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	N=642 3 years	Primary: Mortality Secondary: Effect on left ventricular function	Primary: There was a 34% risk reduction in mortality by 2 years in the ISDN plus hydralazine group compared to placebo ($P<0.028$). Cumulative mortality rates of 25.6% and 36.2% were observed in the ISDN plus hydralazine group at 2 and 3 years respectively, compared to 34.3% and 46.9% in the placebo group (P value not reported). The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the left ventricular ejection fraction was reported at 8 weeks and 1 year in the ISDN plus hydralazine treatment group, but not in either

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				the prazosin or placebo groups.
Cohn et al[47] ISDN 40 mg QID and hydralazine 75 mg QID (individual agents, concurrent therapy) vs enalapril 10 mg BID	AC, DB, RCT Men with heart failure (primarily NYHA class II and III), receiving digoxin and diuretics	N=804 2 years	Primary: All-cause mortality Secondary: Not reported	Primary: The results demonstrated significantly lower mortality after 2 years with enalapril (18%) vs ISDN and hydralazine (25%; *P*=0.016). In addition, overall mortality tended to be lower with enalapril vs ISDN and hydralazine (*P*=0.08). Secondary: Not reported
Taylor et al[48] A-HeFT ISDN 20 mg plus hydralazine 37.5 mg TID increased to ISDN 40 mg plus hydralazine 75 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for at least 3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 10 months	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, quality of life changes Secondary: Individual components of the primary composite score	Primary: Combination of vasodilators in addition to standard therapy had significant mortality benefit (mortality rate of 6.2% vs 10.2%; *P*=0.02). From a range of possible scores of –6 to +2, patients in the active treatment group achieved a significantly better score of –0.1±1.9 compared to –0.5±2.0 in the placebo group (*P*=0.01). Each separate value of the composite score was also significantly better in the active group when compared to placebo. There was a 43% decrease in the rate of death from any cause (HR, 0.57; *P*=0.01), and a 33% reduction in the rate of first hospitalizations (*P*=0.001). This led to the early termination of the trial. Additionally, there was a significant improvement in quality of life scores found with ISDN plus hydralazine when compared to placebo (–5.6±20.6 vs –2.7±21.2; *P*=0.02). Secondary: Results of individual components were not reported.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QAM=every morning, QID=four times daily, TD=transdernal, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, HR=hazard ratio, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations; A-HeFT=African-American Heart Failure Trial, ER=extended release, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, NTG=nitroglycerin, NYHA=New York Heart Association, V-HeFT=Vasodilator Heart Failure Trial

Additional Evidence

Dose Simplification
The COMPASS (Compliance with Oral Mononitrates in Angina Pectoris Study) evaluated the difference in adherence with a once-daily slow-release formulation of isosorbide mononitrate 60 mg and a twice-daily immediate-release formulation of isosorbide mononitrate 20 mg. A total of 101 patients received an amount of medication sufficient for 10 weeks of treatment. The once-daily regimen was shown to have significantly better overall compliance than the twice-daily dose ($P<0.001$). The once daily dose also achieved a reduction in the mean weekly number of chest pain episodes versus the twice daily dose ($P<0.0001$).[49]

A study by Brun assessed compliance with a once-daily controlled-release and a twice-daily oral formulation of 5-isosorbide mononitrate in 31 patients with stable angina pectoris. The once-daily dosing regimen again achieved better compliance over twice a day dosing (*P* value not reported). Additionally, the improvement in adherence resulted in fewer angina attacks as well as a reduction in doses of nitroglycerin tablets for acute angina.[50]

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Nitrates and Nitrites

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amyl nitrite	inhalant	N/A*	N/A	$
isosorbide dinitrate	sublingual tablet, sustained-release capsule, sustained-release tablet, tablet	Dilatrate-SR®, Isordil®*	$$-$$$	$
isosorbide mononitrate	sustained-release tablet, tablet	Imdur®*, Ismo®*, Monoket®*	$$$	$
nitroglycerin	injection, ointment,	Minitran®*, Nitro-	$-$$$	$

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	sublingual tablet, sustained-release capsule, transdermal patch, translingual spray	Bid®, Nitro-Dur®*, Nitroglyn®*, Nitrolingual®, Nitrostat®*		

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

Nitrates and nitrites are indicated for the acute, prophylactic and chronic treatment of angina pectoris due to coronary artery disease. Intravenous nitroglycerin is additionally FDA-approved for the control of congestive heart failure in the setting of myocardial infarction, induction of intraoperative hypotension, treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers and treatment of peri-operative hypertension. Since all nitrates have the same pharmacologic effects, product selection is based on desired onset and duration of action. Nitroglycerin sublingual tablets have long demonstrated their utility as a treatment for acute angina due to their rapid onset of action. The nitroglycerin sublingual spray possesses no known clinical advantage over the sublingual tablets. Nitroglycerin, when administered buccally every 4 hours, has shown similar efficacy to intravenous administration over a 24-hour period in patients with unstable angina.[43] Both isosorbide mononitrate and isosorbide dinitrate are available generically. Furthermore, nitroglycerin extended-release capsules, injection, ointment, sublingual tablets, and transdermal patches are all available generically.

The phosphodiesterase inhibitors, used for erectile dysfunction, are contraindicated in all patients on nitrite or nitrate therapy. The potential for tolerance, and therefore loss of pharmacologic effect, is common to all nitrate formulations. Nitrate tolerance is minimized by ensuring a nitrate-free period and/or use of the lowest effective dose. Transient headache is an adverse effect most often associated with nitrites and nitrates. Amyl nitrite use has fallen out of favor most likely due to its high incidence of headache and other cardiovascular adverse effects as well as its potential for abuse.

The beneficial effects of nitrates for the management of chronic stable angina are evident although there is no known advantage over β-blockers or calcium channel blockers. Tolerance further limits the chronic use of this class of medications and as a result, they are considered second-line to β-blockers for chronic stable angina.[3-5,9] Isosorbide mononitrate has demonstrated statistically significant improvement in exercise duration over placebo in patients with stable angina.[37-39] Isosorbide dinitrate in combination with hydralazine has shown a 34% reduction in mortality in patients with heart failure compared to placebo ($P<0.028$).[46] More specifically in African American patients, this combination of vasodilators produced a lower mortality rate of 6.2% vs 10.2% for placebo.[48] The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.[13-17] The efficacy of intravenous nitroglycerin has been demonstrated in patients with angina unresponsive to standard therapy with a reduction in angina episodes, doses of sublingual nitroglycerin and morphine sulfate ($P<0.001$).[41] Furthermore, sublingual and intravenous nitroglycerin are both recommended in unstable angina, myocardial infarction and acute coronary syndromes.[5-7,10,12]

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brand.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review—Veramyst® (fluticasone furoate)
Intranasal Corticosteroids, AHFS Class 520808
May 14, 2008

I. Overview

Intranasal corticosteroids are primarily used to treat allergic rhinitis, which is the inflammation of the nasal passages in response to an allergen.[1] It is typically characterized by nasal congestion, rhinorrhea, sneezing, and/or nasal itching.[2]

Fluticasone furoate is a nasally inhaled corticosteroid indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥2 years of age.[3] This synthetic corticosteroid has potent anti-inflammatory activity. The precise mechanism of action of corticosteroids is not well understood, but may be due to their immunosuppressive properties, antiproliferative action and anti-inflammatory activity. Fluticasone furoate nasal spray is available in a new delivery device with a side-actuated "mist-release" button that, when pressed, delivers the same amount of drug per actuation. It has a viewing window allowing patients to see how many doses of medication they have remaining.[3]

Current practice guidelines consider intranasal corticosteroids as the most effective treatment of allergic rhinitis and support these agents as first-line therapy, particularly for moderate-to-severe allergic rhinitis. No intranasal corticosteroid has been deemed more effective than the others.[4,6-8] However the World Health Organization, Allergic Rhinitis and its Impact on Asthma Workshop does note that fluticasone propionate aqueous nasal spray improves the nasal symptoms of seasonal allergic rhinitis when used as needed. This guideline also states that the rate of growth was slightly reduced in children regularly treated with intranasal beclomethasone over one year but no growth retardation has been observed in one-year follow-up studies of children treated with fluticasone propionate or mometasone furoate.[5] The most common side effect reported with the use of this product, like other inhaled corticosteroids, includes headache and nosebleed.

Fluticasone furoate has demonstrated a binding affinity for the glucocorticoid receptor that is 1.7 times that of fluticasone propionate; however, the clinical relevance of this is unknown.[3] In the absence of published clinical trials that directly compare the different agents, it is unclear whether there is a therapeutic advantage with fluticasone furoate over generic fluticasone propionate or over alternative nasal steroid agents. The long-term safety and efficacy of fluticasone furoate have yet to be established.

The fluticasone furoate formulations that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Within this review, only clinical trials investigating the safety and efficacy of fluticasone furoate will be summarized. Reference data from unpublished trials and data presented as abstracts or posters for fluticasone furoate were not evaluated and are not included in this review. Flunisolide and fluticasone propionate are currently available generically in nasal preparations.

Table 1. Fluticasone Furoate Product(s) Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
fluticasone furoate	nasal spray	Veramyst®	none

No generic products are available for fluticasone furoate.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate intranasal corticosteroids for the management of allergic rhinitis are summarized in Table 2.

Table 2. Treatment Guidelines for the Management of Allergic Rhinitis

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI). Health Care Guideline**:** **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2008)**[4]	<u>Allergic Rhinitis</u> • If the clinical diagnosis is obvious, symptomatic treatment should be initiated and includes both an education on avoidance and medication therapy. • Intranasal corticosteroids are considered the most effective agents next to systemic steroids. Therefore, they are recommended as first-line therapy in patients with moderate-to-severe symptoms of allergic rhinitis. • Intranasal corticosteroids can be started 1-2 weeks prior to exposure to the allergen or the start of the allergy season. • No preference is made for one intranasal corticosteroid over another. • Systemic corticosteroid use should be reserved for severe cases not controlled by antihistamines or topical agents. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They can also be added to intranasal corticosteroids as an adjunctive agent. • Oral antihistamines are an effective alternative in patients who cannot use or prefer not to use intranasal corticosteroids. • Alternatively, antihistamines or antihistamine/decongestant combinations can be used in mild or episodic cases for rapid relief of symptoms. • Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. • Oral decongestants are effective in reducing nasal congestion and can be a useful addition to antihistamines, and the two are readily available in combined preparations. • Cromolyn is less effective than intranasal corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea, however they have no effect on congestion, sneezing or itching. <u>Nonallergic Rhinitis</u> • Symptomatic nasal obstruction due to nonallergic rhinitis can be treated with azelastine hydrochloride nasal spray, an intranasal corticosteroid spray, oral decongestants, oral antihistamines, Breathe Right® nasal strips, or topical antihistamines. • Topical nasal steroid sprays have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic, rather than sporadic, symptoms. • Chronic nasal obstructive symptoms secondary to non-allergic rhinitis can be managed with intranasal steroid sprays, oral decongestants, or a combination of the two. • The drying effect of antihistamines may be useful in controlling rhinorrhea associated with non-allergic rhinitis. • Breathe Right® nasal strips are effective for some patients with only nocturnal symptoms (dependent nasal obstruction). Breathe Right® nasal strips are more effective for patients with narrow noses or with anterior septal deviations. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Intranasal corticosteroids, ipratropium spray, or nasal saline can be used for the treatment of symptomatic bilateral chronic anterior rhinorrhea due to nonallergic rhinitis. • For postnasal drip, intranasal corticosteroids are the only pharmacologic option. • No preference is made for one intranasal corticosteroid over another. <u>Sinusitis</u> • Intranasal corticosteroid spray may be rational but is an unproven adjunctive therapy for acute sinusitis. The spray may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • No preference is made for one intranasal corticosteroid over another.

Clinical Guideline	Recommendation(s)
World Health Organization (WHO), Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop: **ARIA Update (2007)[5]**	• Second-generation oral or intranasal H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. However first-generation oral H_1-antihistamines are not recommended when second generation ones are available due to safety concerns. • Topical H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis. • Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis. • Topical cromones are recommended in the treatment of allergic rhinitis and conjunctivitis, but they are only modestly effective. • Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age. • Intranasal ipratropium is recommended in the treatment of rhinorrhea associated with allergic rhinitis. • Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction. • Oral decongestants may be used in the treatment of allergic rhinitis in adults, but side effects are common. • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy and availability of drugs. • Fluticasone propionate aqueous nasal spray improves the nasal symptoms of seasonal allergic rhinitis when used as needed. • The rate of growth was slightly reduced in children regularly treated with intranasal beclomethasone over one year. However, no growth retardation has been observed in one-year follow-up studies of children treated with fluticasone propionate or mometasone furoate.
International Primary Care Respiratory Group (IPCRG): **IPCRG Guidelines: Management of Allergic Rhinitis (2006)[6]**	• Pharmacologic treatment of allergic rhinitis should be individualized based on the patient's symptoms and severity. • For mild intermittent allergic rhinitis, treatment options include oral antihistamines, intranasal antihistamines, and decongestants and/or intranasal saline. • For mild persistent allergic rhinitis or moderate/severe intermittent allergic rhinitis, treatment options include oral antihistamines, intranasal antihistamines and/or decongestants, intranasal saline, intranasal corticosteroids, mast-cell stabilizers, and antileukotrienes. • For moderate/severe persistent allergic rhinitis, treatment options include an intranasal glucocorticosteroid, oral antihistamine, decongestant, intranasal saline, and an antileukotriene. • Intranasal corticosteroids are considered the most effective pharmacological treatment for allergic and nonallergic rhinitis.
American Academy of Allergy, Asthma, and Immunology (AAAAI): Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology: **Diagnosis and Management of Rhinitis (1998)[7]**	• Intranasal corticosteroids are the most effective medication class for the treatment of allergic rhinitis. • Systemic side effects associated with intranasal corticosteroids are rare. • Local side effects are minimal, but nasal irritation and bleeding may occur. • Intranasal corticosteroids should be considered before systemic corticosteroids are used for the treatment of severe rhinitis.
European Academy of Allergology and Clinical Immunology (EAACI): **Consensus Statement on the Treatment of Allergic Rhinitis (2000)[8]**	• Intranasal corticosteroids are regarded as a highly effective first-line treatment for patients with severe and/or persistent symptoms of allergic rhinitis. • Intranasal corticosteroids may also be used in patients with mild symptoms that are not controlled with antihistamines. • A topical decongestant or systemic steroid may be given for a short duration of less than

Clinical Guideline	Recommendation(s)
	a week when the nose is extremely congested and intranasal corticosteroids do not easily reach the mucosa. • For the treatment of seasonal allergic rhinitis, it is recommended that intranasal corticosteroids be used throughout the season on a regular daily basis. • For the treatment of perennial allergic rhinitis, intranasal corticosteroids should be used for several months and the patient should be re-assessed after three months of successful therapy. • Intranasal corticosteroids are also considered first-line agents for the treatment of perennial nonallergic rhinitis in patients whose symptoms are bothersome.

III. Indications

Food and Drug Administration (FDA)-approved indications for fluticasone furoate are noted in Table 3. While this agent may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for Fluticasone Furoate[3]

Drug	Indication
Fluticasone furoate	The treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ≥2 years old.

IV. Pharmacokinetics

The pharmacokinetic parameters of fluticasone furoate are noted in Table 4.

Table 4. Pharmacokinetic Parameters of Fluticasone Furoate[3,9]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Renal Excretion (%)	Elimination*	Half-Life* (hours)
Fluticasone furoate	0.5	>99	Hydrolysis	<1	Feces (90%) Urine (2%)	15.1

*Following intravenous administration

V. Drug Interactions

Fluticasone furoate undergoes extensive first-pass metabolism via CYP3A4. Therefore caution is warranted with the concurrent use of fluticasone furoate and ketoconazole or ritonavir, as well as other potent CYP3A4 inhibitors. Coadministration with such CYP3A4 inhibitors may result in the risk of systemic effects secondary to increased fluticasone furoate exposure (eg, cortisol suppression). Significant drug interactions with fluticasone furoate are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with Fluticasone Furoate[3]

Drug(s)	Significance Level[10]	Interaction	Mechanism
Fluticasone furoate	2	Ketoconazole	Fluticasone furoate undergoes extensive first-pass metabolism via CYP3A4. Coadministration with such CYP3A4 inhibitors may result in the risk of systemic effects secondary to increased fluticasone furoate exposure. Therefore caution is warranted with the concurrent use of fluticasone furoate and ketoconazole.
Fluticasone furoate	2	Ritonavir	Fluticasone furoate undergoes extensive first-pass metabolism via CYP3A4. Coadministration with such CYP3A4 inhibitors may result in the risk of systemic effects secondary to increased fluticasone furoate exposure. Therefore the concurrent use of fluticasone furoate and ritonavir is not recommended.

Significance Level 2=moderate severity

VI. Adverse Drug Events

The manufacturer advises that systemic and local corticosteroid use may result in the following: epistaxis, ulcerations, *Candida albicans* infection, impaired wound healing, cataracts and glaucoma, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction.[3] The most common adverse reactions reported with fluticasone furoate are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with Fluticasone Furoate[3]

Adverse Event(s)	Fluticasone furoate
Central Nervous System	
Headache	8-9
Respiratory	
Nasopharyngitis	5
Other	
Back pain	1
Candida albicans infection	✔
Cataracts	✔
Cough	3-4
Epistaxis	4-6
Glaucoma	✔
Growth reduction	✔
Hypothalamic-pituitary-adrenal axis effects	✔
Immunosuppression	✔
Impaired wound healing	✔
Nasal ulceration	1
Pharyngolaryngeal pain	2-4
Pyrexia	4-5

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimen for fluticasone furoate is summarized in Table 7.

Table 7. Usual Dosing for Fluticasone Furoate[3]

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fluticasone furoate	Starting dosage is 110 mcg once daily administered as 2 sprays (27.5 mcg/spray) in each nostril. When the maximum benefit has been achieved and symptoms have been controlled, reducing the dosage to 55 mcg (1 spray in each nostril) once daily may be effective.	Starting dosage for children 2-11 years of age is 55 mcg once daily administered as 1 spray (27.5 mcg/spray) in each nostril. Children not adequately responding to 55 mcg may use 110 mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55 mcg once daily.	Nasal spray: 27.5 µg/spray (120 metered sprays per unit)

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of fluticasone furoate are summarized in Table 8. There are no head-to-head clinical trials comparing fluticasone furoate nasal spray to any other intranasal corticosteroid for the management of allergic or seasonal rhinitis.

