# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Antiarrhythmic Agents
# AHFS Class 240404
# February 22, 2006

## I. Overview

Antiarrhythmic drugs have specific electrophysiologic actions that alter cardiac conductions. These mechanisms usually form the basis for the grouping of these agents into specific categories based on their electrophysiologic mechanisms.[1] Vaughan Williams first proposed the most frequently used classification system. Research in recent years has provided extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs act; however, the general approach to antiarrhythmic therapy remains largely empirical.[1] All of the antiarrhythmic drugs act by altering ion fluxes within the excitable tissues within the heart. The three ions of primary importance are Na+, Ca++, and K+.[2] Finally, recent results of several clinical trials, including the Cardiac Arrhythmia Suppression Trial (CAST), have indicated that many antiarrhythmic agents, in particular the class I agents, may significantly increase mortality rates when compared to placebo.[3]

This review encompasses all dosage forms and strengths. Table 1 lists the antiarrhythmic agents included in this review and their respective Vaughan Williams Classifications.

**Table 1. Antiarrhythmic Agents Included in this Review**

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

*Generic is available in at least one dosage form or strength.
†= Brand is no longer manufactured.

## II. Evidence Based Medicine and Current Treatment Guidelines

The ACC/AHA has developed guidelines to aid clinicians in determining the most safe and effective options to treat multiple arrhythmias. Nevertheless, there has been a decline in antiarrhythmic drug use as a result of the following: 1. Increased mortality with antiarrhythmic agents as observed in clinical trials (e.g., CAST). 2. Risk of serious side effects with certain antiarrhythmic agents (e.g., amiodarone: pulmonary fibrosis, optic neuritis; procainamide: lupus-like syndrome). 3. Advancement in non-pharmacologic therapy (defibrillators, ICDs), which appear more effective than antiarrhythmic agents in decreasing mortality in clinical trials.[4]

Considerations in choosing antiarrhythmic therapy should be based on presence of cardiovascular disease as well as type of arrhythmia. In addition, renal or hepatic dysfunction also plays a role in determining which agent is most appropriate.

Atrial Fibrillation

The AFFIRM trial revealed a trend towards increased mortality and more adverse drug events with antiarrhythmic therapy versus rate control in patients with atrial fibrillation. Patients with left ventricular dysfunction should be treated first-line with digoxin. Digoxin should be avoided in patients with Wolff-Parkinson White (WPW) syndrome because of the risk of paradoxical acceleration of the ventricular rate during atrial fibrillation.[4] Intravenous procainamide is the drug of choice in WPW.

Several treatment options can be used to restore and maintain normal sinus rhythm. However, rate control should be targeted first. For hemodynamically unstable patients, control should be achieved with direct current cardioversion (DCC). For patients that are hemodynamically stable, after the heart rate has been controlled and the patient has been properly anticoagulated, conversion can be achieved with DCC or drug therapy (dofetilide, amiodarone, ibutilide, flecainide, propafenone, or quinidine).[4]

Maintenance of normal sinus rhythm can be treated with antiarrhythmic therapy. For patients with no structural heart disease, the preferred agents are Class IC (flecainide or propafenone) because they are well tolerated with a low incidence of organ toxicity and proarrhythmias. Sotalol or amiodarone are also viable alternatives. Class IA agents should be avoided unless amiodarone fails or is contraindicated. Patients with underlying heart failure should be treated first-line with amiodarone or dofetilide as an alternative.[4]

Acute Treatment of Paroxysmal Supraventricular Tachycardia

DCC is the treatment of choice in patients experiencing severe symptoms. Drug therapy is based on arrhythmia and QRS length. IV adenosine is usually the first-line agent. Procainamide may be substituted when the arrhythmia is presumed to be ventricular tachycardia. Intravenous amiodarone may also be used in patients with wide QRS complex and irregular arrhythmias.[4,5]

Ventricular Arrhythmia

Most antiarrhythmics are no longer used due to the increased incidence of fatal ventricular arrhythmias based on findings from CAST. For premature ventricular contractions (PVCs), lidocaine was associated with excess mortality despite a decrease in ventricular tachycardia. Patients with post-MI and/or left ventricular ejection fraction ≤ 40% and who are symptomatic may be treated with amiodarone. Amiodarone followed by dofetilide are the agents of choice in patients with sustained ventricular tachycardia/ventricular fibrillation, in particular if structural heart disease is present.[6,7]

**Table 2. Treatment Guidelines Using the Antiarrhythmic Agents[8]**

| Arrhythmia | Drug(s) of Choice | Alternatives |
|---|---|---|
| Atrial fibrillation or flutter | | |
| • Acute management | Rate control: IV verapamil, diltiazem, a beta-blocker or digoxin<br>Conversion: DC cardioversion | IV procainamide or ibutilide; single large oral dose of propafenone or flecainide |
| • Chronic treatment | Rate control: verapamil, diltiazem, a beta-blocker or digoxin<br>Maintenance of sinus rhythm: amiodarone, sotalol, flecainide or propafenone, dofetilide | Quinidine, procainamide, disopyramide |
| Other supraventricular tachycardias | | |
| • Acute management | IV adenosine, verapamil or diltiazem | IV esmolol, another beta-blocker or digoxin for termination |
| • Long-term suppression | Beta-blockers, verapamil, diltiazem, flecainide, propafenone, amiodarone, sotalol, or digoxin | Quinidine, procainamide or disopyramide |
| Premature ventricular complexes (PVCs) or non-sustained ventricular tachycardia | For asymptomatic patients without structural heart disease, no drug therapy indicated<br>For symptomatic patients, a beta-blocker | |
| Sustained ventricular tachycardia | Amiodarone | Procainamide, lidocaine |
| Ventricular fibrillation | Amiodarone | Procainamide, lidocaine |

## III. Indications

Table 3 includes indications for the different antiarrhythmic agents included in this review.