Table 8. Comparative Clinical Trials Using Fluticasone Furoate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fokkens et al[11] Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years old with SAR and either a positive skin prick test to grass pollen or a positive in vitro test for the specific IgE within the past year	N=285 2 weeks	Primary: Mean change from baseline in daily rTNSS over the entire treatment period Secondary: Mean change from baseline in iTNSS, iTOSS, rTOSS, overall response to therapy, RQLQ scores, adverse events	Primary: Fluticasone furoate treatment resulted in significantly improved mean change from baseline in daily rTNSS compared with placebo (treatment difference of –1.757; *P*<0.001). Secondary: When compared to placebo, fluticasone furoate produced significantly greater improvements in the morning predose iTNSS (treatment difference of –1.898; *P*<0.001), daily rTOSS (treatment difference of –0.741; *P*<0.001) and morning predose iTOSS (treatment difference of –0.764; *P*<0.001). The overall response to treatment, as well as the RQLQ scores, was significantly greater in the active treatment group as compared to placebo (67% for fluticasone furoate and 39% for placebo; *P*<0.001, and a treatment difference in RQLQ scores of –0.700; *P*<0.001, respectively). The rates of adverse events were similar for both groups (17% for fluticasone furoate vs 16% for placebo; no *P* value reported). The most common reported side effect was headache, which was seen slightly more often with fluticasone furoate than placebo (9% vs 6%). Epistaxis was the most common drug-related adverse event observed with 3% of the active-treatment group effected vs <1% of the placebo group.
Gradman et al[12] Fluticasone furoate 110 µg QD vs placebo	DB, NI, PC, RCT, XO Prepubertal children (6-11 years of age) with a diagnosis of PAR or SAR for at least one year, and either a positive skin prick test	N=58 2 weeks	Primary: Mean growth rate in lower-leg length Secondary: Adverse events	Primary: A prespecified cutoff of no more than –0.20 mm/week was determined to be "noninferior". The treatment difference in adjusted mean lower-leg growth rate between fluticasone furoate and placebo was –0.016 mm/week (95% CI, –0.13 to 0.10) demonstrating noninferiority. Secondary: Reported adverse events were similar between the 2 groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or a positive test for the specific IgE to an appropriate seasonal or perennial allergen			
Kaiser et al[13] Fluticasone furoate 110 µg QD vs placebo	DB, PC, PG, RCT Patients ≥12 years old with documented history of SAR caused by ragweed pollen, with seasonal allergy symptoms during each of the past 2 Fall allergy seasons; positive skin prick test response to ragweed allergen within 12 months prior to start of study	N=299 2 weeks	Primary: Mean change from baseline in daily rTNSS over the entire treatment period Secondary: Mean change from baseline over the entire treatment period in: daily rTOSS, morning predose iTNSS, overall response to therapy, RQLQ, adverse events	Primary: Fluticasone furoate significantly reduced nasal symptoms vs placebo with a treatment difference of –1.473 (*P*<0.001). Secondary: A difference of –0.600 (*P*=0.004) between each group was noted in daily rTOSS. Fluticasone furoate demonstrated a significant reduction in morning predose iTNSS of –1.375 compared with placebo (*P*<0.001). Additionally, 73% of patients receiving fluticasone furoate vs 52% of placebo-treated patients reported improvement in their overall response to therapy (*P*<0.01). Fluticasone furoate-treated patients reported significant improvements in the overall RQLQ score vs placebo (–0.606; *P*<0.001). Adverse events occurred in 21% of patients receiving fluticasone furoate and 12% of patients receiving placebo. The most common side effect was headache (>3%), which was seen more often with fluticasone furoate than placebo. Epistaxis was another commonly reported side effect.
Martin et al[14] Fluticasone furoate 55 µg QD vs fluticasone furoate 110 µg QD vs fluticasone furoate 220 µg QD vs	DB, PC, PG, RCT Patients ≥12 years old with a diagnosis of SAR and a history of nasal allergy symptoms during each of the past 2 mountain cedar allergy seasons; positive skin prick test response to mountain cedar allergen within 12 months prior to the start of the study	N=641 2 weeks	Primary: Mean change from baseline in daily rTNSS over the entire treatment period Secondary: Mean change from baseline over the entire treatment period in: morning predose iTNSS, daily rTOSS, morning predose iTOSS, overall response to	Primary: Fluticasone furoate treatment, at all doses, resulted in significantly improved mean change from baseline in daily rTNSS compared with placebo (–3.19 to –4.02 for fluticasone vs –1.83 for placebo; *P*<0.001). Secondary: Fluticasone furoate demonstrated a significant mean change from baseline in morning predose iTNSS (*P*<0.001 each dose vs placebo), daily rTOSS (*P*≤0.013 each dose vs placebo), and morning predose iTOSS (*P*≤0.019 for 110 µg, 220 µg, 440 µg vs placebo) compared to placebo. Additionally, 16% of patients given 55 µg, 28% of those taking 110 µg, 23% with 220 µg and 26% with 440 µg reported a significant improvement in overall response to treatment, as compared to 8% of patients in the placebo group. All doses of active treatment also produced significant improvements in quality of life scores over placebo (–1.79 to –1.97 for fluticasone versus –0.97 for placebo; *P*≤0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone furoate 440 µg QD vs placebo			therapy, RQLQ, adverse events	Headache and nosebleed were the most frequently reported side effects in any treatment or placebo group. The rate of nosebleed tended to increase with greater doses of fluticasone furoate (3% for 55 µg, 8% for 110 µg, 9% for 220 µg and 7% for 440 µg vs 4% for placebo). On the other hand, the rate of headache did not appear to be dose dependent (6% for 55 µg, 6% for 100 µg, 2% for 220 µg, 3% for 440 µg and 5% for placebo). The differences between other end points used to measure adverse events (24-hour urinary cortisol excretion, clinical laboratory evaluations, nasal exams and ECGs) were insignificant among groups.
Máspero et al[15] Fluticasone furoate 55 µg QD vs fluticasone furoate 110 µg QD vs placebo Loratadine rescue therapy was provided as needed.	DB, MC, PC, PG, RCT Patients 2-11 years old with ≥6-month history of PAR documented by a positive skin prick test to an appropriate perennial allergen within 12 months prior to the start of the study	N=558 12 weeks	Primary: Mean change from baseline over the first 4 weeks in daily rTNSS in 431 patients ages 6-11 Secondary: Mean change from baseline over the first 4 weeks in morning predose iTNSS and overall response to therapy in 431 patients ages 6-11, safety (adverse events, ophthalmic and nasal exams, HPA axis assessment, laboratory tests, ECGs)	Primary: A significant reduction in daily rTNSS was noted with fluticasone furoate 55 µg compared to placebo (difference of –0.754; *P*=0.003), whereas the reduction in daily rTNSS in the fluticasone furoate 110 µg group was not determined to be statistically significant (difference of –0.452; *P*=0.073). Secondary: A significant reduction in morning predose iTNSS was noted with both fluticasone furoate 55 µg and 110 µg as compared to placebo. Again, the difference in the higher dose of fluticasone furoate was not significant in overall response to therapy as compared to placebo (*P*=0.414) but it was significant in the 55 µg treatment group (*P*=0.024). There were no significant differences in safety end points between active treatment and placebo.
Rosenblut et al[16] Fluticasone furoate 110 µg QD	DB, MC, PC, PG, RCT Patients ≥12 years old with ≥2-year documented history and	N=806 12 months There were	Primary: Safety and tolerability (adverse effects, 24-hour urinary cortisol	Primary: Nosebleed was reported more frequently in the fluticasone furoate treatment group (20%) compared to placebo (8%; *P* value not reported). There were no other clinically significant differences in adverse events noted between the active treatment group vs placebo over the 12-month

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	past treatment of PAR and a positive skin prick test to an appropriate allergen within the 12 months prior to, or at, start of study	significantly more patients included in the fluticasone furoate group (N=605) compared to placebo (N=201).	excretion, nasal examinations, ophthalmic examinations, ECGs, laboratory tests) Secondary: Not reported	period. Secondary: Not reported

Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, NI=noninferiority, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Other abbreviations: ECG=electrocardiogram, HPA=hypothalamic-pituitary-adrenal, IgE=immunoglobulin E, iTNSS=instantaneous total nasal symptom score, iTOSS= instantaneous ocular symptom score, PAR=perennial allergic rhinitis, rTNSS=reflective total nasal symptom score, rTOSS=reflective total ocular symptom score, RQLQ= Rhinoconjunctivitis Quality-of-Life questionnaire, SAR=seasonal allergic rhinitis

Additional Evidence

Dose Simplification

An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy

An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits

An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Fluticasone Furoate Products

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
fluticasone furoate	nasal spray	Veramyst®	$$$	N/A

No generic products are available for fluticasone furoate.
N/A=not available.

X. Conclusions

Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate-to-severe symptoms.[4-8] Select intranasal corticosteroids are also FDA approved for the treatment of nasal polyps and nonallergic rhinitis. In general, intranasal corticosteroids are less effective for these indications.[1] Flunisolide and fluticasone propionate are available in generic nasal formulations.

Fluticasone furoate is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥ 2 years of age.[3] Despite a greater binding affinity for the glucocorticoid receptor, it is unclear whether fluticasone furoate offers any additional therapeutic benefit in comparison to fluticasone propionate or any other intranasal corticosteroid.[3] This product utilizes a new nasal inhalation device with a side-actuated "mist-release" button that when pressed delivers the same amount of drug for each dose.

Multiple studies assessed the efficacy of fluticasone furoate compared to placebo in adult and adolescent patients with seasonal and perennial allergic rhinitis.[11-16] Three randomized controlled trials in patients with seasonal allergic rhinitis, each 2 weeks in duration, demonstrated significant improvement in nasal and ocular symptoms when compared to placebo.[11,13-14] Likewise, statistically significant improvement in quality of life scores was

observed in 3 studies of 2 week duration ($P<0.001$).[11,13-14] The intranasal corticosteroids are generally well tolerated with headache and nosebleeds being the most common adverse events reported.[11-16] One 12-month safety trial compared 605 patients on active treatment to 201 patients on placebo.[16] Epistaxis, the most commonly reported side effect, was reported in 20% of the active treatment group versus 8% on placebo. Otherwise, there were no other clinically significant differences in adverse events noted. There are no head-to-head trials comparing the efficacy and safety of fluticasone furoate nasal spray to other nasal corticosteroids for the management of perennial or seasonal allergic rhinitis.

The safety and efficacy of fluticasone furoate 55 µg and/or 110 µg was evaluated in children 2-11 years old with seasonal or perennial allergic rhinitis in two studies for up to 12 weeks of treatment.[12,15] The medication did demonstrate efficacy over placebo at both doses, but did not always achieve statistical significance.[15] Although fluticasone furoate has not shown any adverse effects on growth in the pediatric population after 12 weeks of treatment, the effects of a longer duration of use have not been studied.[15] Additionally, the product information does list hypothalamic-pituitary-adrenal axis effects and growth reduction as side effects of this agent. Overall, there were no meaningful differences in safety end points with fluticasone furoate treatment in children when compared to placebo.[12, 15]

At this time, there is insufficient data to conclude that fluticasone furoate is safer or more efficacious than other brand or generic products within the class reviewed, and that it offers a significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand fluticasone furoate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review—Symbicort®
(budesonide and formoterol fumarate)
Orally Inhaled Corticosteroids, AHFS Class 680400
May 14, 2008

I. Overview

Asthma is a respiratory disorder involving chronic inflammation of the airways. Inflammation is the underlying cause of asthma and is associated with airflow obstruction, bronchial hyperresponsiveness, and clinical symptoms including: wheezing, shortness of breath, and nocturnal awakenings. Symptoms may be exacerbated by physical, environmental, and/or chemical stimuli. The diagnosis of asthma is based on both symptomatic description and objective findings, including pulmonary function tests such as forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF).[1] Asthma is a reversible disorder, and may reverse either spontaneously or with the aid of pharmacological treatment.[2]

Pharmacological therapy for asthma is selected based upon the severity of the patient's disease.[1] Clinical guidelines, including those from the National Heart, Lung, and Blood Institute (NHLBI), state that all patients should be prescribed a rescue inhaler such as albuterol, and that inhaled corticosteroids (ICSs) should be considered as the cornerstone of long-term control therapy. Patients whose asthma cannot be adequately controlled through monotherapy with an ICS will normally require a step-up in therapy. The addition of a long-acting inhaled β_2-agonist to an ICS has been shown to decrease symptoms, improve lung function, and reduce asthma exacerbations in patients that are not adequately controlled on a low or medium dose of ICS.[1] For these patients, it also decreases the need for short-acting β_2-agonist use as a rescue inhaler for acute relief.[1]

Budesonide and formoterol is a combination product consisting of both an ICS and a long-acting β_2-agonist. Budesonide, the ICS, helps mediate the underlying airway inflammation associated with asthma. Formoterol, the long-acting β_2-agonist, exerts its effects locally in the lungs to provide bronchodilation. This combination product is Food and Drug Administration (FDA) approved for the long-term maintenance treatment of asthma in patients 12 years of age and older, and is not indicated for first-line therapy in patients with asthma.[1,3]

The budesonide and formoterol combination products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Budesonide and Formoterol Combination Product(s) Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
budesonide and formoterol fumarate	aerosol inhaler	Symbicort®	none

No generic products are available for budesonide and formoterol fumarate.

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 2 summarizes the current treatment guidelines for the management of asthma.

Table 2. Treatment Guidelines for the Management of Asthma

Clinical Guideline	Recommendation(s)
The National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education	• Treatment of disease is based on severity classifications of disease. • Because the budesonide-formoterol combination product is indicated only for adults and children ≥ 12 years of age, management should be according to the Asthma Severity Classification established in the guideline for adults and children ≥12 years of age.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td>and Prevention Program (NAEPP): Guidelines for the Diagnosis and Management of Asthma (2007)[1]</td><td>
<table>
<tr><th colspan="6">Classifying Asthma Severity in Youths ≥12 Years of Age and Adults</th></tr>
<tr><th>Type of Asthma</th><th>Symptoms/ day</th><th>Symptoms/ night</th><th>FEV_1*</th><th>FEV_1:FVC†</th><th>Medications Indicated</th></tr>
<tr><td>Inter-mittent</td><td>≤2 days per week</td><td>≤2 times per month</td><td>>80%</td><td>Normal</td><td>Short-acting β-agonist as needed for symptoms</td></tr>
<tr><td>Mild Persistent</td><td>>2 days per week but not daily</td><td>3-4 times per month</td><td>>80%</td><td>Normal</td><td>Preferred: Low-dose inhaled corticosteroid
Alternatives: cromolyn, leukotriene receptor antagonist, nedocromil, or theophylline</td></tr>
<tr><td>Moderate Persistent</td><td>Daily</td><td>>1 time per week but not nightly</td><td>>60% to <80%</td><td>Reduced 5%</td><td>Preferred: Low-dose inhaled corticosteroid and long-acting β-agonist or medium-dose inhaled corticosteroid
Alternatives: Low-dose inhaled corticosteroid and either leukotriene receptor antagonist, theophylline, or zileuton</td></tr>
<tr><td>Severe Persistent</td><td>Throughout the day</td><td>Often 7 times per week</td><td><60%</td><td>Reduced >5%</td><td>Preferred: Medium- to high-dose inhaled corticosteroid and long-acting β-agonist
Alternatives: Medium-dose inhaled corticosteroid and either leukotriene receptor antagonist, theophylline, or zileuton; may consider omalizumab</td></tr>
</table>
*FEV_1=forced expiratory volume in 1 second
† FEV_1:FVC=ratio of forced expiratory volume in 1 second to forced vital capacity

• Inhaled corticosteroids (ICSs) are the most potent and effective anti-inflammatory medication currently available, and are the preferred treatment for initiating long-term control therapy.
• Long-acting β-agonists are the preferred therapy to combine with inhaled corticosteroids in youth's ≥12 years of age and adults.
• Long-acting β_2-agonists are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe-persistent asthma.
• Long-acting β_2-agonists are not recommended as monotherapy for long-term control of persistent asthma.
</td></tr>
<tr><td>The American Thoracic Society (ATS)/European Respiratory Society (ERS): Guidelines on the Treatment of</td><td>• Patients should be instructed on asthma action plans and daily peak flow monitoring.
• Initial pharmacological treatment for patients with refractory asthma, should be treated as a starting point, as outlined in the Expert Panel 2 report. This includes a high-dose, high-potency ICS, oral corticosteroid at lowest dose possible, and one to three additional controller agents.
• Generally, high-dose ICS therapy is combined with a long-acting bronchodilator (eg, long-acting inhaled β_2-agonists) or oral theophylline. However, there is no data evaluating the benefits of multiple combinations of such alternative therapies.</td></tr>
</table>

Clinical Guideline	Recommendation(s)
Refractory Asthma (2000)[4]	
British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN): **British Guideline on the Management of Asthma (2007)[2]**	• A stepwise approach is recommended for the management of asthma in adults. • For step 1—mild intermittent therapy: an inhaled short-acting β_2-agonist should be used as required. • For step 2—regular preventer therapy: the initiation of a low-dose ICS or dose appropriate to severity of disease is recommended. • For step 3—add-on therapy: the addition of an inhaled long-acting β_2-agonist to current ICS therapy is recommended. If patient's asthma is not adequately controlled, may increase ICS and continue or stop long-acting β_2-agonist based on patient response. • For step 4—persistent poor control: high-dose ICSs are recommended. Another alternative is the addition of a fourth drug such as leukotriene receptor antagonist, sustained-release theophylline, or β_2-agonist tablet. • For step 5—continuous or frequent use of oral steroids: a daily steroid tablet in the lowest dose providing adequate control may be given. Other alternatives include maintaining the high-dose ICS or consider other treatments to limit the use of oral corticosteroids. Patient should be referred to specialist care. • ICSs are the most effective preventer drug for both adults and older children for achieving overall treatment goals. • The first choice as an add-on therapy to ICS in adults and children (5-12 years) is an inhaled long-acting β_2-agonist. • Long-acting inhaled β_2-agonists should not be used without ICS, and should only be initiated in patients who are already on ICS.
The Canadian Asthma Consensus Group: **Summary of Recommendations from the Canadian Asthma Consensus Report (1999)[5]**	• Treatment should be individualized to a patient's needs and severity. • Inhalers are the preferred delivery method over oral preparations. • ICSs offer the best option for the initial anti-inflammatory treatment of asthma. • ICSs should be used in all patients but those with the mildest of symptoms. • Short-acting β_2-agonists should be used for relief of acute symptoms. • Inhaled long-acting β_2-agonists (formoterol and salmeterol) may be considered as an alternative to increased doses of inhaled glucocorticosteroids and should be used as an add-on therapy to moderate or higher doses of inhaled glucocorticosteroids to achieve control of persistent asthma symptoms. • Leukotriene receptor antagonists may be considered an alternative to long-acting β_2-agonists when additional medication is needed. • Nedocromil is a safe alternative to steroids in mild asthma but is not proven to be as effective as steroids. • Theophylline should be considered third-line therapy for the treatment of asthma due to a high side effect burden even at small doses.
The Global Initiative for Asthma (GINA) Executive Committee: **Global Strategy for Asthma Management and Prevention (2007)[6]**	• A step-wise approach is recommended for the management of asthma. • For step 1: the recommended treatment is a rapid-acting β_2-agonist used on an as needed basis. • For step 2: inhaled glucocorticosteroids in low doses are recommended as initial controller treatment for asthma patients of all ages. • For step 3: inhaled glucocorticosteroids at a low dose plus a long-acting β_2-agonist, or inhaled glucocorticosteroids at a medium dose is the recommended treatment. • For step 4: inhaled glucocorticosteroids at a medium to high dose plus a long-acting β_2-agonist is the recommended treatment. • For step 5: an oral glucocorticosteroid at the lowest dose or anti-IgE treatment are possible treatment options. • A rapid-acting inhaled β_2-agonist should be provided to all asthma patients regardless of disease severity. • Inhaled glucocorticosteroids are the preferred treatment for patients with persistent asthma at all levels of severity. • Long acting inhaled β_2-agonists, including formoterol and salmeterol, are most effective when

Clinical Guideline	Recommendation(s)
	combined with inhaled glucorticosteroids, and this combination therapy is the preferred treatment when a medium-dose of inhaled glucocorticosteriod alone fails to achieve control of asthma. • Long acting inhaled β_2-agonists should not be used as monotherapy in asthma.
International Primary Care Respiratory Group (IPCRG) Guidelines: **Management of Asthma (2006)**[7]	• Treatment guidelines are consistent with the GINA guidelines. • As in the GINA guidelines, asthma is classified as mild intermittent, mild persistent, moderate persistent and severe persistent. • Patients with mild intermittent asthma should receive short-acting β_2-agonists as needed. In patients older than 60 years of age anticholinergics can be considered. • Patients with mild persistent asthma should be treated with a low-dose corticosteroid inhaler. • In moderate persistent asthma, ie, mild persistent asthma that has proven refractory to inhaled corticosteroids at low doses, these patients should receive ICSs and a long-acting β_2-agonist. An alternative to this therapy would be an ICS combined with a leukotriene modifier or sustained-release theophylline. • In severe persistent asthma, ie, moderate persistent asthma that is refractory to treatment, these patients should receive a high dose ICS and long-acting β_2-agonist twice daily. An alternative to this therapy would be sustained-release theophylline, leukotriene receptor antagonists, and short-term systemic steroids. These patients must also be counseled in trigger avoidance and proper implementation of the asthma action plan.

III. Indications

Food and Drug Administration (FDA)-approved indications for the budesonide and formoterol combination products are noted in Table 3. While this agent may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Budesonide and Formoterol Combination Products[3]

Drug	Indication(s)
Budesonide and formoterol	Long-term maintenance treatment of asthma in patients 12 years of age and older

IV. Pharmacokinetics

The pharmacokinetic parameters for the budesonide and formoterol combination products are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Budesonide and Formoterol Combination Products[3, 8-11]

Drug	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Budesonide and formoterol	0.25*	12	~60 (budesonide) 59-62 (formoterol)	No	4.7 (budesonide) 7.9 (formoterol)

***** Formoterol onset is approximately 3 minutes

V. Drug Interactions

Significant drug interactions reported with the budesonide and formoterol combination products are summarized in Table 5.

Table 5. Significant Drug-Drug Interactions with the Budesonide and Formoterol Combination Products[8,12]

Drug	Significance Level	Interaction	Mechanism
Formoterol fumarate	1	Monoamine oxidase inhibitors (MAOIs)	Monoamine oxidase is an enzyme that is involved with the metabolism of catecholamines. Use of β_2-agonists with MAOIs may result in a hypertensive crisis (elevated risk of tachycardia, agitation, or hypomania). Caution is warranted in patients currently taking MAOIs, or if formoterol is given within two weeks of stopping the MAOI.
Budesonide	2	Azole antifungals	Azole antifungals may inhibit the metabolism of corticosteroids (via CYP3A4), leading to increased corticosteroid plasma concentrations, effects, and toxicity. Doses of inhaled corticosteroids may require adjustment.
Formoterol fumarate	2	β-adrenergic antagonists	β-adrenergic antagonists, particularly those that are non-selective (eg, propranolol), can block the therapeutic effects of β_2-agonists and may cause severe bronchospasm in patients with asthma or chronic obstructive pulmonary disease.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the budesonide and formoterol combination products are summarized in Table 6.

It is important to note that budesonide and formoterol should not be used to treat acute asthma symptoms or be initiated in patients during a rapidly deteriorating or potentially life-threatening asthma episode. A black box warning has been issued for the combination of budesonide and formoterol concerning the relationship between long-acting β_2-adrenerigc agonists and an increase in asthma-related deaths. Details of the black box warning are given in Table 7.

Table 6. Adverse Drug Events (%) Reported for the Budesonide and Formoterol Combination Products[3]

Adverse Event(s)	Budesonide and Formoterol
Cardiovascular	
Atrial tachyarrhythmias	✔
Coronary ischemia	✔
Hypertension	✔
Hypertensive crisis	✔
Hypotension	✔
Palpitations	✔
Tachycardia	✔
Ventricular tachyarrhythmias	✔
Central Nervous System	
Aggressive reactions	✔
Agitation	✔
Anxiety	✔
Behavioral disturbances	✔
Depression	✔
Dizziness	✔
Dysphonia	✔
Headache	6.5-11.3

Adverse Event(s)	Budesonide and Formoterol
Irritability	✔
Migraine	✔
Nervousness	✔
Psychosis	✔
Restlessness	✔
Tension headache	✔
Dermatologic	
Skin bruising	✔
Gastrointestinal	
Diarrhea	✔
Dyspepsia	✔
Gastroenteritis viral	✔
Nausea	✔
Oral candidiasis	1.4-3.2
Stomach discomfort	1.1-6.5
Vomiting	1.4-3.2
Genitourinary	
Urinary tract infection	✔
Hypersensitivity	
Anaphylactic reaction	✔
Angioedema	✔
Bronchospasm	✔
Pruritus	✔
Rash	✔
Urticaria	✔
Metabolic	
Hypercorticism	✔
Hyperglycemia	✔
Hypocorticism	✔
Hypokalemia	✔
Musculoskeletal	
Arthralgia	✔
Myalgia	✔
Respiratory	
Asthma	✔
Bronchitis	✔
Bronchitis (acute)	✔
Cough	✔
Influenza	2.4-3.2
Lower respiratory tract infection	✔
Nasal congestion	2.5-3.2
Nasopharyngitis	9.7-10.5
Pharyngitis	✔
Pharyngolaryngeal pain	6.1-8.9
Rhinitis	✔
Rhinitis (allergic)	✔
Sinus congestion	✔
Sinus headache	✔
Sinusitis	4.8-5.8
Upper respiratory infection	7.6-10.5
Special Senses	
Cataracts	✔

Adverse Event(s)	Budesonide and Formoterol
Glaucoma	✔
Taste disturbance	✔
Other	
Back pain	1.6-3.2
Muscle spasms	✔
Pain in extremity	✔
Postprocedural pain	✔
Tremor	✔
Upper abdominal pain	✔

✔ Percent not specified

Table 7. Black Box Warning for the Budesonide and Formoterol Combination Products[3]

Drug-Related Asthma Deaths
Long-acting β_2-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, Symbicort should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting β_2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting β_2-adrenergic agonist), one of the active ingredients in Symbicort.

VII. Dosing and Administration

The usual dosing regimens for the budesonide and formoterol combination products are summarized in Table 8.

Table 8. Usual Dosing for the Budesonide and Formoterol Combination Products[3]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Budesonide and formoterol	Patients not currently receiving inhaled corticosteroid therapy, but whose disease severity warrants treatment with two maintenance therapies: 80/4.5 µg or 160/4.5 µg, 2 inhalations twice daily (depending on asthma severity); maximum of 640/18 µg daily (given as 2 inhalations of 160/4.5 µg twice daily) Patients currently receiving low to medium doses of inhaled corticosteroids, and whose disease severity warrants treatment with two maintenance therapies: 80/4.5 µg, 2 inhalations twice daily; maximum of 640/18 µg daily (given as 2 inhalations of 160/4.5 µg twice daily) Patients currently receiving medium to high doses of inhaled corticosteroids, and whose disease severity warrants treatment with two maintenance therapies: 160/4.5 µg, 2 inhalations twice daily; maximum of 640/18 µg daily (given as 2 inhalations of 160/4.5 µg twice daily)	Safety and efficacy in children <12 years of age has not been established.	Aerosol inhalation: 80/4.5 µg 160/4.5 µg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the budesonide and formoterol combination products are found in Table 9.

Table 9. Comparative Clinical Trials Using the Budesonide and Formoterol Combination Products

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Corren et al[13] Budesonide-formoterol pMDI 80/4.5 µg, 2 inhalations BID vs budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	DB, DD, MC, PC, RCT Patients ≥12 with predominantly mild to moderate persistent asthma treated with an ICS for ≥4 weeks before screening and with a prebronchodilator FEV_1 60%-90% of predicted normal on ICS at screening	N=480 12 weeks	Primary: Changes from baseline in morning predose FEV_1 and 12-hour mean FEV_1 after morning dose Secondary: Morning and evening predose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma	Primary: The mean change from baseline in predose FEV_1 was greater in patients who received budesonide-formoterol compared with those who received budesonide, formoterol, and placebo (P<0.005). Observed mean changes from baseline in 12-hour FEV_1 were greater in patients who received budesonide-formoterol compared with those who received budesonide or placebo (P<0.001). There was no evidence of diminution of the 12-hour bronchodilatory effect of budesonide-formoterol during the study period. Secondary: Patients who received treatment with budesonide-formoterol had greater mean increases from baseline in morning and evening predose PEF compared with budesonide or formoterol (P<0.001). Mean decreases in symptom scores were greater with the budesonide-formoterol treatment group compared with formoterol and placebo (P<0.046). Active treatments were associated with greater mean increases in awakening-free nights compared with placebo (P<0.012). Patients who received budesonide-formoterol had a greater mean reduction from baseline in daily rescue medication use compared with formoterol (P=0.006). The percentage of patients experiencing worsening asthma was reduced with budesonide-formoterol compared with formoterol or placebo (P≤0.01).
Murphy et al[14] Budesonide-formoterol pMDI 80/4.5 µg, 2	DB, DD, MC, PC, RCT Patients ≥18 with	N=405 12 weeks	Primary: AQLQ, MOS Sleep Scale, asthma control variables (daily	Primary: A significantly greater improvement from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores, and asthma control variables was seen in the budesonide-formoterol group compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations BID vs budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	predominantly mild to moderate persistent asthma		asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, and percentage of asthma control days), PSAM Secondary: Not reported	(P<0.033). A significantly greater improvement from baseline in AQLQ overall and domain scores, daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, and percentage of asthma control days was seen in the budesonide-formoterol group compared to formoterol (P<0.042). A significantly greater PSAM scores were reported in the budesonide-formoterol group compared to all other treatment arms (P<0.004). Secondary: Not reported
Noonan et al[15] Budesonide-formoterol pMDI 160/4.5 µg, 2 inhalations BID vs budesonide pMDI* 160 µg, 2 inhalations plus formoterol DPI 4.5 µg, 2 inhalations, both BID vs budesonide pMDI* 160 µg, 2 inhalations BID vs	DB, DD, MC, PC, RCT Patients ≥12 years, documented diagnosis of asthma for ≥6 months, moderate to high ICS use for ≥4 weeks, prebronchodilator FEV_1 45%-85% of predicted normal	N=596 12 weeks	Primary: Mean change from baseline in morning predose FEV_1, mean change from baseline in 12-hour FEV_1 after administration of morning dose Secondary: PEF, asthma symptoms, rescue medications use, and worsening asthma	Primary: Greater improvements in morning predose FEV_1 were obtained in patients treated with budesonide-formoterol (0.19 L) than those with budesonide (0.10 L), formoterol (-0.12 L), and placebo (-0.17 L); P≤0.049. Patients who received budesonide-formoterol also demonstrated a greater improvement in 12-hour FEV_1 than budesonide, formoterol, and placebo at 2 weeks and end of treatment (P≤0.001). Fewer patients receiving budesonide-formoterol pMDI than with the individual products or placebo met worsening asthma criteria. Secondary: Budesonide-formoterol treatment resulted in greater improvements in morning and evening PEF, daytime and nighttime symptoms, worsening asthma, and percentage of symptom-free days than budesonide, formoterol, and placebo (P≤0.05). Patients receiving budesonide-formoterol demonstrated reduction in asthma symptoms, use of rescue medication and improvement in PEF within the first day, and effects were maintained over the course of the 12-week study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol DPI 4.5 µg, 2 inhalations BID vs placebo				Significant reductions in the use of rescue medication were observed in patients with budesonide-formoterol treatment compared with formoterol (P<0.001) and placebo but not with budesonide (P=0.066). Awakenings due to asthma were not significantly different between active treatment groups. Similar results were obtained for treatment arms with combination budesonide-formoterol and concurrent administration of the individual components. No clinically significant differences in adverse events were observed between treatment groups. Patients who received budesonide-formoterol had clinically significant bronchodilation, defined as >15% improvement in FEV_1, within 15 minutes and effect was maintained over 12 hours.
Palmqvist et al[16] Budesonide-formoterol 160/4.5 µg, 1 inhalation vs budesonide-formoterol 160/4.5 µg, 2 inhalations vs fluticasone-salmeterol 250/50 µg, 1 inhalation vs placebo	DB, PC, RCT, XO Adult asthmatic patients (mean predicted FEV_1 of 78%, mean reversibility of 19%)	N=30 4 days	Primary: Mean FEV_1 at 15 minutes after inhalation Secondary: Time to bronchodilation (defined as >15% increase in FEV_1 from baseline), absolute FEV_1 at 3 minutes, FEV_1 at time points ≤60 minutes	Primary: Both budesonide-formoterol doses demonstrated improvements in FEV_1 compared with fluticasone-salmeterol and placebo at 15 minutes postdose (P<0.001). Secondary: At 1 hour, bronchodilation was achieved in 47% of patients in the fluticasone-salmeterol group, 73% of those in the budesonide-formoterol one inhalation group, and 77% of those in the budesonide-formoterol two inhalations group. Both doses of budesonide-formoterol also demonstrated significant improvements in FEV_1 at 3 minutes (P<0.001) and at 60 minutes (no P values reported) compared with fluticasone-salmeterol and placebo.
Lötvall et al[17] Study A: Fluticasone-salmeterol 100/50 µg, single dose	Study A: DB, PC, RT, SC, 3-way XO Study B: DB, MC, RT, XO	N=108 Study A: N=33 3 weeks	Primary: Study A: Mean change from predose FEV_1 to 16 hours postdose	Primary: Study A: Patients in both the fluticasone-salmeterol and budesonide-formoterol groups had statistically significant greater FEV_1 values at 16 hours postdose in comparison to those in the placebo group (-0.5 L difference; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide-formoterol 160/4.5 µg, single dose vs placebo, single dose Study B: Fluticasone-salmeterol 100/50 µg, 1 inhalation BID vs budesonide-formoterol 160/4.5 µg, 1 inhalation BID Patients in Study B received BDP 400 µg, 1 inhalation BID during 4 week run-in and 4 week wash-out between active treatments.	Both: Patients ≥18 years of age with diagnosis of asthma for at least 6 months, prebronchodilator FEV_1 of >50% predicted of normal, FEV_1 ≥15% of predicted value 15 min after receiving 400 µg salbutamol† Study A: Patients on budesonide 400-1,200 µg (or equivalent) at least 4 weeks prior to study Study B: Patients on 800-1,200 µg of budesonide or BDP or 400-600 µg/day of fluticasone or QVAR® for at least 4 weeks prior to study	Study B N=75 12 weeks	Study B: Slope of decline in FEV_1 from 2 hours postdose, area under FEV_1 curve, mean change from predose FEV_1 at 12 hours postdose Secondary: Study A: Mean change in FEV_1 from predose over 24 hours postdose Study B: Serial FEV_1 measurements following single dose after 4 weeks treatment	There was no statistically significant difference in FEV_1 values at 16 hours postdose between the active treatment groups (P=0.617) Study B: There were no statistically significant differences between the fluticasone-salmeterol and budesonide-formoterol groups in regards to all primary end points. Secondary: Study A: Patients in both the fluticasone-salmeterol and budesonide-formoterol groups had a statistically significant mean change in FEV_1 at each scheduled evaluation compared to those in the placebo group. There was no statistically significant difference in mean change of FEV_1 between the active treatment groups. Study B: There was no statistically significant difference in mean FEV_1 from baseline or FEV_1 from predose over 24 hours after 4 weeks treatment between the active treatment groups.
Rosenhall, Borg, et al[18] Budesonide-formoterol 160/4.5 µg, 2 inhalations	ES, MN, OL, PG, RT Adult patients with	N=320 12 months	Primary: Efficacy and safety parameters	Primary: There was no statistically significant differences observed between the two treatment groups in regards to safety and efficacy, with the exception of lower withdrawal proportions in patients treated with budesonide-formoterol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID (via same inhaler) vs budesonide plus formoterol, 2 inhalations BID (via separate inhalers)	asthma		Secondary: Not reported	via single inhaler versus those treated with separate inhalers (9.2% and 19.4%, respectively; *P*=0.008). Secondary: Not reported
FitzGerald et al[19] CONCEPT Fluticasone-salmeterol propionate 250/50 µg, 1 inhalation BID vs budesonide-formoterol 200/6 µg, 2 inhalations BID-AMD There was a 2-week open-label run-in period in which patients continued their current asthma medication and were evaluated for randomization eligibility. Patients in the budesonide-formoterol-AMD group initially halved their dose, then stepped up or down on the dose depending on symptoms, PEF, and rescue medication use.	DB, DD, MC, PG, RCT Patients 18-70 years of age with persistent asthma, FEV_1 60%-90% of predicted normal, uncontrolled on 200-500 µg/day of ICS (equivalent to BDP) plus long-acting β_2-agonist, or ICS dose >500-1,000 µg alone (equivalent to BDP) ≥12 weeks prior to study To be eligible for randomization, patients had to have a total daily symptom score of >2 (on a scale of 0 to 5) on >4 of the last 7 evaluable days of the run-in period and had to	N=688 1 year	Primary: Symptom-free days Secondary: Daily asthma symptom scores, morning PEF night-time awakenings, days free of rescue medication, use of daily rescue medications, weeks of well-controlled asthma, number of exacerbations resulting in ED visits/ hospitalization or use of oral steroids	Primary: Patients receiving stable dosing of fluticasone-salmeterol had a statistically significant higher percentage of symptom-free days (median) in comparison to those in the budesonide-formoterol-AMD group throughout weeks 1-52 (58.8% and 52.1%, respectively; *P*=0.034). The percentage of symptom free days was greater for those in the fluticasone-salmeterol treatment group during weeks 5-52 in comparison to those in the budesonide-formoterol-AMD group (73.8% and 64.9%, respectively; *P*=0.030.) The percentage of symptom free days was similar for both treatment groups (stable dosing of fluticasone-salmeterol and budesonide-formoterol) during the first 4 weeks of treatment. Secondary: Patients in the stable dosing fluticasone-salmeterol group had a significantly greater percentage of days free of rescue medication and a lower percentage of daily rescue medication use throughout the study period in comparison to those in the budesonide-formoterol treatment group (*P*=0.008 and *P*=0.006, respectively). Patients in the fluticasone-salmeterol group experience a 47% reduction in the rate of exacerbations in comparison to those in budesonide-formoterol-AMD group, with an adjustable annual mean exacerbation rate of 0.18 and 0.33, respectively (adjustment treatment ratio 0.53; 95% CI, 0.34 to 0.85; *P*=0.008). The use of oral corticosteroids was significantly different among the 2