**Table 3. FDA-Approved Indications for the Antiarrhythmic Agents[9]**

| Type | Generic Name | Indication |
|---|---|---|
| I | Moricizine | VT |
| Ia | Disopyramide | AF, VT |
| | Procainamide | AF, Aflutter, VT, WPW |
| | Quinidine | AF, PSVT, VT, WPW |
| Ib | Mexiletine | VT |
| Ic | Flecainide | VT, PSVT, AF |
| | Propafenone | VT, PAF, PSVT |
| III | Amiodarone | VT |
| | Dofetilide | AF, Cardioversion AF |

AF= Atrial Fibrillation
VT= Ventricular Tachycardia
PAF= Paroxysmal Atrial Fibrillation
PSVT= Paroxysmal Supraventricular Tachycardia
WPW= Wolff-Parkinson White

## IV. Pharmacokinetics

Table 4 includes the pharmacokinetic properties for each of the antiarrhythmics.

**Table 4. Pharmacokinetic Parameters of the Antiarrhythmic Agents[1]**

| Drug | Bioavailability (%) | Elimination | Protein Binding (%) | Half-life | Therapeutic Range (mcg/ml) |
|---|---|---|---|---|---|
| Moricizine | 34-38 | Hepatic | 92-95 | 1-6 h | - |
| Disopyramide | 70-95 | Hepatic/Renal | 50-80 | 4-8 h | 2-6 |
| Procainamide | 75-95 | Hepatic/Renal | 10-20 | 2.5-5 h | 4-15 |
| Quinidine | 70-80 | Hepatic | 80-90 | 5-9 h | 2-6 |
| Mexiletine | 80-95 | Hepatic | 60-75 | 6-12 h | 0.8-2 |
| Flecainide | 90-95 | Hepatic/Renal | 35-45 | 13-20 h | 0.3-2.5 |
| Propafenone | 11-39 | Hepatic | 85-95 | 12-32 h | - |
| Amiodarone | 22-28 | Hepatic | 95-99 | 15-100 d | 1-2.5 |
| Dofetilide | 85-95 | Renal | 60-70 | 6-10h | - |

## V. Drug Interactions[10]

Clinically significant (rated major or moderate) drug interactions are listed below.

Moricizine

- Cimetidine increases moricizine by 50%
- Moricizine decreases diltiazem levels
- Vardenafil have additive prolongation of the QTc interval

Disopyramide

- Certain macrolides increase disopyramide blood levels; may cause QRS prolongation
- Drugs that prolong the QT interval (quinolones, cisapride, ziprasidone, vardenafil)
- Rifampin may decrease serum levels of disopyramide

Procainamide

- Amiodarone increases procainamide or NAPA levels; consider reducing dose by 25%
- Cimetidine increases serum procainamide concentrations
- Drugs that prolong the QT interval (quinolones, cisapride, ziprasidone, macrolides, vardenafil)
- Trimethoprim increases procainamide or NAPA blood levels

Quinidine

- CYP3A4 inhibitors (azole antifungals, protease inhibitors) may increase quinidine levels
- Amiodarone, cimetidine, verapamil and diltiazem may increase quinidine levels
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone, macrolides)
- Codeine: analgesic efficacy is reduced
- May increase digoxin blood levels
- Antacids may increase serum quinidine levels
- Effects of certain beta-blockers will be increased by quinidine
- Non-depolarizing muscle relaxant effects may be enhanced by quinidine
- Amiloride may cause proarrhythmias

Mexiletine

- Decreased plasma levels: phenobarbital, phenytoin and other inducers
- Increased toxicity/levels of caffeine and theophylline

Flecainide

- Ritonavir increases flecainide concentrations
- Amiodarone increases flecainide plasma levels; consider reducing dose by 25%

Propafenone

- Certain SSRIs (fluoxetine, paroxetine, fluvoxamine) may increase propafenone serum levels
- Digoxin blood levels are increased
- Rifampin may decrease propafenone blood levels
- Metoprolol, propranolol, and theophylline blood levels may be increased
- Quinidine increases propafenone blood levels
- Ritonavir increases propafenone serum concentrations

Amiodarone

- Protease Inhibitors increase amiodarone levels
- Anticoagulant levels are increased
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone, macrolides, vardenafil)
- Cyclosporine levels are increased
- Digoxin levels may be increased
- Fentanyl co-administration may result in hypotension, bradycardia, and decreased cardiac output
- Phenytoin concentrations are increased due to reduction in phenytoin metabolism
- Procainamide concentrations may be increased
- Quinidine concentrations may be increased and can cause potentially fatal arrhythmias

Dofetilide

- CYP3A4 inhibitors (azole antifungals, protease inhibitors) may increase dofetilide levels
- Cimetidine inhibits dofetilide elimination
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone, macrolides)
- Verapamil causes an increase in dofetilide plasma levels by 42%
- Renal cationic transport inhibitors such as amiloride may increase dofetilide levels
- Ziprasidone has additive prolongation of the QTc interval

## VI. Adverse Drug Events

Table 5 includes possible adverse drug events associated with antiarrhythmic therapy.

**Table 5. Adverse Events for the Antiarrhythmic Agents[1,11]**

| Drug | Side Effects |
|---|---|
| Moricizine | Dizziness, headache, GI, aggravation of underlying conduction disturbance or ventricular arrhythmias |
| Disopyramide | Anticholinergic symptoms, Torsades de pointes, heart failure, hypoglycemia, GI, aggravation of underlying conduction disturbances and/or ventricular arrhythmias, hepatic cholestasis |
| Procainamide | SLE, Torsades de pointes, aggravation of underlying heart failure, conduction disturbances or ventricular arrhythmias, agranulocytosis, GI |
| Quinidine | Cinchonism, diarrhea, hypotension, Torsades de pointes, conduction disturbances or ventricular arrhythmias, hepatitis, thrombocytopenia, hemolytic anemia, GI |
| Mexiletine | CNS, psychosis, aggravation of underlying conduction disturbances or ventricular arrhythmias, GI |
| Flecainide | Blurred vision, dizziness, headache, bronchospasm, aggravation of underlying heart failure, conduction disturbances or ventricular arrhythmias, GI |
| Propafenone | Blurred vision, dizziness, headache, bronchospasm, aggravation of underlying heart failure, conduction disturbances or ventricular arrhythmias, GI |
| Amiodarone | CNS, corneal micro deposits/blurred vision, optic neuropathy/neuritis, aggravation of underlying ventricular arrhythmias, Torsades de pointes, bradycardia or AV block, bruising without thrombocytopenia, pulmonary fibrosis, hepatitis, hypo/hyperthyroidism, photosensitivity, blue-gray skin discoloration, myopathy, hypotension, phlebitis (IV use), GI |
| Dofetilide | Chest pain (10%), diarrhea (3%), nausea (5%), dizziness (8%), headache (11%), dyspnea (6%), respiratory tract infection (7%), atrioventricular block (1%), cardiac dysrrhythmia, Torsades de pointes (<1%), prolonged QT interval, ventricular arrhythmia (4%) |

Dofetilide

Dofetilide carries the following warning: "To minimize the risk of induced arrhythmia, place patients initiated or reinitiated on dofetilide in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic (ECG) monitoring, and cardiac resuscitation for a minimum of 3 days. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education."[9]

## VII. Dosing and Administration

Table 6 includes usual doses for the antiarrhythmic agents included in this review.

**Table 6. Dosing and Administration for the Antiarrhythmic Agents[8,9]**

| Drug | Maintenance Doses |
|---|---|
| Moricizine | PO: 200-300 mg q8h |
| Disopyramide<br>Disopyramide CR | PO: 100-200 mg q6-8h or 150-300 mg q12h (long-acting formulation) |
| Procainamide | PO: 50 mg/kg/day in divided doses, q3-4h or q6h (sustained-release) or q12h (extended-release) |

| Drug | Maintenance Doses |
|---|---|
| Procainamide ER | IV loading: 20 mg/min (up to 17 mg/kg)<br>IV maintenance: 2-4 mg/min |
| Quinidine gluconate SR<br>Quinidine sulfate | PO: 324-648 mg q8-12h (gluconate)<br>200-400 mg q6h (sulfate) |
| Mexiletine | PO initial dose: 150-200 mg q8h taken with food<br>PO maintenance: 150-300 mg q6-12h, maximum 1200 mg/day |
| Flecainide | PO initial dose: 50-100 mg q12h, increase q4 days if required, by 50 mg q12h<br>PO maintenance: ≤400 mg/day<br>Cardioversion: 300 mg single dose PO |
| Propafenone<br>Propafenone SR | PO initial dose: 150 mg q8h, increase q3-4 days if required or 225 mg q12h, increase q5 days if needed (sustained-release)<br>PO maintenance: 225-425 mg q12h (sustained-release)<br>Cardioversion: 600 mg single dose PO |
| Amiodarone | PO loading: 800-1200 mg/day for 1-2 weeks then 600-800 mg/day for 4 weeks<br>PO maintenance: 100-200 mg/day<br>IV loading: 150 mg over 10 minutes, which can be repeated once if needed, followed by 360 mg over 6 hours<br>IV maintenance: 0.5-1 mg/min<br>Cardiac arrest: 300 mg IV push |
| Dofetilide | PO: 500 mcg bid |