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	demonstrate the ability to use a peak flow meter and accurately record values in a diary			treatments groups (*P*=0.026) with fluticasone-salmeterol having a 46% lower total number of days of exposure versus that observed in the budesonide-formoterol group. There was no statistically significant difference in night-time awakenings or daily symptom scores observed between the 2 treatment groups, but patients in the fluticasone-salmeterol group had a statistically significant improvement in morning PEF in comparison to the budesonide-formoterol group (adjusted mean difference 9.5 L/min; 95% CI, 2.7 to 16.3; *P*=0.006).
Scicchitano et al[20] Budesonide 160 µg, 2 inhalations BID plus terbutaline 0.4 mg inhalations PRN vs budesonide-formoterol 160/4.5 µg, 2 inhalations QD with additional inhalations PRN	DB, PG, RT Patients 11-80 years of age with symptomatic asthma, mean FEV_1 70% of predicted, mean ICS dose 746 µg/day	N=1,890 12 months	Primary: Time to first severe exacerbation (defined as hospital/ER visit, oral steroids, or fall in morning PEF to <70% of baseline for 2 consecutive days) Secondary: Number of severe exacerbations, use of as-needed medication, mean daily ICS dose, number of asthma control days	Primary: Patients in the budesonide-formoterol group had prolonged time to first exacerbation, and a 39% lower risk of having a severe exacerbation compared to budesonide (*P*<0.001). Secondary: Patients in the budesonide-formoterol group had 45% fewer severe exacerbations resulting in medical interventions per patient compared to those in the budesonide group (*P*<0.001). Patients in the budesonide-formoterol group also had less utilization of as-needed medication compared to those in the budesonide group (*P*<0.001), and a lower mean daily ICS dose (466 µg/day vs 640 µg/day, respectively). Overall, those in the budesonide-formoterol group experienced 31 more asthma control days and 12 more undisturbed nights per patient-year versus those in the high-dose budesonide group (no *P* value reported).
Rabe et al[21] Budesonide-formoterol 80/4.5 µg, 2 inhalations QD in the evening plus additional inhalations PRN vs budesonide 160 µg, 2	AC, DB, MC, PG, RT Patients 11-79 years if age with an asthma diagnosis for ≥6 months, FEV_1 60%-100% predicted normal, >12% reversibility	N=697 6 months	Primary: Morning PEF Secondary: FEV_1, evening PEF, PRN inhalations, PRN medication-free days, asthma symptom score, nighttime	Primary: Patients in the budesonide-formoterol maintenance and relief group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the 6 month treatment period (34.5 L/min vs 9.5 L/min, respectively; *P*<0.001). Secondary: Both treatment groups were associated with an increase in mean FEV_1, but those in the budesonide-formoterol group had statistically significant greater improvements compared to those receiving budesonide alone (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations QD in the evening plus terbutaline 0.4 mg PRN There was a 14-18 day-run-in period in which patients received budesonide 100 µg BID and terbutaline 0.5 mg PRN, both via DPI.	of baseline FEV_1 15 min after terbutaline 1 mg inhalation, all patients had received ICS 200-500 µg/day for ≥3 months at a constant dose for ≥30 days prior to study and were required to have had ≥7 inhalations of as-needed medication during the last 10 days of the run-in period but <10 inhalations on any single day		awakenings, symptom free days, asthma control days, risk of exacerbation	Patients in the budesonide-formoterol maintenance and relief group also had greater improvements in evening PEF from baseline than those in the budesonide group. Patients in the budesonide-formoterol maintenance and relief group had statistically significantly lower asthma symptom scores in comparison to those who were receiving budesonide (*P*<0.001). There was also a statistically significant improvement in both symptom free days and asthma control-days observed in the budesonide-formoterol maintenance and relief group versus those in the budesonide group (*P*<0.01). Those in the budesonide-formoterol maintenance and relief group had less utilization of as-needed medication, along with 8% more as-needed medication-free days versus those in the budesonide group (*P*<0.001). Patients in the budesonide-formoterol maintenance and relief group had a 54% lower risk in having an exacerbation in comparison to those in the budesonide group (*P*=0.0011), as well as 90% fewer hospitalizations/ED treatments versus those in the budesonide group (*P*=0.026).
Price et al[22] Budesonide-formoterol 200/6 µg, 2 inhalations BID-AMD vs fluticasone-salmeterol 250/50 µg, 1 inhalation BID-FD During weeks 1-4, patients received either 1 inhalation of fluticasone-salmeterol 250/50 µg BID or 2	DB, DD, MC, PG, RT Outpatients 18-70 years of age, a clinical asthma history with FEV_1 60%-90% predicted normal, received and ICS dose equal to 200-500 µg/day BDP plus LABA, or ICS alone at dose equal to >500-1,000 µg BDP (at least 12 weeks prior to	N=688 1 year	Primary: Symptom-free days (defined as symptom score of zero in a 24-hour period) Secondary: Rate of exacerbations	Primary: Patients in the FD fluticasone-salmeterol group had a significantly greater percentage of symptom-free days (58.8%) over the entire year, compared to budesonide-formoterol AMD group (52.1%; *P*=0.034). Secondary: The adjusted annual mean exacerbation rate was also significantly lower in the FD fluticasone-salmeterol group compared to the AMD budesonide-formoterol group (47%; *P*=0.008)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations of budesonide-formoterol 200/6 µg and during weeks 5-52, those who met the criteria, received budesonide-formoterol-AMD or fluticasone-salmeterol-FD.	enrollment)			
Dahl et al[23] Fluticasone-salmeterol 250/50 µg, 1 inhalation BID vs budesonide-formoterol 200/6 µg, 2 inhalations BID	DB, DD, MC, PG, RCT Patients with persistent asthma, currently receiving 1,000-2,000 µg/day of ICS, FEV_1 reversibility of ≥12% (and ≥200 mL), 15 min after salbutamol† 200-400 µg, and an asthma symptom score of at least 2 on at least 4 of the last 7 evaluable days of the run-in period	N=1,391 24 weeks	Primary: Rate of exacerbations Secondary: Lung function, asthma symptoms, use of rescue medications, adverse events	Primary: There were no statistically significant differences in mean rate of exacerbations over 24 weeks, or severity of exacerbations observed between treatment groups. The adjusted mean rates of moderate/severe exacerbations per year calculated at weeks 1-24, 1-8, and 9-16 were similar between treatment groups (*P*=NS). The adjusted mean rate of moderate/severe exacerbations per year calculated at weeks 17-24 of fluticasone-salmeterol was lower than budesonide-formoterol (*P*=0.006). Secondary: There were no statistically significant differences in morning and evening PEF, asthma symptoms, symptom-free days, symptom-free nights, rescue medication usage, asthma control, and incidence and types of adverse events observed between treatment groups.
Ringdal et al[24] EDICT Fluticasone-salmeterol 250/50 µg, 1 inhalation BID vs	DB, DD, PG, RCT Patients 16-75 years of age with clinical history of reversible airway obstruction, symptomatic on 1,000-1,600 µg/day of budesonide, BDP, or flunisolide,	N=428 12 weeks	Primary: Mean morning PEF (during week 12 of treatment) Secondary: Morning and evening PEF, day and nighttime symptom scores, nighttime	Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 L/min to 386 L/min with fluticasone-salmeterol treatment compared to an increase of 348 L/min to 389 L/min observed with budesonide-formoterol treatment (-3.2 L/min mean difference; 95% CI, –15.0 to 8.6; *P*=0.593). Similar results in mean morning PEF were seen in the intent to treat population for both treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
budesonide (800 µg) plus formoterol (12 µg), each 1 inhalation BID	or 500-800 µg/day of fluticasone, FEV_1 50%-85%, increased symptom scores or reliever use		awakenings, FEV_1, rate and severity of exacerbations, use of rescue medication, withdrawals from study	The mean rate of exacerbation per patient per 84 days of treatment was significantly lower in those in the fluticasone-salmeterol group in comparison to the budesonide-formoterol treatment group with a risk reduction of 36% (0.472 vs 0.735, respectively; 95% CI, 0.51 to 0.80; *P*<0.001). Over the entire treatment period, patients in the fluticasone-salmeterol treatment group had a statistically significant greater percentage of nights with no awakenings, without symptoms, and a symptom score of <2 in comparison to those in the budesonide-formoterol treatment group (*P*=0.02, *P*=0.04, and *P*=0.03, respectively). There was no significant difference in morning and evening PEF, clinic-measured FEV_1, improvement in day-time symptoms, and use of relief medication (salbutamol†) between the two treatment groups.
Pohl et al[25] Budesonide-formoterol 160/4.5 µg, 2 inhalations BID-AMD vs budesonide 320 µg, 2 inhalations BID-AMD	DB, PG, RT Patients >19 years of age with asthma, FEV_1 reversibility of ≥15% (or 200 mL) within 1 month prior to enrollment, FEV_1 40%-85% of predicted normal, requirement of ICS or ICS-LABA combination within given starting dose range	N=133 20 weeks	Primary: Number of patients per treatment group with ≥1 treatment failure (defined as hospitalization, oral steroids, nebulized β_2-agonists, withdrawal due to lack of efficacy or life-threatening/fatal condition) Secondary: Health-related quality of life measured by the SF-36, dose of study medication, days of reliever medication use, treatment satisfaction	Primary: The rate of treatment failures were comparable between the 2 treatment groups with 5/63 patients in the budesonide-formoterol group and 2/63 patients in the budesonide group experiencing treatment failure throughout the duration of the study. Secondary: Patients in the budesonide-formoterol group had a statistically significant improvement in health-related quality of life and treatment satisfaction (for patients and physicians) versus those in the budesonide group (*P*<0.05). Patients in the budesonide-formoterol group also had a lower use of daily inhalations of study drug versus budesonide (*P*=0.024). Both groups had minimal use of reliever medications.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Remington et al[26] Budesonide (range: 200, 400, and 800 µg) vs budesonide (range: 200, 400, and 800 µg) plus formoterol (range: 9-24 µg)	MA Patients ≥12 years of age with mild to severe asthma	N=4,079 in 5 studies 12 weeks to 12 months	Primary: Frequency of mild and severe exacerbations, time to first severe exacerbation, poorly controlled asthma days, PEF, asthma symptoms, rescue medication use Secondary: Not reported	Primary: The addition of formoterol to high-dose budesonide resulted in a greater reduction in both mild and severe exacerbation rates compared to low-dose budesonide (*P*<0.001). High-dose budesonide monotherapy was more efficacious in reducing the rates of severe exacerbations in comparison to low-dose budesonide and formoterol (*P*=0.03), but similar results were observed between the two groups in regards to the rate of mild exacerbations. The addition of formoterol to either budesonide 200 or 400 µg in patients who were previously on low-medium doses of ICS led to a greater reduction in the risk of first severe exacerbation, as well as a reduction in the frequency of poorly controlled asthma days compared to budesonide alone. Combination of budesonide and formoterol in separate devices or a single inhaler had significantly greater improvements in morning PEF compared to budesonide alone (*P*<0.0001), and improvements were maintained over the entire study period. Combination therapy was associated with grater improvements in symptom scores, symptom-free days, and rescue medication use. There were no observed differences between the treatment groups in regard to the number of severe exacerbations. Budesonide and formoterol were equally efficacious, whether in a single or separate inhaler, and were more effective than budesonide alone. Patients in the high dose budesonide plus formoterol group had improved AQLQ scores during both the run-in period and during the treatment period (*P*<0.001 and *P*=0.028, respectively). Secondary: Not reported
Tal et al[27] Budesonide-formoterol 80/4.5 µg, 2 inhalations	DB, DD, MC, PG, RCT Asthmatic children	N=286 12 weeks	Primary: PEF Secondary:	Primary: Patients receiving budesonide-formoterol had greater increases in morning and evening PEF than with those treated with budesonide (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID vs budesonide 100 µg, 2 inhalations BID	(mean age, 11 years) with mean predicted FEV_1 of 75% and treated with ICSs (average baseline dose, 548 µg/day)		FEV_1, asthma symptoms, use of rescue medications, adverse events	Secondary: Patients in the budesonide-formoterol group had greater increases in mean FEV_1 and serial FEV_1 measured over 12 hours than those treated with budesonide (P<0.05). There were no significant differences in asthma symptoms and use of rescue medications observed between treatment groups. Adverse events reported by ≥5% of patients were pharyngitis (8% vs 12%), respiratory infection (8% vs 6%), rhinitis (7% vs 4%), coughing (5% vs 5%), headache (6% vs 4%), viral infection (7% vs 3%), fever (6% vs 2%), and aggravated asthma (5% vs 3%) in the budesonide-formoterol and budesonide groups, respectively.
Lalloo et al[28] Budesonide-formoterol 80/4.5 µg BID vs budesonide 200 µg BID There was a 2-week-run-in period in which patients received budesonide 100 µg BID.	DB, MC, PG, RCT Adult patients with mild-to-moderate asthma not fully controlled on low doses of ICS alone, mean baseline predicted FEV_1 of 82%	N=467 12 weeks	Primary: PEF Secondary: Asthma symptoms, use of reliever medication, adverse events	Primary: The budesonide-formoterol group showed greater improvements from baseline in morning PEF (P=0.002), and evening PEF (P<0.001). Secondary: Patients receiving budesonide-formoterol showed greater improvements from baseline in symptom-free days (P=0.007), asthma-control days (P=0.002) and use of rescue medications (P=0.025) than the budesonide group. Fewer patients in the budesonide-formoterol group experienced at least one mild asthma exacerbation (48% vs 57%; no P value reported) and nighttime awakenings due to asthma (33% vs 44%; no P value reported) compared with budesonide group. The rate of severe exacerbations (7% of each group) and time to first severe exacerbation were similar for both treatment groups. No between treatment group differences in adverse events were observed with respiratory infection, pharyngitis, and rhinitis being the most common.
Rosenhall, Elvstrand, et al[29] Budesonide-formoterol 160/4.5 µg, 2 inhalations BID	MC, OL, PG, RCT Adult patients with asthma of ≥6 months duration, predicted FEV_1	N=321 6 months	Primary: Lung function, asthma control, health-related quality of life	Primary: There were no significant differences in lung function measurements, time to first exacerbation (defined as first use of oral glucocorticosteroids), or health-related quality of life observed between treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide 200 µg plus formoterol 4.5 µg, each administered as 2 inhalations BID	≥50%, receiving constant ICS dose of ≥400-1,200 µg for ≥30 days, and daily use of inhaled short- and/or long-acting β_2-agonists		Secondary: Adverse events	There were no significant differences in incidence and severity of adverse events observed between treatment groups. More patients from the budesonide-formoterol group than the budesonide plus formoterol group remained in the study (*P*=0.008).
Rosenhall, Heinig, et al[30] Budesonide-formoterol 160/4.5 µg, 2 inhalations BID vs formoterol 4.5 µg plus budesonide 160 µg, each administered as 2 inhalations BID (via separate inhalers)	MC, OL, RT Patients with moderate persistent asthma (average age of 45 years)	N=586 6 months	Primary: Safety and efficacy (FEV_1, Mini Asthma Quality of Life Questionnaire, Asthma Control Questionnaire, exacerbations Secondary: Not reported	Primary: Patients in both treatment groups had a mean FEV_1 increase of 5%-6% from baseline (no *P* value reported). There was no significant change in response using the Mini Asthma Quality of Life Questionnaire and the Asthma Control Questionnaire from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency (no *P* value reported). The withdrawal rate in both groups was also similar (*P*=0.085). Secondary: Not reported
Papi et al[31] ICAT SY Beclomethasone 100 µg plus formoterol 6 µg, 2 inhalations BID via pMDI vs budesonide 200 µg plus formoterol 6 µg, 2 inhalations BID via DPI‡ There was a 2-week run-in	DB, DD, MC, MN, PG, RT Patients 18-65 years of age with moderate-to-severe persistent asthma and FEV_1 of 50%-80% of predicted normal; previously treated with ICS <1,000 µg daily of BDP equivalent, uncontrolled asthma symptoms	N=219 12 weeks	Primary: Morning predose PEF measured by patients (weeks 11-12) Secondary: FEV_1, FVC, PEF, and $MEF_{50\%}$, symptom scores, time to first exacerbation	Primary: There was no significant difference in morning predose PEF observed between beclomethasone-formoterol and budesonide-formoterol (difference between adjusted means, 0.49 L/min; CI, –11.97 to 12.95). Secondary: Patients in the beclomethasone-formoterol and budesonide-formoterol groups had a significant improvement from baseline in their morning PEF (mean increase, 29.43±52.8 L/min; 95% CI, 19.31 to 39.54 and mean increase, 28.63±43.4 L/min; 95% CI, 20.39 to 36.87). There was no significant difference in evening PEF between the two treatment groups. Patients in both treatment groups had significant improvements in FEV_1, FVC, PEF, and $MEF_{50\%}$ from baseline beginning at week 2 of treatment and continuing throughout the study period (no *P* value reported). There was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period in which patients were allowed to continue their stable dose of ICS and use salbutamol† PRN, except ≥6 hours prior to pulmonary function test				statistically significant difference reported between the two treatment groups at the end of the study. There were statistically significant improvements in both daytime and nighttime symptom scores from baseline observed between the 2 treatment groups (*P*<0.001), Patients in the beclomethasone-formoterol and budesonide-formoterol groups had a reduction in the daily use of rescue medication in the last week of the run-in period to the last 2 weeks of the treatment period (2.16±1.15 to 0.76±0.92 puffs/day and 2.28±1.50 to 0.87±1.04 puffs/day, respectively). There was no statistically significant difference in the time to first exacerbation observed between the 2 groups.
Bateman et al[32] Budesonide-formoterol 160/4.5 µg, 1 inhalation BID vs fluticasone proprionate 250 µg, 1 inhalation BID There was a 2-week-run-in period in which patients received budesonide 200 µg BID.	DB, DD, PG, RT Patients with asthma (average age of 42 years, FEV_1 78% predicted, reversibility 21%)	N=373 12 weeks	Primary: Morning PEF Secondary: Evening PEF, clinic FEV_1, use of reliever medication, symptom-free days, asthma-control days, night-time awakenings, risk of having an exacerbation	Primary: Patients in the budesonide-formoterol group had significantly greater increases in morning PEF than those in the fluticasone propionate group (27.4 L/min vs 7.7 L/min, respectively; *P*<0.001). Secondary: Those in the budesonide-formoterol group had a significant improvement in their evening PEF and FEV_1 compared to the fluticasone propionate group. Also, patients in the budesonide-formoterol group utilized less reliever medication (*P*=0.04) and had a greater proportion of reliever-free days (*P*<0.001). Patients in the budesonide-formoterol group had a 32% risk reduction of having an exacerbation compared to those in the fluticasone propionate group (*P*<0.05). Although not statistically significant, patients in the budesonide-formoterol group had improvements in regards to symptom-free days, asthma-control days, and nighttime awakenings versus those in the fluticasone propionate treatment group (60.4% vs 55.5%; 57.8% vs 52.4%; and 7.9% vs 9.6%, respectively; no *P* values reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ericsson et al[33] Budesonide-formoterol 160/4.5 µg BID vs fluticasone propionate 250 µg BID There was a 2-week-run-in period in which patients received budesonide 200 µg BID	DB, DD, MC, PG, RT Patients ≥18 years of age with moderate-persistent asthma, diagnosis ≥6 months, on ICS (200-1,000 µg) ≥30 days, FEV_1 60%-90% predicted normal, ≥12% reversibility after inhalation of terbutaline or salbutamol†	N=339 12 weeks	Primary: Morning PEF Secondary: Time to first exacerbation, asthma symptom score, rescue medication use	Primary: Patients in the budesonide-formoterol treatment group had a statistically significant greater improvement in morning PEF of 27.4 L/min in comparison to 7.7 L/min observed in the fluticasone propionate treatment group (19.7% difference; 95% CI, 13.6 to 25.9; *P*<0.001). Secondary: Patients in the budesonide-formoterol treatment group had a statistically significant greater increase in the time to first mild exacerbation in comparison to those in the fluticasone propionate treatment group (*P*=0.04). Budesonide-formoterol was associated with a greater reduction in the use of rescue medications in comparison to fluticasone propionate –0.31 inhalations/day versus –0.13 inhalations/day, respectively; *P*=0.04).
Zetterström et al[34] Budesonide-formoterol 160/4.5 µg, 2 inhalations BID vs budesonide 200 µg, 2 inhalations BID vs budesonide 200 µg plus formoterol 4.5 µg, 2 inhalations BID	DB, DD, MC, PG, RCT Adult patients with moderate persistent asthma (mean ICS dose 960 µg/day, mean predicted FEV_1 of 73.8%)	N=362 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, asthma control/symptoms, use of reliever medication, night-time awakenings, exacerbations, safety	Primary: Patients in the budesonide-formoterol and budesonide plus formoterol groups had greater improvements in morning PEF compared with those in the budesonide group (35.7 L/min vs 32.0 L/min vs 0.2 L/min, respectively; *P*<0.001). Secondary: Evening PEF, total asthma symptom score, use of reliever medication, reliever use-free days, percentage of symptom-free days, percentage of asthma control days, and risk of mild exacerbations were all significantly improved in the budesonide-formoterol and budesonide plus formoterol groups compared with budesonide (*P*<0.01). No significant differences between treatment groups in night-time asthma awakenings or adverse events were observed.
Kuna, Creemers, et al[35] Budesonide-formoterol 80/4.5 µg, 2 inhalations in	AC, DB, DD, PG, RT Adult patients with	N=617 12 weeks	Primary: Morning PEF Secondary:	Primary: Patients in both budesonide-formoterol regimens showed greater improvements in morning PEF (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
the evening vs budesonide-formoterol 80/4.5 µg, 1 inhalation BID vs budesonide 200 µg, 1 inhalation in the evening	mild to moderate persistent asthma who were not optimally controlled on ICS dose of 200-500 µg/day, mean predicted FEV_1 at baseline was 78.5%		Evening PEF, symptom-free days, reliever-free days, asthma-control days, adverse events	Secondary: Patients in both budesonide-formoterol regimens showed greater improvement in evening PEF, symptom-free days, reliever-free days, and asthma-control days than budesonide alone (P<0.05). Both the twice-daily and once-daily budesonide-formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the twice-daily regimen (18.3 L/min vs 9.6 L/min; P<0.05). There were no between-group differences in nighttime awakenings due to asthma, or in the number and nature of adverse events.
Jenkins et al[36] Budesonide-formoterol 320/9 µg, 2 inhalations BID vs budesonide 400 µg plus formoterol 9 µg, via separate inhalers, each administered as 2 inhalations BID vs budesonide 400 µg, 2 inhalations BID for 12 weeks followed by either budesonide-formoterol or budesonide plus formoterol via separate inhalers for 12 weeks	DB, DD, MC, RCT Patients ≥12 years of age with asthma for ≥6 months who used ICS for ≥4 months at a constant daily dose of ≥750 µg for at least 4 weeks prior to study entry	N=456 24 weeks	Primary: PEF Secondary: Use of rescue medications, asthma symptoms, FEV_1, adverse events	Primary: Patients in both the budesonide-formoterol and budesonide plus formoterol groups had significantly improved morning PEF, and evening PEF (P<0.01). No significant difference was observed in morning PEF and evening PEF between budesonide-formoterol and budesonide plus formoterol (P=NS). Secondary: Patients in both the budesonide-formoterol and budesonide plus formoterol groups had significantly improved symptom-free days, reliever-free days, FEV_1, asthma-control days, and risk of mild asthma exacerbation compared with those in the budesonide group (P<0.01). No significant differences in total asthma symptoms, symptom-free days, reliever-free days, asthma-control days, or risk of mild exacerbation were observed between budesonide-formoterol and budesonide plus formoterol (P=NS). The frequency and profile of adverse events were similar for all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pohunek et al[37] Budesonide-formoterol 80/4.5 µg, 2 inhalations BID vs budesonide 100 µg, 2 inhalations BID vs budesonide 100 µg plus formoterol 4.5 µg, each administered as 2 inhalations BID	AC, DB, DD, MC, PG, RCT Pediatric asthmatic patients (4-11 years of age) receiving constant dose of ICS (375-1,000 µg/day)	N=630 12 weeks	Primary: Morning PEF Secondary: Lung function, asthma symptoms, adverse events	Primary: Greater improvements in morning PEF, evening PEF, and FEV_1 were observed with budesonide-formoterol compared with budesonide (*P*<0.001), but not compared with budesonide plus formoterol (*P*=NS). Secondary: No statistically significant differences were observed between the 3 treatment groups in asthma symptom scores, use of reliever medications, symptom-free days, reliever-free days, health-related quality of life, night-time awakenings, and adverse events (*P*=NS).
Morice et al[38] Budesonide pMDI* 200 µg vs budesonide-formoterol DPI‡ 160/4.5 µg vs budesonide-formoterol pMDI 160/4.5 µg	DB, DD, MC, PG, RCT Outpatients ≥12 years with asthma for ≥6 months with inadequate control on ICS alone, FEV_1 of 50%-90% predicted normal, reversibility of >12% after inhalation of terbutaline 1 mg, and daily ICS use history ≥3 months	N=680 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, nighttime awakenings, asthma symptom score, symptom-free days, and asthma-control days	Primary: Patients in the budesonide-formoterol DPI and budesonide-formoterol pMDI groups had improved morning PEF compared with those in the budesonide group by 31.4 L/min and 28.6 L/min, respectively (*P* <0.001). Secondary: Patients in the budesonide-formoterol group had greater improvements observed compared to those in the budesonide group. End points were similar between the two budesonide-formoterol devices, with the exception of symptom-free and asthma-control days, which were slightly improved with the DPI.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kuna, Peters, et al[39] Budesonide-formoterol 160/4.5 µg, 1 inhalation BID (for maintenance) plus additional inhalations PRN vs fluticasone-salmeterol 125/25 µg, 2 inhalations BID and terbutaline as relief medication vs budesonide-formoterol 320/9 µg, 1 inhalation BID plus terbutaline Patients who used their rescue medication ≥5 times during the last 7 days of the 2-week-run-in period we rerandomized to treatment.	DB, DD, MC, PG, RCT Patients ≥12 years of age with asthma diagnosis of at least 6 months, use of an ICS for at least 3 months, FEV_1 ≥50% predicted normal, ≥12% reversibility following terbutaline use, ≥1 asthma exacerbation in past 1-12 months	N=3,335 6 months	Primary: Time to first severe exacerbation (defined as hospitalization or ER visit, or ≥3 days of oral corticosteroids) Secondary: Number of severe exacerbations, number of mild exacerbations, asthma symptom score, inhalations of PRN medication, change in morning and evening PEF, FEV_1, night awakenings, symptom-free days, as-needed-free days, asthma-control days	Primary: Patients in the maintenance and relief budesonide-formoterol group had a significant prolonged time to first severe exacerbation compared to those in the fixed dose fluticasone-salmeterol and budesonide-formoterol groups (*P*=0.0034, *P*=0.023, respectively). There was no difference in time to first exacerbation observed between the two fixed-dose groups. Secondary: There was a 39% reduction in the number of severe exacerbations observed in the maintenance and relief budesonide-formoterol group in comparison to the fixed-dose fluticasone-salmeterol group (RR, 0.61; 95% CI, 0.49 to 0.76; *P*<0.001) There was a 28% reduction in the number of severe exacerbation observed in the maintenance and relief budesonide-formoterol group versus the fixed-dose budesonide-formoterol group (RR, 0.72; 95% CI, 0.57 to 0.90; *P*=0.0048). There were similar findings in the total number of severe exacerbations observed between the two fixed-dose groups. There were no significant differences in the number of mild exacerbations, asthma symptoms, asthma symptom scores, use of as-needed medications, and lung function between the maintenance and relief budesonide-formoterol group and the two fixed-dose groups.
Aalbers et al[40] Budesonide-formoterol 160/4.5 µg, 2 inhalations BID-AMD vs budesonide-formoterol	DB (4 weeks), ES (6 months), OL Patients with moderate-severe asthma, mean symptom score 1.5, mean FEV_1 84% predicted, mean ICS	N=658 4 weeks DB period and 6 month open extension	Primary: Odds of achieving a WCAW Secondary: Exacerbation rate, use of reliever medication	Primary: There was no difference in the OR pertaining to WCAW observed in the fixed dosing treatment groups. There was a significant increase in the odds of achieving WCAW observed in the budesonide-formoterol adjustable maintenance dosing group in comparison to the budesonide-formoterol fixed dosing group during the open period, regardless of a 15% decrease in the average use of study drug (OR, 1.335; 95% CI, 1.001 to 1.783; *P*=0.049).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
160/4.5 µg, 2 inhalations BID-FD vs fluticasone-salmeterol 250/50 µg, 1 inhalation BID-FD During 4 week DB period, the budesonide-formoterol AMD and FD groups received 2 inhalations BID, and those in the fluticasone-salmeterol group received 1 inhalation BID and during 6 month extension period, all FD groups remained the same and the budesonide-formoterol AMD group could decrease dose to 1 inhalation BID, or increase dose up to 4 inhalation BID for 7-14 days based on asthma symptoms.	dose 735 µg/day			Secondary: Patients in the budesonide-formoterol AMD group had a significantly lower exacerbation rate (40%) compared to those in the fluticasone-salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (*P*=0.018 and *P*=NS, respectively). Patients in the budesonide-formoterol AMD group used significantly less reliever medication during the open study period versus those in the budesonide-formoterol and fluticasone-salmeterol FD groups (*P*=0.001 and *P*=0.011, respectively).
Pauwels et al[41] FACET Budesonide 100 µg BID plus placebo vs budesonide 400 µg BID	DB, MC, PC, PG, RCT Adult patients with persistent asthma (mean ICS dose 829 µg/day, mean predicted FEV_1 of 76%, mean reversibility of	N=852 1 year	Primary: Frequency of asthma exacerbations, lung function, asthma symptoms Secondary: Adverse events	Primary: The estimated yearly rates of severe asthma exacerbations were as follows: 0.34 for higher dose budesonide plus formoterol, 0.46 for those receiving higher dose budesonide plus placebo, 0.67 for those receiving lower dose budesonide plus formoterol, and 0.91 for those receiving lower dose budesonide plus placebo (*P*=0.01 for formoterol vs placebo, *P*<0.001 for lower vs higher dose of budesonide, no *P* value reported for lower dose budesonide plus formoterol vs higher dose budesonide plus placebo). The estimated yearly rates of mild asthma exacerbations were as follows:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus placebo vs budesonide 100 µg BID plus formoterol 12 µg BID vs budesonide 400 µg BID plus formoterol 12 µg BID	21%)			13.4 for patients receiving higher dose budesonide plus formoterol, 22.3 for higher dose budesonide plus placebo, 21.3 for those receiving lower dose budesonide plus formoterol, and 35.4 for those receiving lower dose budesonide plus placebo (*P*<0.001 for formoterol vs placebo, *P*<0.001 for lower vs higher dose of budesonide, no *P* value reported for lower dose budesonide plus formoterol vs higher dose budesonide plus placebo). Secondary: All treatments were well tolerated throughout the study.
Canonica et al[42] CAST Budesonide-formoterol 80/4.5 µg, 2 inhalations BID-FD vs budesonide-formoterol 160/4.5 µg, 2 inhalations BID-FD vs budesonide-formoterol 80/4.5 µg, 2 inhalations BID-AMD vs budesonide-formoterol 160/4.5 µg, 2 inhalations BID-AMD	RT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations, changes in asthma symptom severity Secondary: Asthma control, safety and health economics	Primary: Both fixed dosing and adjustable maintenance dosing budesonide-formoterol treatment groups had similar low frequency of exacerbations, as well as improved comparable lung function. However, results did not reach statistical significance (*P*=NS). Secondary: Both treatment groups had improved lung function, less asthma symptoms, and fewer nighttime awakenings compared to the mean value of run-in period (*P* value not reported). Patients in the adjustable maintenance budesonide-formoterol dose group utilized 24% less of the study drug in comparison to those in the fixed maintenance dose group (2.95 vs 3.86 daily inhalations, respectively; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Edwards et al[43] Budesonide vs budesonide-formoterol vs budesonide-formoterol-AMD vs fluticasone-salmeterol	MA Patients with moderate to severe asthma	N=15 studies 12-52 weeks	Primary: Treatment failure Secondary: Hospitalizations, emergency visits, use of oral steroids	Primary: Patients in the budesonide-formoterol group demonstrated 50% less treatment failure in comparison to those who received budesonide treatment alone (RR 1.50; 95% CI, 1.12 to 2.02; *P*=0.007). Although there seemed to be a favorable trend in the reduction of treatment failure observed in the budesonide-formoterol-AMD group versus the budesonide-formoterol group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; *P*=0.09). There was no significant difference observed detected between those in the budesonide-formoterol group and those in the fluticasone-salmeterol group in regards to treatment failure (*P*=0.86). Secondary: Patients in the fluticasone-salmeterol group had a 49% greater risk of hospitalizations/accident and emergency visits compared to those in the FD budesonide-formoterol group (RR, 1.49; 95% CI, 1.07 to 2.08; *P*=0.02). Patients in the budesonide-formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits versus those treated with FD budesonide-formoterol (RR, 0.72; 95% CI, 0.52 to 0.99; *P*=0.04). Budesonide alone, was associated with a greater risk (51%) in the use of oral steroids in comparison to budesonide-formoterol (RR, 1.51; 95% CI, 1.10 to 2.09; *P*=0.01). Patients in the budesonide-formoterol-AMD group had a lower requirement for oral steroids than those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; *P*=0.01). Patients in the budesonide-formoterol-AMD treatment group experienced a 19% decreased risk in use of oral steroids versus those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; *P*=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sears et al[44] Budesonide-formoterol 160/4.5 µg, 1 inhalation BID plus additional doses as needed vs conventional best practice therapy (could include any therapy including either ICS-LABA combination product, but not the use of budesonide-formoterol as both maintenance and reliever therapy	MC, OL, PG, RT Patients ≥12 with asthma for a minimum of 3 months, use of ≥400 µg of ICS daily, treatment with ICS alone and a history of uncontrolled disease (≥3 inhalations of as needed rescue therapy during the last 7 days prior to enrollment) or daily maintenance treatment with an ICS and LABA	N=1,538 6 months	Primary: Time to first severe asthma exacerbation (hospitalization, emergency room visit, use of oral corticosteroids for ≥ 3days due to asthma Secondary: Number of severe asthma exacerbations, mean use of as needed medication, PEF, ACQ-5	Primary: No significant difference was found between the two treatment groups in time to first severe exacerbation (HR, 0.99; 95% CI, 0.70 to 1.41; *P*=0.95. Secondary: The mean number of exacerbations per patient per year was 0.19 for the budesonide-formoterol group compared to 0.21 for the convention treatment group (HR, 0.92; 95% CI, 0.67 to 1.28; *P*=0.63). Total days of oral corticosteroid use were 17% lower in the budesonide-formoterol group compared to the conventional group (590 vs 709 days). Mean as-needed reliever use decreased from 1.25 to 0.94 inhalations per day with budesonide-formoterol compared to a decrease from 1.22 to 1.09 inhalations per day in the conventional therapy (*P*=0.0036). 15 subjects in the budesonide-formoterol group required >8 as needed inhalations on at least one day, compared to 30 subjects in the conventional treatment group (*P*=0.028). PEF increased from 94.8% to 98.0% predicted in the budesonide-formoterol group compared to an increase from 84.1% to 96.3% in the conventional group a difference that was not significant (*P*=0.46). The ACQ-5 score decreased from 1.27 to 1.08 in the budesonide-formoterol group compared to a decrease from 1.24 to 1.09 in the conventional treatment group, a difference that was not significant (*P*=0.46).

*Budesonide is not currently available as a pMDI in the United States.
†Synonym for albuterol
‡Budesonide-formoterol is not currently available as a DPI in the United States
Drug regimen abbreviations: AMD=adjustable maintenance dosing, BID=twice daily, FD=fixed dose, PRN=as needed, QD=once daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MN=multi-national, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, RT=randomized trial, SC=single center, XO=crossover
Miscellaneous abbreviations: ACQ-5=Asthma Control Questioner 5 question version, AQLQ=standardized Asthma Quality of Life Questioner, BDP=beclomethasone dipropionate, CAST=Control Of Asthma By Symbicort Turbuhaler, CONCEPT=CONtrol CEntred Patient Treatment, DPI=dry powder inhaler, ED=emergency department, EDICT=Evaluation of Different Inhaled Combination Therapies, ER=emergency room, FACET=Formoterol and Corticosteroids Establishing Therapy, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, ICAT SY=Inhaled Combination Asthma Treatment versus SYmbicort , ICS=inhaled corticosteroids, LABA=long-acting β_2-agonist, $MEF_{50\%}$ =mid-expiratory flow at 50% vital capacity, MOS Sleep Scale=Medical Outcomes Study Sleep Scale, PEF=peak expiratory flow, pMDI=pressurized metered dose inhaler, PSAM=Patient Satisfaction with Asthma Medication questioner, SF-36=Short-Form Health Survey, WCAW=well-controlled asthma week