## VIII. Effectiveness

**Table 7. Outcomes Evidence for the Antiarrhythmics**

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| **Antiarrhythmic drugs** | | | |
| CAST[12]<br><br>Administration of encainide*, flecainide, moricizine, and placebo<br><br>Doses not specified (open labeled titration) | International, prospective, multicenter, randomized, placebo controlled trial<br><br>n = 3549<br><br>1 year | Overall survival and survival free of cardiac arrest or arrhythmic death | • 90% of active drug-treated patients compared to 95% of placebo treated patients remained alive (p = 0.0006)<br>• 93% of active drug-treated patients compared to 96% of placebo treated patients remained free of cardiac arrest or arrhythmic death (p = 0.003) |
| AFFIRM[13]<br><br>Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs. Doses not specified (adjusted to | Randomized, multicenter study<br><br>n = 4060<br><br>3.5 years | Overall mortality | • The difference in mortality between the two groups was not statistically significant (p = 0.08) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| maintain normal sinus rhythm) [14]<br><br>Rate control therapy: beta-blockers, calcium-channel blockers, digoxin, and combinations of these drugs. Doses not specified (adjusted to achieve target heart rate)[14] | | | |
| Van Gelder IC et al[15]<br><br>Rhythm control therapy: flecainide 200-300 mg/day, propafenone 450-900 mg/day, amiodarone 600 mg/day for 4 weeks, and sotalol<br><br>versus<br><br>Rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and beta-blocker, alone or in combination | Randomized prospective multi-center study<br><br>n = 522<br><br>2.3 years | Composite of clinical events (death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs) | • No significant difference in the risk of the composite of clinical events in the rate control group as compared with the rhythm-control group (p =0.11) |
| Kochiadakis GE et al[16]<br><br>200 mg/day amiodarone vs. 450 mg/day propafenone | Prospective, randomized, single-blind trial<br><br>n = 146<br><br>3 years | Recurrence of AF or occurrence of side effects necessitating discontinuation of medication | • No significant differences between the two drugs for the suppression of recurrent symptomatic AF or in side effects (p = 0.44) |
| **Amiodarone** | | | |
| CAMIAT[17]<br><br>Loading dose 10 mg/kg amiodarone vs. placebo for 2 weeks then 400 mg daily, 6-45 days after an acute MI | Randomized, double-blind, placebo controlled trial<br><br>n = 1202<br><br>1.79 years | Resuscitated ventricular fibrillation or arrhythmic death | • 15 patients receiving amiodarone compared to 31 patients receiving placebo experienced an RVF or AD (p = 0.016) |
| EMIAT[18]<br><br>800 mg/day amiodarone vs. placebo for 14 days, then 400 mg/day for 14 weeks, then 200 mg/day | Randomized, double-blind, placebo controlled trial<br><br>n = 1486<br><br>2 years | Primary: All-cause mortality | • All-cause mortality did not differ between the treatment groups (p=0.96) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| CHF-STAT[19]<br><br>800 mg/day amiodarone vs. placebo for 2 weeks, then 400 mg/day for 50 weeks, then 300 mg/day | Multicenter, double-blind, placebo controlled trial<br><br>n = 667<br><br>4 years | Rate control vs. conversion to sinus rhythm in AF patients | • 31 patients receiving amiodarone compared to 39 patients receiving placebo reduced mean VR (p = 0.006)<br>• 16 patients receiving amiodarone compared to 4 patients receiving placebo converted to NSR (p = 0.002)<br>• 46% decrease in hospital admissions for patients with non-ischemic, chronic heart disease |
| **Dofetilide** | | | |
| DIAMOND[20]<br><br>500 mcg bid dofetilide vs. placebo to no AF patients, 250 mcg bid to AF patients | Randomized, double-blind, placebo controlled trial<br><br>n = 1518<br><br>1 year | Death from any cause | • No significant differences in survival (P=0.54) |

*not available in the US
AF = atrial fibrillation
AD=arrhythmic death
EFS=ejection fraction stratum
RVF=resuscitated ventricular fibrillation
VR=ventricular response
NSR= normal sinus rhythm

**Additional Evidence**

Dose Simplification
The Canadian Trial of Atrial Fibrillation found that a low dose amiodarone of 200mg per day was more efficacious than propafenone 300mg twice daily or 150mg every 6 hours and sotalol 160mg twice daily at maintaining sinus rhythm. Recurrence of atrial fibrillation occurred in 35 percent of patients taking amiodarone and 63 percent of patients assigned to propafenone or sotalol (P<0.001). Patients taking amiodarone stayed in sinus rhythm, over 400 days, while patients on propafenone or sotalol had a recurrence within 90 days.[21]

Stable Therapy
A search of Medline and Ovid did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and Ovid 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 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-$50 per Rx |
| $$ | $51-$75 per Rx |
| $$$ | $76-$100 per Rx |
| $$$$ | $101-$150 per Rx |
| $$$$$ | Over $150 per Rx |

Rx = Prescription

**Table 8. Relative Cost of Antiarrhythmic Agents**

| Generic Name | Formulations | 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®* | $$$$ | $ |
| Moricizine | tablet | Ethmozine® | $$$$ | N/A |
| Procainamide | capsule, injection, sustained-release tablet, tablet | Procanbid®, Pronestyl®*, Pronestyl-SR® | $$ | $ |
| 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.
N/A = not available
† Brand is no longer manufactured.

## X. Conclusions

As a result of the CAST study, Class I antiarrhythmics should be reserved for special or unique situations and when other more effective and safer alternatives have been exhausted. With the exceptions of dofetilide and moricizine, all other antiarrhythmics reviewed are available in a generic formulation.

All brand products within the class reviewed are comparable to each other and to the generic products within the 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 of the antiarrhythmic agents to determine cost effective products and possibly designate one or more preferred agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Cardiotonic Agents**
**AHFS Class 240408**
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# I. Overview

Digoxin was initially obtained from the foxglove plant and later found to possess positive inotropic effects on the heart. The efficacy of digoxin in patients with heart failure and atrial fibrillation has been well established and widely accepted.[1] Digoxin is a potent and selective inhibitor of the active transport of $Na^+$ and $K^+$ across the cell membrane. Its narrow therapeutic concentration range makes dosing of digoxin extremely vital in order to limit incidences of toxicity.[2] This review encompasses all dosage forms and strengths. Table 1 includes those cardiotonic agents in this review.

**Table 1. Cardiotonic Agents Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| digoxin | capsule, elixir, injection, tablet | Digitek®^, Lanoxicaps®, Lanoxin®*, Lanoxin Pediatric®* | digoxin, Lanoxicaps® |

^Product is a branded generic.
*Generic is available in at least one dosage form or strength.

# II. Evidence Based Medicine and Current Treatment Guidelines

Heart Failure
The American College of Cardiology/American Heart Association 2005 guidelines state that digitalis can be beneficial in patients with current or prior symptoms of heart failure (Stage C) to decrease hospitalization.[3] Digoxin can decrease the symptoms of heart failure and increase exercise tolerance.[4] The results of a large long-term study indicate that adding digoxin to other drugs decreases the rate of hospitalization, especially among the sickest patients, but does not affect survival. Digoxin should not be used in patients with low ejection fraction, sinus rhythm, and no history of heart failure symptoms due to potential harm with no known benefit.[3]

Other recommendations include dosing of digoxin as 0.125mg to 0.25mg daily. Evidence suggests that the major benefit in heart failure is probably from neurohormonal modulation. This usually occurs at lower doses than needed for digoxin's inotropic effects.[5]

Atrial Fibrillation
Guidelines for the use of digoxin for the treatment of arrhythmias are listed in Table 2.

**Table 2. Treatment Guidelines Using the Cardiotonic Agents[6]**

| Arrhythmia | Drug(s) of Choice | Alternatives |
|---|---|---|
| Atrial fibrillation or flutter | | |
| • Acute management | Rate control: IV verapamil, diltiazem, a beta-blocker or digoxin<br>Conversion: DC cardioversion | IV procainamide or ibutilide; single large oral dose of propafenone or flecainide |
| • Chronic treatment | Rate control: verapamil, diltiazem, a beta-blocker or digoxin<br>Maintenance of sinus rhythm: amiodarone, sotalol, flecainide or propafenone, dofetilide | Quinidine, procainamide, disopyramide |

| Arrhythmia | Drug(s) of Choice | Alternatives |
|---|---|---|
| Other supraventricular tachycardias<br>• Acute management<br><br>• Long-term suppression | <br>IV adenosine, verapamil or diltiazem<br><br>Beta-blockers, verapamil, diltiazem, flecainide, propafenone, amiodarone, sotalol, or digoxin | <br>IV esmolol, another beta-blocker or digoxin for termination<br><br>Quinidine, procainamide or disopyramide |
| Premature ventricular complexes (PVCs) or non-sustained ventricular tachycardia | For asymptomatic patients without structural heart disease, no drug therapy indicated<br><br>For symptomatic patients, a beta-blocker | |
| Sustained ventricular tachycardia | Amiodarone | Procainamide, lidocaine |
| Ventricular fibrillation | Amiodarone | Procainamide, lidocaine |

## III. Indications[7]

Heart Failure
For the treatment of mild-to-moderate heart failure. Whenever possible, digoxin should be used with a diuretic and an ACE Inhibitor.

Atrial Fibrillation
For the control of ventricular response rate in patients with chronic atrial fibrillation.

## IV. Pharmacokinetics[7,8]

Absorption:
- Absorption is delayed by food.
- Onset of action for oral formulations is generally 30 minutes to 2 hours.
- Peak response for the oral formulations is observed within 2 to 6 hours.

**Table 3. Comparisons of Bioavailability and Equivalent Doses for Oral Digoxin Products[7]**

| Formulation | Absolute Bioavailability | Equivalent Doses (mcg) Among Dosage Formulations | | | |
|---|---|---|---|---|---|
| Tablet | 60-80% | 62.5 | 125 | 250 | 500 |
| Pediatric Elixir | 75-85% | 62.5 | 125 | 250 | 500 |
| Capsule | 90-100% | 50 | 100 | 200 | 400 |
| Injection/IV | 100% | 50 | 100 | 200 | 400 |

Distribution:
- Following administration, a 6-8 hour tissue distribution phase is observed.
- Vd (normal renal function): 6-7L/kg.
- Decreased Vd with: hyperkalemia, concomitant quinidine therapy, renal failure.
- Increased Vd with: hypokalemia, hyperthyroidism.

Metabolism:
- Not dependent on cytochrome P-450 system.
- Usually metabolized (16%) by hydrolysis.

Excretion:

- 50-70% excreted unchanged in the urine.
- Half-life: 38-48 hours (dependent upon age, renal, and cardiac function).

## V. Drug Interactions[9]

Tables 4 and 5 include digoxin drug interactions that may either increase or decrease digoxin serum levels.

**Table 4. Drugs That Increase Digoxin Serum Levels**

| | |
|---|---|
| Amiodarone | Propafenone |
| Benzodiazepines (alprazolam, diazepam) | Propantheline |
| Bepridil | Quinidine |
| Cyclosporine | Quinine |
| Diphenoxylate | Spironolactone |
| Indomethacin | Tetracycline |
| Itraconazole | Verapamil |
| Macrolides (clarithromycin, erythromycin) | |

**Table 5. Drugs That Decrease Digoxin Serum Levels**

| | |
|---|---|
| Aminoglycosides | Metoclopramide |
| Antacids (Al & Mg) | Neomycin |
| Antineoplastics | Penicillamine |
| Colestipol | Rifampin |
| Charcoal | St. John's Wort |
| Cholestyramine | Sulfasalazine |
| Kaolin/pectin | |

## VI. Adverse Drug Events[8,9]

Table 6 includes reported adverse drug reactions to digoxin.