Additional Evidence

Dose Simplification
A recent study by Sovani et al randomized patients with poorly controlled asthma who used less than 70% of their prescribed dose of inhaled corticosteroid to either budesonide 200 µg one puff twice a day in addition to their a short acting β_2-agonists as required (control group) or the combination of budesonide-formoterol 200/6 µg one puff once daily and as required (active group).[45] With the primary outcome being inhaled corticosteroid dose the study was aimed to determine whether treatment with a single inhaler could overcome the issue of poor compliance. At the completion of the 6 month study the control group adherence with budesonide was approximately 60% of the prescribed dose. Also, compared to the control group, participants in the active group used approximately 80% more budesonide (448 vs 252 µg, a mean difference of 196 µg; 95% CI, 113 to 279; $P<0.001$). Although patients in the active group were less likely to withdraw from the study (3 vs 13; $P<0.01$), there were no safety issues identified in the study.[45] The true clinical significance of these results is not known.

Stable therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on physician visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Budesonide and Formoterol Combination Product(s)

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
budesonide and formoterol furoate	aerosol inhaler	Symbicort®	$$$$	N/A

No generic products are available for budesonide and formoterol furoate.
N/A=not available.

X. Conclusions

The combination of an inhaled corticosteroid and long-acting β_2-agonist is currently the preferred controller combination regimen for patients $\geq$ 12 years of age with moderate to severe asthma for both the long-term control and prevention of symptoms.[1] Budesonide and formoterol is a combination product that is FDA indicated for the

long-term maintenance treatment of asthma in patients 12 years of age and older. The individual components of this combination are also commercially available. Current national and international guidelines support the use of an inhaled corticosteroid with a long-acting β_2-agonist as treatment for patients with moderate-persistent to severe-persistent asthma that is inadequately controlled with inhaled corticosteroid monotherapy.[1-5]

There are numerous studies that have evaluated the efficacy of the combination of budesonide, a corticosteroid, and formoterol, a long-acting β_2-agonist, in the treatment of asthma.[13-45] Studies have shown that treatment with budesonide-formoterol resulted in improved lung function, including peak expiratory flow, forced expiratory volume in 1 second values, and a reduction in the use of daily rescue medications.[14] Head-to-head studies have compared budesonide-formoterol to fluticasone-salmeterol another inhaled corticosteroid and long-acting β_2-agonist combination product, with mixed results. When Dahl et al compared the two medication combinations, budesonide-formoterol failed to demonstrate a statistically significant difference compared to fluticasone-salmeterol in parameters such as morning and evening PEF values, asthma symptoms, rescue medication usage, or asthma control, as well as no difference in the severity of exacerbations or the mean rate of exacerbations over a 24 week period.[23] On the contrary, there was a short-term study that reported a significantly greater increase in FEV_1 (15 min postdose) and a higher percentage of patients who achieved bronchodilation within 1 hour in the budesonide-formoterol group compared to those receiving fluticasone-salmeterol.[16] Rosenhall et al looked at the efficacy of budesonide-formoterol in a single inhaler versus its individual components. Results showed that there were no significant differences between the two groups in regards to lung function measurements, time to first exacerbation, or health-related quality of life.[29] The efficacy of adjustable maintenance dosing of budesonide-formoterol has also been evaluated in clinical studies.[19,22,25,40]

Although the combination of budesonide and formoterol has shown to be efficacious compared to monotherapy, guidelines state that patients should be initiated on inhaled corticosteroid monotherapy if they are classified as having mild to moderate disease.

Therefore all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over the other alternatives in general use.

XI. Recommendations

No brand budesonide and formoterol combination product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review—Altabax® (retapamulin)
Skin and Mucous Membrane Antibacterials, AHFS Class 840404
May 14, 2008

I. Overview

Impetigo is a superficial skin infection that commonly occurs on areas of the face or extremities and is usually caused by *Staphylococcus aureus, Streptococcus pyogenes,* or a combination of the two.[1-2] Its presentation may include few or multiple lesions, and occasionally may lead to more serious skin disease or other complications. Although the occurrence of impetigo is highest among younger children (2-5 years old), both older children and adults may become infected as well. Topical antibacterials such as mupirocin are most commonly used to treat mild cases of impetigo. Due to emerging antibiotic resistance, especially among *S aureus* (methicillin-resistant organisms) and *S pyogenes* (erythromycin-resistant organisms) finding appropriate treatment choices is becoming more challenging.[2]

Retapamulin is the first Food and Drug Administration (FDA)-approved drug in a new class of antibacterials called the pleuromutilins. This antibacterial ointment was approved in April 2007 for the treatment of impetigo due to *S aureus* (methicillin-susceptible isolates only) or *S pyogenes*. Retapamulin's safety and efficacy have been studied in patients aged 9 months or older.[3] Retapamulin is currently classified under Antibacterials within the Skin and Mucous Membrane Agents by the American Hospital Formulary Service (AHFS).[4]

Retapamulin has a mechanism through which it inhibits bacterial protein synthesis, allowing a low potential for bacterial resistance. Specifically, it works by binding to a particular site on the 50S subunit of the bacterial ribosome, involving ribosomal protein L3.[3] The ribosomal protein L3 is located in the ribosomal P site and peptidyl transferase center. This leads to the inhibition of protein synthesis, peptidyl transfer, normal ribosome formation, and the blocking of interactions at the P site.[3] Retapamulin's unique binding interaction makes it an option in patients who have developed resistant bacterial infections to other topical agents such as mupirocin, or bacitracin and neomycin. To prevent bacterial resistance, retapamulin use should be reserved for treatment of susceptible bacteria.[3]

The retapamulin formulations that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Within this review, only clinical trials investigating the safety and efficacy of retapamulin will be summarized. Reference data from unpublished trials and data presented as abstracts or posters for retapamulin were not evaluated and are not included in this review.

Table 1. Retapamulin Product(s) Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
retapamulin	ointment	Altabax®	none

No generic products are available for retapamulin.

Common bacterial infections of the skin are classified as primary or secondary.[1] Primary infections usually involve previously healthy skin and are typically caused by a single pathogen. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobic (see Table 2).

Table 2. Bacterial Classification of Important Skin and Soft Tissue Infections[1]

Type of Infection	Microorganisms
Primary	
Impetigo	*Staphylococcus aureus*, group A streptococci (*Streptococcus pyogenes*)

Retapamulin has been shown to be active against the strains of microorganisms indicated in Table 3. This activity has been demonstrated in clinical infections and is represented by the FDA-approved indications for retapamulin

that are noted in Table 5. This agent may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since its safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 3. Microorganisms Susceptible to Retapamulin[3]

Organism	Retapamulin
Aerobic Gram-Positive Organisms	
Staphylococcus aureus (methicillin-susceptible isolates only)	✔
Streptococcus pyogenes	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 4 summarizes the current treatment guidelines for the management of impetigo. These guidelines were published prior to the FDA approval of retapamulin.

Table 4. Treatment Guidelines for the Diagnosis and Management of Impetigo

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America (IDSA): **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)[2]**	• Impetigo may be caused by infection with *S aureus* and/or *S pyogenes*. • The decision to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the necessity to prevent the spread of infection to others. • The most effective topical agent for patients presenting with limited lesions is mupirocin; however, cases of resistance have been reported. • Bacitracin and neomycin are alternative, yet less effective topical options. • Systemic therapy with agents effective against both *S aureus* and *S pyogenes* is recommended for more widespread disease or in situations where there is no response to topical agents. • Topical therapy with mupirocin is equivalent to oral systemic antimicrobials and is preferred when lesions are limited in number. • Dicloxacillin, cephalexin, erythromycin, clindamycin, and amoxicillin/clavulanate are the preferred agents however resistance to erythromycin has been documented in several strains.
American Academy of Family Physicians (AAFP): **Diagnosis and treatment of impetigo (2007)[5]**	• Topical antibiotics such as mupirocin and fusidic acid (not available in the United States) are the preferred first-line therapy(s) for impetigo involving limited body surface area. • Oral antibiotics (eg, antistaphylococcal penicillins, amoxicillin/clavulanate, cephalosporins, and macrolides) are effective for the treatment of impetigo; erythromycin is less effective. • Oral antibiotics should be considered for patients with impetigo who have more extensive disease and for disease associated with systemic symptoms. • Oral penicillin V, amoxicillin, topical bacitracin, and neomycin are not recommended for the treatment of impetigo. • Topical disinfectants such as hydrogen peroxide should not be used in the treatment of impetigo.

III. Indications

FDA-approved indications for retapamulin are noted in Table 5. While this agent may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for Retapamulin[3]

Drug	Indication
Retapamulin	For use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo* due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*.†

*Up to 100 cm^2 in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older.
†Retapamulin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

IV. Pharmacokinetics

Retapamulin is administered topically and low systemic exposure was reported after application to either intact or abraded skin. The pharmacokinetic parameters for retapamulin are summarized in Table 6.

Table 6. Pharmacokinetic Parameters of Retapamulin[3,6,7]

Drug	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Retapamulin	94	Hepatic (CYP3A4)	None	Not reported	Not reported	Not reported

V. Drug Interactions

There are currently no documented drug interactions reported with retapamulin.[3,8] Due to low systemic exposure of retapamulin, it is unlikely that coadministration with oral ketoconazole or other CYP3A4 inhibitors will require dose adjustments. The effect of concurrent application of retapamulin and other topical products to the same area of the skin has not been studied at this point in time.[3]

VI. Adverse Drug Events

Application-site irritation and headache were reported as the most common drug-related adverse events associated with retapamulin. If local irritation worsens or becomes severe the ointment should be discontinued, wiped off and another appropriate option should be selected by the physician. The most common adverse drug events reported with retapamulin are noted in Table 7.

Table 7. Adverse Drug Events (%) Reported with Retapamulin[3]

Adverse Event(s)	Retapamulin
Central Nervous System	
Headache	1.2-2.0
Pyrexia	1.2
Dermatological	
Application site irritation	1.6
Application site pain	✔
Application site pruritus	1.9
Contact dermatitis	✔
Eczema	1.0
Erythema	✔
Pruritus	1.5
Gastrointestinal	
Diarrhea	1.4-1.7
Nausea	1.2
Respiratory	
Nasopharyngitis	1.2-1.5
Other	
Creatinine phosphokinase increased	<1.0

✔ Percent not specified

VII. Dosing and Administration

In order to decrease the development of drug-resistant bacteria and sustain effectiveness, retapamulin should only be administered to treat or prevent infections that are proven or have strong evidence indicating susceptible bacteria. The treated area may be covered with a sterile bandage or gauze dressing. The usual dosing regimens for retapamulin are summarized in Table 8.

Table 8. Usual Dosing for Retapamulin[3,6]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Retapamulin	Impetigo due to *S aureus* (methicillin-susceptible only) or *S pyogenes*: Thin layer applied topically to affected area (up to 100 cm^2 in total area) twice daily for 5 days, treated area may be covered with a sterile bandage or gauze dressing if desired	Impetigo due to *S aureus* (methicillin-susceptible only) or *S pyogenes*: For children ≥9 months of age, thin layer applied topically to affected area (up to 2% total body surface area) twice daily for 5 days, treated area may be covered with a sterile bandage or gauze dressing if desired Safety and efficacy in children <9 months of age have not been established.	Ointment 1%: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of retapamulin are found in Table 9.

Table 9. Comparative Clinical Trials Using Retapamulin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oranje et al[9] Retapamulin ointment 1% twice daily for 5 days vs sodium fusidate* ointment 2%, 3 times daily for 7 days Patients were randomized to treatment using a 2:1 ratio of retapamulin to sodium fusidate.	MC, NI, RCT Patients ≥9 months of age with clinical diagnosis of primary bullous or nonbullous impetigo identified by presence of either ≥1 lesion characterized by red spots, or blisters without crusts that progressed to those that ooze and form yellow or honey-colored crusts surrounded by an erythematous margin	N=519 14 days End of therapy was defined as day 7 for the retapamulin treatment group and day 9 for the sodium fusidate treatment group Follow-up took place on day 14 for both treatment groups.	Primary: Clinical response (absence of treated lesions, or treated lesions had become dry without crusts with or without erythema compared to baseline, or had improved [defined as a decline in the size of the affected area, number of lesions or both] such that no further antimicrobial therapy was required) Secondary: Bacteriological responses (eradication of pathogen verified via culture) at end of therapy and at follow-up	Primary: Patients in the clinical PP population had a statistically significant greater clinical success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.1% vs 94.0%, respectively, 5.1% difference; 95% CI, 1.1 to 9.0; *P*=0.003). Patients in the clinical ITT population had a clinical success rate of 94.8% at the end of therapy with retapamulin treatment compared to 90.1% observed with sodium fusidate treatment (4.7% difference; 95% CI, –0.4 to 9.7; *P*=0.062). Patients in the clinical PP population had a clinical success rate of 96.4% at follow-up with retapamulin treatment compared to 93.7% observed with sodium fusidate treatment (2.7% difference; 95% CI, –1.8 to 7.2; *P*=0.221). Patients in the clinical ITT population had a clinical success rate of 89.9% at follow-up with retapamulin treatment compared to 87.2% observed with sodium fusidate treatment (2.6% difference; 95% CI, –3.3 to 8.6; *P*=0.374). Secondary: Patients in the bacteriological PP population had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin treatment compared to sodium fusidate treatment (99.2% vs 93.0%, respectively, 6.2% difference; 95% CI, 1.4 to 11.0; *P*=0.002). Patients in the bacteriological ITT population also had a statistically significant greater bacteriological success rate at the end of therapy with retapamulin compared to sodium fusidate treatment (95.1% vs 88.5%, respectively, 6.5% difference; 95% CI, 0.5 to 12.6; *P*=0.022).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients in the bacteriological PP population had a bacteriological success rate of 96.6% at follow-up with retapamulin treatment compared to 92.5% observed with sodium fusidate treatment (4.1% difference; 95% CI, –1.4 to 9.6; *P*=0.106). Patients in the bacteriological ITT population had bacteriological success rate of 90.1% at follow-up with retapamulin compared to 84.7% observed with sodium fusidate treatment (5.4% difference; 95% CI, –1.8 to 12.5; *P*=0.134).
Parish et al[10] Retapamulin ointment 1% twice daily for 5 days vs cephalexin 500 mg PO twice daily for 10 days	DB, DD, MC, NI, RCT Patients ≥9 months of age with underlying inflammatory skin disease (atopic dermatitis, psoriasis, or allergic contact dermatitis) experiencing one or more signs or symptoms of secondarily infected dermatitis	N=547 17-19 days Follow-up was defined as days 12-14 for retapamulin treatment group and days 17-19 for cephalexin treatment group.	Primary: Clinical response at follow-up (total resolution of all signs and symptoms of infection such that no additional antibiotic necessary) Secondary: Clinical response at end of therapy, microbiologic response (elimination [verified via culture] or presumed elimination of the baseline pathogen, without infection with a new pathogen) at follow-up and end of therapy	Primary: Patients in the PP clinical population had a clinical success rate of 85.9% at follow-up with retapamulin treatment compared to 89.7% observed with oral cephalexin treatment (–3.8% difference; 95% CI, –9.9 to 2.3). Patients in the ITT clinical population had a clinical success rate of 82.9% at follow-up with retapamulin treatment compared to 86.3% observed with oral cephalexin treatment (–3.4% difference; 95% CI, –9.7 to 2.9). Secondary: Patients in the PP clinical population had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.0% vs 93.8%, respectively, –1.8% difference; no *P* value reported). Patients in the ITT clinical population also had similar clinical success rates at end of therapy between retapamulin and oral cephalexin (92.3% vs 91.8%, respectively, 0.5% difference; no *P* value reported). Patients in the PP bacteriologic group had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.0% vs 94.1%, respectively, –1.1% difference) and at follow-up (87.2% vs 91.8%, respectively, –4.6% difference). Patients in the ITT bacteriologic population had similar microbiologic success rates at the end of therapy between retapamulin and oral cephalexin (93.4% vs 91.3%, respectively, 2.1% difference) and at follow-up (83.5% vs 87.8%, respectively, –4.3% difference).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Free et al[11] Retapamulin ointment 1% twice daily for 5 days vs cephalexin 500 mg PO twice daily for 10 days	2 DB, DD, MC, NI, RCT Patients ≥9 months of age with a secondarily infected traumatic lesion (abrasion, small laceration, sutured wound) Study consisted of results from 2 identical clinical trials.	N=1,904 17-19 days Follow-up was defined as days 12-14 for retapamulin treatment group and days 17-19 for cephalexin treatment group.	Primary: Clinical response (resolution or improvement of infection signs and symptoms) at follow-up in the PP clinical population for both studies Secondary: Microbiologic response (culture-confirmed or presumed eradication of baseline pathogen) at follow-up in the PP clinical population for both studies	Primary: Patients in the PP clinical population had comparable clinical success rates of 88.7% and 90.4% at follow-up with retapamulin treatment compared to 91.9% and 92.0% observed with oral cephalexin treatment (–3.2% difference; 95% CI, –7.4 to 0.9) and (–1.6% difference; 95% CI, –5.8 to 2.6) in each of the studies, respectively. Overall, clinical success rates for patients in the PP clinical population were 89.5% at follow-up with retapamulin treatment compared to 91.9% observed with oral cephalexin treatment combined for both studies (–2.4% difference; 95% CI, –5.4 to 0.5). Secondary: Patients in the PP bacteriologic population had microbiologic success rates of 87.1% and 91.7% at follow-up with retapamulin treatment compared to 89.4% and 91.1% observed with oral cephalexin treatment (–2.3% difference; no *P* value reported) and (0.6% difference; no *P* value reported) in each of the studies, respectively. Overall, microbiologic success rates for patients in the PP bacteriologic population were 89.2% at follow-up with retapamulin treatment compared to 90.2% observed with oral cephalexin treatment combined for both studies (–1.0% difference; no *P* value reported).