**Table 6. Adverse Events by System for the Cardiotonic Agents**

| | |
|---|---|
| **Cardiovascular** | Heart block, asystole, atrial tachycardia, ventricular tachycardia, PR prolongation, ST segment depression |
| **CNS** | Visual disturbances (blurred vision), headache (3.2%), weakness, dizziness (4.9%), apathy, confusion, mental disturbances (4.1%), anxiety, depression, delirium, hallucinations, fever |
| **Dermatologic** | Maculopapular rash (1.6%), erythematous, vesicular or bullous rash, urticaria, pruritus, laryngeal edema, alopecia, shedding of fingernails or toenails |
| **GI** | Nausea (3.2%), vomiting (1.6%), diarrhea (3.2%), abdominal pain |
| **Miscellaneous** | Gynecomastia, thrombocytopenia |

## VII. Dosing and Administration

**Table 7. Usual Adult and Pediatric Doses for Digoxin[10]**

| | |
|---|---|
| Adult Dose | • Congestive heart failure, Rapid digitalization: tablet or elixir, 0.5-0.75 mg ORALLY; monitor response; additional doses of 0.125-0.375 mg ORALLY may be given cautiously at 6-8 hr intervals<br>• Congestive heart failure, Rapid digitalization: intravenous or oral capsule, 0.4-0.6 mg; additional doses of 0.1-0.3 mg given cautiously at 6-8 hr intervals<br>• Congestive heart failure, 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 wk<br>• Supraventricular arrhythmia: 8-12 mcg/kg |
| Pediatric Dose | • Congestive heart failure, Maintenance or gradual digitalization: elixir, give ORALLY in divided dose; (premature) 20-30% of ORAL digitalizing dose/day; (infant to 2 yr) 25-35% of ORAL digitalizing doses/day; (2-5 yr) 10-15 mcg/kg/day; (5-10 yr) 7-10 mcg/kg/day; (over 10 yr) 3-5 mcg/kg/day<br>• Congestive heart failure, Maintenance or gradual digitalization: intravenous, (premature) 20-30% of IV digitalizing dose/day; (infant to children over 10 yr) 25%-35% of IV digitalizing dose/day<br>• Congestive heart failure, Maintenance or gradual digitalization: oral capsule, 25%-35% of the ORAL CAP or IV rapid digitalization dose; give in divided doses for children under 10 yr<br>• Congestive heart failure, Rapid digitalization: elixir, give ORALLY in divided doses; (premature) 20-30 mcg/kg; (full-term) 25-35 mcg/kg; (1-24 mo) 35-60 mcg/kg; (2-5 yr) 30-40 mcg/kg; (5-10 yr) 20-35 mcg/kg; (over 10 yr) 10-15 mcg/kg<br>• Congestive heart failure, Rapid digitalization: intravenous, (premature) 15-25 mcg/kg; (full-term) 20-30 mcg/kg; (1-24 mo) 30-50 mcg/kg; (2-5 yr) 25-35 mcg/kg; (5-10 yr) 15-30 mcg/kg; (over 10 yr) 8-12 mcg/kg IV; give in divided doses<br>• Congestive heart failure, Rapid digitalization: oral capsule, (2-5 yr) 25-35 mcg/kg; (5-10 yr) 15-30 mcg/kg; (over 10 yr) 8-12 mcg/kg<br>• Supraventricular arrhythmia: 8-12 mcg/kg |
| Dose Adjustments | • Geriatrics: (over 70 yr with good renal function) initial, 0.125 mg ORALLY once daily<br>• Renal impairment: initial 0.125 mg ORALLY daily; severe impairment, initial 0.0625 mg ORALLY daily; titrate dose every 2 wks |

## VIII. Effectiveness

**Table 8. Outcomes Evidence for the Cardiotonic Agents**

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Roberts SA et al[11]<br><br>Mean dose 0.80 mg/day digoxin in AF or Aflutter | Prospective, observational study<br><br>n = 115<br><br>duration - hours | Clinical outcomes | • Loss of control (resting ventricular rate returned to ≥ 120 beats/min) occurred at least once in 50% of patients ($p < 0.05$) |
| Koh KK et al[12]<br><br>Group I – without digoxin, diltiazem, or betaxolol<br><br>Group II – 0.125 to 0.5 mg/day digoxin<br><br>Group III – 0.125 to 0.5 mg/day digoxin and 90 mg bid diltiazem<br><br>Group IV – 0.125 to 0.5 mg/day digoxin and 20 mg/day betaxolol | Prospective, randomized study<br><br>n = 45<br><br>4 weeks | Heart rate (HR), blood pressure (BP), rate-pressure product | • Resting ventricular rates were lower in all patients receiving active treatment (groups II, III, IV) compared to group I ($p= <0.01$)<br>• Ventricular rates during exercise were lower in groups III and IV compared to groups I and II ($p<0.01$)<br>• No significant differences in ventricular rate at rest or during exercise between groups III and IV ($p<0.01$)<br>• Systolic blood pressure was not significantly different between the four groups ($p = 0.09$)<br>• Rate-pressure product at rest and during exercise was significantly lower in groups III and IV compared with groups I and II ($P<0.01$) |
| DIG[13]<br><br>Mean dose 0.25 mg/day digoxin vs. placebo<br><br>Patients were encouraged to receive an ACE inhibitor | Randomized, double-blind, placebo controlled trial<br><br>n = 6800<br><br>37 months | Mortality | • 1181 (34.8%) deaths in patients receiving digoxin compared to 1194 (35.1%) deaths in patients receiving placebo ($p = 0.80$)<br>• Lower risk of mortality attributable to worsening heart failure in the digoxin group (5.8% of patients) compared to placebo (6.6%) ($p= 0.06$)<br>• Fewer hospitalizations for worsening heart failure in the digoxin group<br>• ($p = <0.001$) |
| PROVED[14]<br><br>Digoxin standard diuretic therapy vs. placebo | n = 88<br><br>12 weeks | Incidence of worsening heart failure | • The incidence of worsening heart failure was higher in the placebo group compared to the digoxin group<br>• ($p = <0.02$) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| RADIANCE[15]<br><br>Mean dose 0.38 mg/day digoxin vs. placebo<br><br>Patients remained taking a background therapy of diuretics and an ACE inhibitors (captopril 74 mg/day and enalapril 15 mg/day) | Randomized, double-blind, placebo controlled study<br><br>n = 178<br><br>3 months | Rates of withdrawal from the study due to worsening heart failure, time to withdrawal, changes in exercise tolerance | • 4 patients receiving digoxin, compared to 23 patients receiving digoxin required therapeutic intervention due to worsening of heart failure ($p<0.001$)<br>• Exercise tolerance remained stable in patients receiving digoxin compared to a deterioration in exercise tolerance in patients receiving placebo, difference in exercise duration after 12 weeks was 42 sec ($p = 0.006$)<br>• Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo, distance traversed after 10 weeks was 41 m ($p = 0.01$) |

**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.

Stable Therapy
A search of Medline and Ovid did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and Ovid 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 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 AL 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 AL 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 AL Medicaid program via pharmaceutical manufacturer rebating.

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

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$50 per Rx |
| $$ | $51-$75 per Rx |
| $$$ | $76-$100 per Rx |
| $$$$ | $101-$150 per Rx |
| $$$$$ | Over $150 per Rx |

Rx = Prescription

**Table 9. Relative Cost of Cardiotonic Agents**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Digoxin | capsule, elixir, injection, tablet | Digitek®^, Lanoxicaps®, Lanoxin®*, Lanoxin Pediatric®* | $-$$ | $ |

^Product is a branded generic.
*Generic is available in at least one dosage form or strength.

## X. Conclusions

Ample evidence supports the use of digoxin, particularly in the management of heart failure and atrial fibrillation. Considering minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. All brand products within the class reviewed are comparable to each other and to the generics 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 agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Nitrates and Nitrites**
**AHFS Class 241208**
**February 22, 2006**

## I. Overview

The organic nitrates relax most smooth muscle, including that in the arteries and veins. These effects subsequently lead to a reduction of myocardial oxygen demand secondary to venodilation. Organic nitrates are converted intracellularly to nitric oxide. Frequent repeated or continuous exposure to organic nitrates leads to a decrease in its pharmacological effects. Tolerance to nitrates is a result of dosage and frequency of administration of the preparation. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route. Nitrate-free interval dosing can limit the degree of tolerance produced from chronic nitrate therapy.[1] Table 1 lists the nitrates and nitrites included in this review. This review encompasses all dosage forms and strengths.

**Table 1. Nitrates and Nitrites Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| amyl nitrite | inhalant | N/A | none |
| isosorbide dinitrate | chewable tablet, 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 | controlled-release tablet, injection, ointment, spray, sublingual tablet, sustained-release capsule, transdermal patch | Minitran®*, Nitrek®*, Nitro-Bid®, Nitro-Dur®*, Nitroglyn®*, Nitrolingual®, Nitroquick®, Nitrostat®*, Nitrotab®, Nitro-Time® | nitroglycerin, Nitro-Bid®, Nitrostat®* |

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

## II. Evidence Based Medicine and Current Treatment Guidelines

Chronic Stable Angina

Treatment goals for chronic stable angina include: 1. To relieve acute symptoms of myocardial ischemia, 2. To prevent symptoms of myocardial ischemia, and 3. To prevent unstable angina, myocardial infarction, and death.[2] Nitrates are recommended for the treatment or relief of acute symptoms of myocardial ischemia as well as for the prevention of symptoms associated with myocardial ischemia.[3]

Short-acting nitrates (sublingual tablets and spray) are recommended agents for relief of acute symptoms of myocardial ischemia. Their primary mechanism is to decrease myocardial volume oxygen consumption ($MVO_2$) through systemic venodilation, which results in a reduction of preload and ventricular wall stress. Nitrates also increase oxygen supply by dilating coronary arteries and relieving vasospasm. Nitrates can also be utilized to prevent effort-induced angina.

Long-acting nitrates (transdermal and oral) are also recommended for the prevention of symptoms associated with myocardial ischemia. Nitrates can also be added to therapy in cases when first-

line agents are contraindicated or if symptoms persist. A nitrate free interval of 8-12 hours should be followed to minimize tolerance to nitrates.[2]

Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction
Sublingual nitroglycerin is considered a first-line agent to relieve symptoms of acute ischemia. Intravenous nitroglycerin is used for ongoing or recurrent pain of myocardial ischemia despite sublingual nitroglycerin and beta-blockers. Contraindications to nitroglycerin therapy include systolic BP < 90 and concurrent phosphodiesterase inhibitor (e.g., sildenafil, tadalafil, vardenafil) use.[4]

Chronic Heart Failure
The ACC/AHA 2005 guideline recommends that a combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction (LVEF) who cannot be given an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker because of drug intolerance, hypotension, or renal insufficiency.[5] Isosorbide dinitrate was one of the first vasodilators reported to be effective in the treatment of chronic heart failure. Nitrates may decrease symptoms of dyspnea at night and during exercise and may improve exercise tolerance in patients who have persistent limitations despite optimization of other therapies. In clinical use, nitrates are frequently prescribed to patients with persistent congestive symptoms. There is limited data regarding the use of hydralazine alone in heart failure.