*Sodium fusidate (fusidic acid) is not available in the United States (US).
Abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ITT=intent-to-treat, MC=multicenter, NI=non-inferiority, PO=by mouth, PP=per protocol, RCT=randomized controlled trial

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on physician visits
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Retapamulin Product(s)

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
retapamulin	ointment	Altabax®	$$$	N/A

No generic products are available for retapamulin.
N/A=not available.

X. Conclusions

The bacterial organisms most often associated with impetigo include *Staphylococcus aureus* and *Streptococcus pyogenes*.[2,5] The Infectious Diseases Society of America (IDSA) skin and soft-tissue infection guidelines state that the decision to treat impetigo depends on the number of lesions, their location, and the necessity to prevent the spread of infection to others, and that the most effective topical agent for patients presenting with limited lesions is mupirocin.[2] It is important to note that these guidelines were published prior to the FDA approval of retapamulin.

Retapamulin, a topical antibacterial agent, is FDA indicated for the treatment of impetigo due to *S aureus* (methicillin-susceptible only) or *S pyogenes*.[3] Resistance has become a concern with regards to the use of other topical agents in the treatment of bacterial skin infections. Retapamulin's unique mechanism of action enables it to have a low propensity of bacterial resistance. In order to preserve this benefit, the manufacturer recommends that retapamulin should be prescribed only when there is strong proof or evidence regarding the presence of susceptible bacteria. Although there have been reports of bacterial resistance to mupirocin ointment, it is currently recognized as a first-line topical treatment option for impetigo by the IDSA.[2]

There are limited published clinical trials evaluating the safety and effectiveness of retapamulin ointment. One trial compared retapamulin to sodium fusidate ointment in the treatment of impetigo. Overall clinical and bacteriological success rates were over 90% for both treatment groups in the clinical per-protocol populations.[9] Two other trials reported similar cure rates for retapamulin ointment and an oral antibiotic, cephalexin, when used to treat certain other skin infections.[9-11] Currently there are no published studies comparing retapamulin to mupirocin, which is available in a generic ointment for the treatment of impetigo.

At this time, there is insufficient data to conclude that retapamulin is safer or more efficacious than other brands, generics and over-the-counter products in this class and offers a significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand retapamulin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Dyslipidemia
May 14, 2008

I. Overview

The use of pharmacological agents to reduce elevated blood cholesterol has become an established practice over the last few decades, on the basis of many studies showing that decreases in certain kinds of cholesterol are related to reductions in morbidity and mortality from coronary heart disease (CHD).[1,2] Cholesterol is a non-water-soluble lipid which is transported through the bloodstream as part of a lipoprotein.[3] There are 3 main classifications of lipoproteins: low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL).[3] Epidemiological observations and over 4 decades of clinical trials have demonstrated a correlation between lowering of LDL cholesterol (LDL-C) and a reduced incidence of CHD and CHD mortality.[1,2,4,5] In 2002, this evidence was examined by the National Cholesterol Education Program (NCEP), part of the National Heart, Lung, and Blood Institute (NHLBI), in a comprehensive treatment guideline known as the Adult Treatment Panel (ATP) III.[4] This guideline identifies LDL-C, which accounts for 60% to 70% of total serum cholesterol, as the major atherogenic lipoprotein associated with CHD risk, and further specifies LDL-C as the primary target of cholesterol-lowering therapy. Among other lipid risk factors are elevated triglycerides (TG), non-HDL cholesterol (defined as VLDL+LDL), and low HDL cholesterol levels (HDL-C).[4]

As a basic principle, therapeutic intervention for the prevention of CHD considers multiple risk factors, one of which is elevated LDL-C levels. This approach takes into account the findings of the Framingham Heart Study, which evaluated the relationship between serum cholesterol levels and other factors contributing to the lifetime risk for the development of CHD.[6] An estimate of a patient's risk of developing CHD or experiencing a coronary event in the next 10 years can be calculated based on age, total cholesterol, HDL-C, systolic blood pressure, and smoking status.[6] Therefore, nonlipid risk factors associated with CHD risk should also be considered in preventive efforts.[4] Some risk factors, namely hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, and atherogenic diet, are modifiable and would be appropriate targets for intervention. The nonmodifiable factors of advancing age, male sex, or a family history of premature CHD may signal the need for more intensive lowering of LDL-C. The NCEP ATP III guideline assigns therapeutic goals to individual patients depending upon risk level. This approach follows earlier guidelines from the NCEP and employs a system for assessing short-term (≤10 years) CHD risk which was developed in the course of the Framingham Heart Study.[4,6]

Therapeutic lifestyle changes (TLC) are an essential modality in clinical management and consist of a multifactorial lifestyle approach to reducing risk for CHD. TLC may reduce cardiovascular risk through several mechanisms beyond LDL lowering, and they are recommended as initial therapy in all patients with lifestyle-related risk factors requiring lipid management, regardless of LDL level.[4,7] The use of TLC, including LDL-lowering dietary options, can achieve therapeutic LDL goals in many patients. TLC may also be important in the management of patients with the constellation of risk factors referred to as the metabolic syndrome.[8] This syndrome is characterized by the simultaneous presence of major metabolic risk factors for atherosclerotic cardiovascular disease (CVD), which include atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose.[4,9] These risk factors often lead to prothrombotic and pro-inflammatory states in affected individuals.[9] Metabolic syndrome increases the risk for CHD regardless of LDL-C level.[4] Contributing factors may include abdominal obesity, insulin resistance, physical inactivity, aging, hormonal imbalance, and an atherogenic diet, making TLC a priority for this population.[9]

If TLC alone fails to achieve target goals, consideration can be given to adding drug therapy.[4,7] The American Hospital Formulary Service (AHFS) classifies several types of drugs in the class of Antilipemic Agents, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, nicotinic acid (niacin), and omega-3 acid ethyl esters.[10] These drugs differ in

mechanisms of action, as well as types and degrees of lipid-lowering abilities. Therefore, the selection of a particular drug is influenced by the type of lipid abnormality.

The HMG-CoA reductase inhibitors, also called the statins, are the only class of drugs that have demonstrated significant improvements in overall mortality in primary and secondary prevention.[11] As a result, statins are often the first choice for treating hyperlipidemia in which the goal is primary or secondary cardiovascular risk reduction. Statins are the most potent LDL-C lowering agents with LDL-C reductions ranging from 20% to 60%.[4,6,11] If desired LDL-C levels cannot be attained with the use of statin monotherapy, additional antilipemic agents are often added to the treatment regimen. The choice of an additional agent may be influenced by the presence of other lipid abnormalities in addition to LDL-C.

If TG levels are high, non-HDL cholesterol can serve as a secondary target of therapy.[4] If hypertriglyceridemia is the primary lipid abnormality, fibric acid derivatives are particularly effective. They are also effective for raising HDL-C levels. Overall, the fibric acid derivatives lower TG levels by 25%-50% and increase HDL-C by 10%-35%.[12] They may lower LDL-C in some patients, but when they decrease elevated TG, LDL-C may increase.[12] Niacin shares a similar lipid-lowering profile as the fibric acid derivatives and decreases TG by 20%-35% and increases HDL-C by 15%-35%. Total plasma and LDL-C may decrease by 5%-25%.[12] The use of niacin has been limited historically by poor tolerability.[11-13]

Cholesterol absorption inhibitors (eg, ezetimibe) are most commonly used in combination with statins to maximize LDL-C lowering. This is particularly useful when circumstances preclude titration of a statin. Bile acid sequestrants (eg, cholestyramine, colesevelam, colestipol) are useful in instances of mild-to-moderate LDL-C elevation. The use of these agents, as with niacin, is often limited by poor tolerability. Omega-3 fatty acid esters are also a treatment option; however, their use is not routinely addressed in treatment guidelines.

The Fredrickson classification, which identified various types of dyslipidemias according to abnormal lipoprotein patterns, was developed at the NHLBI in the 1960s.[14-16] After its original definition by Fredrickson, Levy, and Lees,[17] it was taken up in publications by the World Health Organization (WHO) and others.[18,19] Although this classification had outlived its scientific usefulness by the 1970s,[15,20-23] some of its terminology has been retained in practice, and it is referenced in product information for many of the antilipemic agents.[24-38] The NCEP ATP III report and other guidelines now generally approach the treatment of lipid disorders through identification of risk categories and cut points rather than through Fredrickson phenotypes.[22]

Table 1. Fredrickson Classification of Hyperlipoproteinemias

Product Information (Package Inserts)[24-29,31,34,36-38]				Beaumont et al, WHO (1970)[18]	Lipid Levels, Hilbert and Lifshitz (2006)[23]		Comments, Hilbert and Lifshitz (2006)[23]
Type	Lipoproteins Elevated	Lipid Elevations					
		Major	Minor		TG	C	
I (rare)	chylomicrons	TG	↑→C	C usually ↑; TG ↑	Very high	Normal	Low cardiac risk; hereditary
IIa	LDL	C	—	C usually ↑; TG normal	Low	High	High cardiac risk
IIb	LDL, VLDL	C	TG	C usually ↑; TG ↑	High	High	High cardiac risk
III (rare)	IDL	C/TG	—	C ↑; TG ↑; C:TG ratio 0.3–2.0	High	High	High cardiac risk; dietary control; presence of β-VLDL; VLDL-cholesterol to plasma TG ratio >0.3
IV	VLDL	TG	↑→C	C → ↑; TG ↑	Very high	Low	Lower cardiac risk than types 2 and 3
V (rare)	chylomicrons, VLDL	TG	↑→C	C ↑; TG ↑; C/TG ratio 0.15–0.6	Very high	Normal	Low cardiac risk; acquired

C=cholesterol, IDL=intermediate-density lipoprotein, LDL=low-density lipoprotein, TG=triglycerides, VLDL=very-low-density lipoprotein

At the present time, the most widely used guidelines for the management of patients with lipid disorders are the NCEP ATP III treatment recommendations, which were published in 2002 and updated in 2004.[4,7] The next update to this guideline is expected in 2009.[39] Recently published guidelines by the American Heart Association (AHA) and American College of Cardiology (ACC), the Institute for Clinical Systems Improvement (ICSI), the AHA Atherosclerosis, Hypertension, and Obesity in Youth Committee, and the Joint Task Force of the European Society of Cardiology present treatment goals and recommendations similar to the NCEP ATP III.[40-43] Also forthcoming is the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guideline on lipid modification, which is due to be published in May 2008.[44] Current treatment guidelines are summarized in Table 2.

II. Evidence-Based Medicine and Current Treatment Guidelines

Table 2. Current Treatment Guidelines for Dyslipidemia

National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): Implications of Recent Clinical Trials for the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines (2004)[4]

- This 2004 update to the NCEP ATP III guideline, which evaluates the impact of 5 major clinical trials with HMG-CoA reductase inhibitor (statin) therapy, maintains the same approach as the 2002 NCEP ATP III Guideline.
- The goals of therapy according to the NCEP ATP III guideline, published in 2002, are based on 3 categories of risk level for CHD:
  - Patients with CHD and "CHD risk equivalents" (see below)
  - Patients with multiple (2+) risk factors
  - Patients with 0 to 1 risk factor
- CHD risk equivalents include noncoronary forms of clinical atherosclerotic disease (abdominal aortic aneurysm, carotid artery disease, and peripheral arterial disease), diabetes and multiple (2+) CHD risk factors with a 10-year risk for CHD >20%.
- The intensity of LDL-lowering therapy should be adjusted to the individual's absolute risk for CHD. Ultimately, LDL-C goals vary depending on the presence of particular CHD risk factors.
- Persons with CHD are at very high risk for future CHD events (10-year risk >20%). CHD is defined here as a history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
- ATP III employs a system of calculating 10-year risk for CHD based upon the results and methodology of the Framingham Heart Study (and therefore known as "Framingham risk scoring"). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL-C, systolic blood pressure, treatment for hypertension, and cigarette smoking. Framingham scoring tables are included in the full ATP III guideline. Persons whose Framingham risk calculation shows a 10-year risk for CHD of >20% are considered to have a CHD risk equivalent.
- ATP III and the current update also use an alternative approach to risk assessment for persons in lower risk categories (eg, without CHD or CHD risk equivalents), which is to count the number of other major risk factors for CHD. Calculated CHD risk scores help guide the determination of therapeutic goals and treatment selection. The guideline recommends that the factors listed in the following table be used to establish the count of risk factors.

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals[13]	
Positive Risk Factors (Increase the Risk for CHD; Add 1 to Count)	**Negative Risk Factors (Decrease the Risk for CHD; Subtract 1 from Count)**
Cigarette smoking	
Hypertension (blood pressure 140/90 mm Hg or on antihypertensive medication)	
Low HDL-C (<40 mg/dL)	HDL-C ≥60 mg/dL
Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)	
Age (men ≥45 years; women ≥55 years)	

- This update to the ATP III guideline recommends that lipid management be guided according to the categories and cutoff points outlined in the following table.

Therapy in Different Risk Categories			
Risk Category	**LDL-C Goal**	**LDL-C Level at Which to Initiate TLC**	**LDL-C Level at Which to Consider Drug Therapy***
High Risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)†	≥100 mg/dL‡	≥100 mg/dL (<100 mg/dL: consider drug options)§
Moderately High Risk: 2+ risk factors (10-year risk 10%-20%)	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL‡	≥130 mg/dL (100-129 mg/dL: consider drug options)‖
Moderate Risk: 2+ risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower Risk: 0-1 risk factor¶	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-C-lowering drug optional)

*When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels.
†For very high-risk patients, an LDL-C goal of <70 mg/dL is favored, and in patients with high triglycerides, a non–HDL-Cgoal of <100 mg/dL is favored.
‡Any person at high risk or moderately high risk who has lifestyle-related risk factors is a candidate for TLC to modify these risk factors regardless of LDL-C level.
§If baseline LDL-C is <100 mg/dL, institution of an LDL-C-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.
‖For moderately high-risk persons, when LDL-C level is 100-129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.
¶Almost all people with 0-1 risk factor have a 10-year risk ≤10%, and 10-year risk assessment is not necessary.

Treatment

- TLC remains an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.

Lipid Targets of Therapy

- As in the NCEP ATP III guideline, LDL-C is identified as the primary target of lipid-lowering therapy.
- For every 1% reduction in LDL-C levels, the relative risk for major CHD events is reduced by approximately 1%.
- As in the NCEP ATP III guideline, non–HDL-C(VLDL+LDL-C) is a secondary target in patients with TG ≥200 mg/dL.
- The non–HDL-Cgoal is 30 mg/dL higher than the LDL-C goal (the normal VLDL is <30 mg/dL).
- The recent trials that were evaluated for this update provide no new evidence to warrant setting a specific goal for HDL-C.
- Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
- Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins.
- In high-risk patients with high TG or low HDL levels as the predominant lipoprotein abnormality, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-C-lowering agent.
- When TG levels are ≥200 mg/dL, non–HDL-Cis a secondary target of therapy, with a goal 30 mg/dL higher than identified LDL-C goal.

High-Risk Patients

- High-risk patients are defined as in ATP III, and this category includes all patients with CHD or CHD risk equivalents (noncoronary forms of clinical atherosclerotic disease, diabetes, and multiple [2+] CHD risk factors with 10-year risk for CHD >20%).
- The recommended LDL-C goal for high-risk patients was set in ATP III at <100 mg/dL; however, an LDL-C goal of <70 mg/dL can be a therapeutic option on the basis of available clinical evidence, especially for patients at very high risk.
- This update to the ATP III guideline establishes a subset of high-risk patients as "very high-risk." This includes all patients with established cardiovascular disease (CVD) plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high TG ≥200 mg/dL in addition to non–HDL-C≥130 mg/dL with low HDL-C [<40 mg/dL]), and (4) acute coronary syndromes (on the basis of PROVE-IT).
- The cutoff point for considering drug therapy in all high-risk patients has been lowered from ≥130 mg/dL in ATP III to ≥100 mg/dL in this update.
- When LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction.
- Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols).
- When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
- If a high-risk person has high TG or low HDL-C levels, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When TG are >200 mg/dL, non–HDL-Cis a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- In all high-risk patients, if baseline LDL-C level is ≥130 mg/dL, LDL-lowering agents should be started simultaneously with dietary therapy.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated TG, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

Moderately High-Risk Patients

- Moderately high-risk patients are those with 2+ risk factors and a 10-year CHD risk of 10%-20%.
- Their recommended LDL-C goal remains <130 mg/dL; however, an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical evidence.
- When LDL-C level is 100-129 mg/dL, at baseline or on TLC, initiation of an LDL-lowering drug to achieve an LDL-C level ≤100 mg/dL is a therapeutic option on the basis of available clinical evidence.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction.
- Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols).
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

Moderate-Risk Patients

- Moderate-risk patients are those with 2+ risk factors and a 10-year CHD risk of <10%.
- The LDL-C goal for them remains at <130 mg/dL, as in the ATP III guideline.
- If LDL-C is ≥160 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding a cholesterol-

lowering agent.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy as presented in the ATP III guideline.

Lower-Risk Patients

- Lower-risk patients are those with 0-1 risk factor.
- The LDL-C goal for them remains at <160 mg/dL, as in the ATP III guideline.
- If LDL-C is ≥190 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding a cholesterol-lowering agent.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy as presented in the ATP III guideline.

Familial Disorders That Cause Very High LDL-C Levels (≥190 mg/dL)
Clinical Condition -Therapeutic Considerations

Heterozygous familial hypercholesterolemia (FH)
- Begin LDL-C-lowering drugs in young adulthood
- TLC indicated for all persons.
- Statins: first line of therapy (start dietary therapy simultaneously)
- Bile acid sequestrants (if necessary in combination with statins)
- If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid)

Homozygous FH
- Dietary therapy not effective
- Bile acid sequestrants not effective
- Nicotinic acid mildly effective
- Statins may be moderately effective in some persons
- Ileal exclusion operation not effective
- Liver transplant effective, but impractical
- LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia)

Familial defective apolipoprotein B-100 (FDB)
- TLC indicated
- All LDL-C-lowering drugs are effective
- Combined drug therapy required less often than in heterozygous FH

Polygenic hypercholesterolemia
- TLC indicated for all persons
- Consider for drug therapy (if LDL-C ≥190 mg/dL after dietary therapy [all persons])
- All LDL-C-lowering drugs are effective
- If necessary to reach LDL-C goals, consider combined drug therapy

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002)[2]

General Recommendations

- This section summarizes certain recommendations, especially regarding the use of specific antilipemic agents, that were set forth in the NCEP ATP III report but not discussed or revised in the 2004 update.
- Initiate LDL-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid.
- After 6 weeks if LDL goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid.

- After 6 weeks, if LDL goal is not achieved, intensify drug therapy or refer patient to a lipid specialist. If LDL goal is not achieved, treat other lipid risk factors.
- After 4-6 months, monitor response and adherence to therapy.

Specific Drug Regimens

Bile Acid Sequestrants
- Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, and for persons needing only modest reductions in LDL cholesterol to achieve target goals.
- Bile acid sequestrants should be considered in combination therapy with statins in persons with very high LDL cholesterol levels.

Fibric Acid Derivatives (Fibrates)
- Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis.
- They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL).
- Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia.
- They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) Reductase Inhibitors (Statins)
- Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Nicotinic Acid
- Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia.
- Nicotinic acid should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a sustained increase in LDL levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL levels.
- Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes.
- High doses of nicotinic acid (>3 grams/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.

Omega-3 Fatty Acids
- Omega-3 fatty acids (linolenic acid, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) have 2 potential uses.
- In higher doses, DHA and EPA lower serum TG by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3-12 grams/day have been used depending on tolerance and severity of hypertriglyceridemia.
- Recent clinical trials also suggest that relatively high intakes of omega-3 fatty acids (1-2 grams/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive clinical trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1-2 grams/day) for either primary or secondary prevention.

Other
- Cholesterol absorption inhibitors (eg, ezetimibe) are not mentioned in this guideline.
- Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD. Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.

American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart, Lung, and Blood Institute: AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Disease: 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute (2006)[9]

- Two new trials published since the 2004 ATP III update (see above) demonstrated cardiovascular benefit for lowering LDL-C to <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease; additionally, an LDL-C level of <70 mg/dL is reasonable in these patients.
- For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP Panel III guidelines and their 2004 update should still be considered current.

For lipid management in all patients with established coronary or other atherosclerotic disease, the following are recommended:

- Assess fasting lipid profile.
- Start dietary therapy, reducing the intake of saturated fats, trans-fatty acids, and cholesterol.
- Consider adding plant stanol/sterols and viscous fiber.
- Promote daily physical activity and weight management.
- Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 gram/day) for risk reduction.
- The goal of lipid management is an LDL-C <100 mg/dL. If TG are ≥200 mg/dL, non–HDL-Cshould be <130 mg/dL.

Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Lipid Management in Adults (2007)[10]

Algorithm for Lipid Management in Adults

See Figure 1, below, for a graphic representation of the treatment algorithm from the ICSI.

Step 1:
- Consider secondary causes of abnormal lipid levels and treat if appropriate. Diet and exercise are recommended as the cornerstone of treatment for asymptomatic patients with dyslipidemia.

Step 2:
- Calculation of risk is based upon the National Cholesterol Education Program Adult Treatment Panel III guidelines. Once risk level is calculated, proceed to steps 3, 4, 5, or 6 as indicated.

Steps 3-6: Lifestyle modification/drug therapy/adjunctive measures
- Lifestyle modifications may include the following: diet, aerobic exercise, weight management, aspirin, evaluation of alcohol consumption, fish oil (EPA-DHA), smoking cessation, and sitostanol ester.
- Vitamin E supplements should not be used.

Step 8:
- LDL goal is <100 mg/dL. In patients with CHD, consider LDL goal of <70 mg/dL.
- In patients with coronary artery disease or coronary artery disease equivalents, statin treatment should be recommended regardless of LDL level.
- The specific statin and dose selected should be determined by the amount of lipid-lowering required.
- If patients are not able to tolerate a statin, clinicians are encouraged to have the patients try the other statins in reduced doses before ruling out all statins.
- If patients are unable to take a statin, then bile-acid sequestrants, ezetimibe, fibric acid derivatives and niacin are available.
- Dosage adjustments should only be made following a lipid panel and no more often than every 4 weeks.
- Proceed to Step 7.

Step 7:
- The decision to initiate and continue drug therapy should be made jointly by the patient and physician.

- Pharmacologic treatment is selected according to risk level and patient preference.
- There is no evidence to support pharmacological treatment in low-risk individuals.
- Adjunctive measures should be reinforced.
- Secondary causes for hyperlipidemia should be examined.
- Lipid levels should be evaluated at 6 weeks.
- Proceed to Step 9.

Step 9:
- Therapy must be intensified if lipid goals are not met. If goal is met, proceed to Step 11. If goal is not met, proceed to Step 10.

Step 10:
- Potential adherence should be identified and then addressed by assessing the patient's knowledge of his/her medication(s) and condition, the patient's medication administration process, and the patient's barriers to adherence.
- Return to Steps 7 and 9 and reevaluate.

Step 11:
- If HDL is equal to or greater than 40 mg/dL and TG is less than 200 mg/d, proceed to Step 12. If goals are not met, proceed to Step 14.
- If TG are between 200-499 mg/dL, non-HDL cholesterol is a secondary target (non-HDL target is 30 mg/dL higher than LDL target).

Step 12:
- A fasting lipid panel or lipid panel with direct LDL and transaminase should be obtained as indicated.

Step 13:
- Periodic monitoring, risk factor modification, and reinforcement of adjunctive measures are recommended.

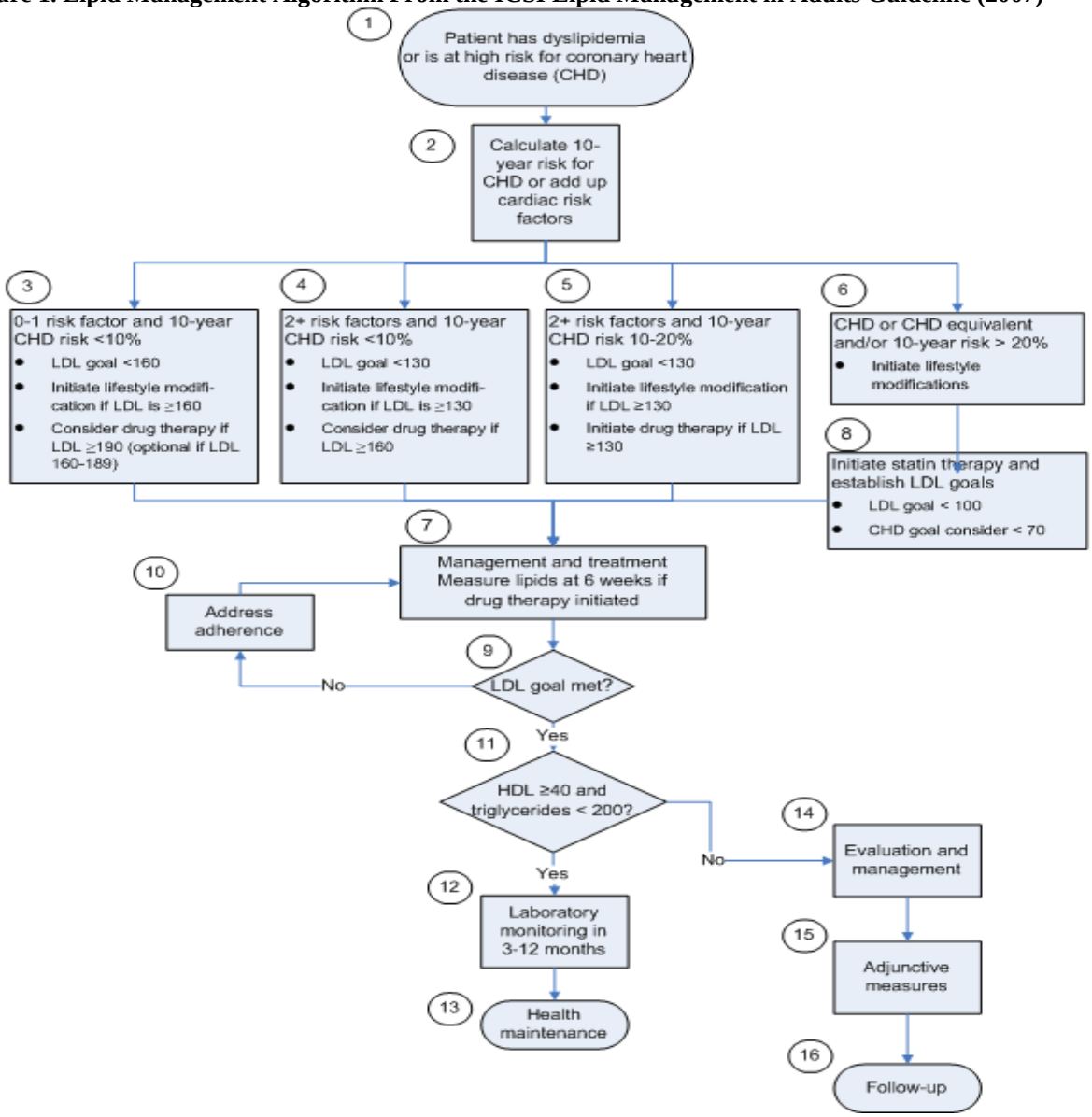
Step 14:
- Patients with elevated TG levels and normal or moderately elevated cholesterol should be treated if there is evidence of cholesterol-rich VLDL and intermediate-density lipoproteins (IDL). If TG are >500 mg/dL, TG-lowering drugs become first-line therapy. Statin therapy may also be considered especially if there is a strong family history of CHD and dyslipidemia or if the patient has evidence of atherosclerotic disease. Patients with TG >1,000 mg/dL are at an increased risk of hepatic steatosis, hepatomegaly, pancreatitis and splenomegaly and are candidates for dietary and drug therapy. If potential secondary causes have been addressed, the National Institutes of Health recommend dietary measures for initial management of borderline and high TG. If lifestyle modifications alone do not reduce TG to the desired level, then drug therapy is indicated. Treatment is also suggested in patients with diabetes whether or not they have low HDL cholesterol. Glucose levels should be controlled in diabetic patients since uncontrolled glucose levels contribute to hypertriglyceridemia.

Step 15:
- Adults with elevated lipids should follow the therapeutic lifestyle change or another equivalent diet. It is recommended that a registered dietitian perform a nutritional assessment.

Step 16:
- Coronary risk status and a lipid panel should be obtained at least once per year.

<u>General Treatment Recommendations</u>
- For monotherapy, statins are the drugs of choice for lowering LDL.
- If a patient is intolerant to a statin, other statins should be tried before ruling them all out.
- If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used.
- Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it.
- Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects.
- In very resistant cases, triple therapy may be needed.

Figure 1. Lipid Management Algorithm From the ICSI Lipid Management in Adults Guideline (2007)



Drug Companion Document

The following summarizes primary and secondary therapies for various types of dyslipidemias.

Type of Dyslipidemia	Primary Therapy	Secondary Therapy
LDL ↑, HDL ≥40 mg/dL, TG >200 mg/dL	Weight loss Physical activity Discontinue smoking No alcohol Improve diabetes mellitus control Therapeutic lifestyle change	Statin Niacin* Omega-3 fatty acids
LDL ↑, HDL <40 mg/dL, TG >200 mg/dL		Statin Fibric acids Niacin* Omega-3 fatty acids Ezetimibe

Type of Dyslipidemia	Primary Therapy	Secondary Therapy
LDL ↑, HDL ≥40 mg/dL	Weight loss Physical activity Therapeutic lifestyle change Discontinue smoking	Statin Fibric acids Niacin* Ezetimibe Bile acid sequestrant
LDL ↑, HDL <40 mg/dL		Statin Fibric acids Niacin* Bile acid sequestrant Ezetimibe
LDL normal, HDL <40 mg/dL	Physical activity Discontinue smoking	Fibric acids Statin Niacin* (Note: drug recommendations for treatment remain controversial except in CHD.)
TG ↑	Weight loss Discontinue smoking No alcohol Improve diabetes mellitus control Therapeutic lifestyle change Physical activity	Fibric acids Niacin* Omega-3 fatty acids

*Niacin can elevate glucose in patients with diabetes.

Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents. A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing (2007)[11]

Original Recommendations of the National Cholesterol Education Program (NCEP) Expert Panel

- Drug therapy should be considered in children ≥10 years of age (usually waiting for menarche in females) and following 6-12 months of fat- and cholesterol-restricted dietary management.
- Drug therapy should be considered if LDL level remains ≥190 mg/dL or ≥160 mg/dL with a positive family history of premature cardiovascular disease or the presence of ≥2 other risk factors following vigorous attempts to control these risk factors.

Consider referral to specialized lipid center.

Treatment goals: minimal, LDL <130 mg/dL; ideal, LDL <110 mg/dL.

Modifications to the NCEP Expert Panel

- If the patient is overweight and/or obese, a fasting lipid profile should be obtained. If lipid abnormalities are present, the patient should be screened for other aspects of the metabolic syndrome.

- For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime.

- For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age.

- Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (2007)[12]

Management

- Patients should be evaluated for exclusion of hyperlipidemias secondary to other conditions, since often the treatment of underlying disease improves hyperlipidemia.
- Patients with atherosclerotic disease and those at high risk for atherosclerotic disease should follow a diet designed to reduce cardiovascular risk and be engaged in physical exercise.
- Patients can be considered for drug therapy.
- Plasma lipids should be evaluated at baseline and again at 4-6 weeks and 3 months following an acute event and/or initiation of lipid-lowering therapy.

Cholesterol goals, general:

- <5 mmol/L (190 mg/dL), total
- <3 mmol/L (115 mg/dL), LDL

Cholesterol goals, patients with atherosclerotic disease and diabetes:

- <4.5 mmol/L (~175 mg/dL), total; <4 mmol/L (~155 mg/dL), total if feasible
- <2.5 mmol/L (~100 mg/dL), LDL; <2 mmol/L (~80 mg/dL), total if feasible

Drug Therapy

Statins

- HMG-CoA reductase inhibitors (statins) are considered first-line drugs for lowering LDL cholesterol.
- When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs.

Fibric Acid Derivatives

- Fibric acid derivatives are considered useful only for the treatment of patients with low HDL, high TG, and other characteristics of insulin resistance syndrome and type 2 diabetes.
- Fibrate monotherapy cannot be recommended as first-line therapy in diabetic patients but may be considered in those with persistently low HDL levels or severely elevated TG.
- When TG are between ~450-900 mg/dL, fibrates (or statins) may be considered as first-choice drugs.

Bile Acid Sequestrants

- Bile acid sequestrants can serve as effective lipid-lowering alternatives.
- Bile acid sequestrants tend to increase TG; should only be used when TG are <~180 mg/dL or given in conjunction with TG-lowering agents.

Niacin

- Niacin is more effective at increasing HDL levels than fibrates.
- When TG are between ~450-900 mg/dL, either fibrates or statins may be used as first-line drugs, and niacin is a good drug and can serve as an effective lipid-lowering alternative in selected patients.

Cholesterol Absorption Inhibitors

- As monotherapy, cholesterol absorption inhibitors have mild LDL-lowering effects and can be used for patients with active liver disease, having adverse effects on statins or when statins, fibrates and nicotinic acid are contraindicated.
- Their primary role in therapy is in combination with statins.
- Cholesterol absorption inhibitors have not shown in clinical trials to reduce myocardial infarction and coronary death.

Combination Therapy

- Combination therapy may be used in patients needing additional therapy to reach goals.
- The selection of appropriate drugs should vary based upon lipid levels..

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