In June 2005, the FDA approved a combination product containing hydralazine and isosorbide dinitrate for the treatment of heart failure in black patients. Fixed dose combination of hydralazine and isosorbide dinitrate added to standard therapy in black patients with Class III-IV heart failure significantly lowered mortality and the rate of first hospitalization while improving quality-of-life scores.[6] No data is available on the use of hydralazine/isosorbide dinitrate in addition to standard therapy in other populations.

Hypertension
JNC-7 guidelines list intravenous nitroglycerin as a treatment option for the management of hypertensive emergencies, particularly in the setting of coronary ischemia.[7] Intravenous nitroglycerin's onset and duration of action are 2-5 minutes and 5-10 minutes, respectively.

## III. Indications

Table 2 includes availability and respective indications for the nitrates and nitrites.

**Table 2. Indications for the Nitrates and Nitrites**

| Generic Name | FDA Approved Indications |
|---|---|
| Amyl nitrite | Rapid relief of angina pectoris |
| Isosorbide dinitrate | Prophylaxis and treatment of angina<br>Not for acute attacks |
| Isosorbide mononitrate | Prophylaxis and treatment of angina<br>Not for acute attacks |
| Nitroglycerin | Acute relief of angina attacks<br>Prophylaxis of angina pectoris |
| Nitroglycerin ointment | Prophylaxis and treatment of angina<br>Not for acute attacks |
| Nitroglycerin transdermal | Prophylaxis and treatment of angina<br>Not for acute attacks |

## IV. Pharmacokinetics

Nitrates, excluding isosorbide mononitrate, have short to very short half-lives due to their hepatic metabolism and associated considerable first-pass effect. Nitrates also have large volumes of distribution, high clearance rates, and large individual variations in plasma and blood concentrations. The route of administration generally affects nitrate concentrations. There are also numerous problems limiting reliable pharmacokinetic estimates for nitrates.[1] Table 3 lists the pharmacokinetic parameters of different nitrate and nitrite formulations.

**Table 3. Pharmacokinetic Parameters of the Nitrates and Nitrites**

| Drug | Dosage Form | Onset (minutes) | Duration |
|---|---|---|---|
| Nitroglycerin | IV | 1-2 | 3-5 min |
| | Sublingual | 1-3 | 30-60 min |
| | Translingual Spray | 2 | 30-60 min |
| | Transmucosal tablet | 1-2 | 3-5 hrs |
| | Oral, sustained-release | 20-45 | 3-8 hrs |
| | Ointment | 30-60 | 2-12 hrs |
| | Transdermal | 30-60 | Up to 24 hrs |
| Isosorbide dinitrate | Sublingual | 2-5 | 1-3 hrs |
| | Oral | 20-40 | 4-6 hrs |
| | Oral, sustained-release | Up to 4 hrs | 6-8 hrs |
| Isosorbide mononitrate | Oral | 30-60 | 5-12 hrs |
| Amyl nitrite | Inhalant | 0.5 | 3-5 min |

## V. Drug Interactions

Table 4 includes clinically significant drug interactions for the nitrates and nitrites.

**Table 4. Significant Drug Interactions with the Nitrates and Nitrites [8]**

| Drug | Description |
|---|---|
| Alcohol | Severe hypotension and cardiovascular collapse may occur |
| Dihydroergotamine | Increased ergot bioavailability with resulting increased blood pressure or antagonism effect of vasodilating properties of nitrates |
| Sildenafil, vardenafil, tadalafil | Potentiates the hypotensive effects of nitrates |

## VI. Adverse Drug Events

Common side effects of organic nitrates are generally all secondary to actions on the cardiovascular system. Headache is the most common side effect and it can be severe. It usually decreases over a few days if treatment is continued. Transient episodes of dizziness and weakness associated with postural hypotension may develop and can occasionally progress to loss of consciousness. In addition, all the nitrates can occasionally produce drug rash particularly with transdermal nitroglycerin.[8] Table 5 lists potential adverse drug events related to nitrate use.

**Table 5. Adverse Events (%) by System for the Nitrates and Nitrites**

| | |
|---|---|
| Cardiovascular (1-10%) | Tachycardia, palpitations, hypotension, syncope, rebound hypertension, arrhythmias, atrial fibrillation, postural hypotension |
| CNS (>10%) | Headache, restlessness, weakness, vertigo, dizziness, agitation, anxiety, confusion, insomnia, nervousness, nightmares |
| Dermatologic (<1%) | Drug rash, flushing, pruritus, erythematous, local burning, itching |
| GI (<1%) | Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, tooth disorder |
| GU (<1%) | Dysuria, impotence, urinary frequency |
| Musculoskeletal (<1%) | Arthralgias |
| Respiratory (<1%) | Bronchitis, pneumonia, upper respiratory infection |
| Miscellaneous (<1%) | Muscle twitching, pallor, perspiration, cold sweat, hemolytic anemia, blurred vision, edema, malaise, neck stiffness, rigors, increased appetite |

## VII. Dosing and Administration

**Table 6. Dosing and Administration for the Nitrates and Nitrites**

| Drug | Dosage Form | Usual Dose |
|---|---|---|
| Nitroglycerin | IV | 5μg/min: increase in 5μg/min increments |
| | Sublingual | 0.3-0.6mg prn |
| | Translingual Spray | 0.4mg/spray prn |
| | Transmucosal tablet | 1mg every 3-5 hours |
| | Oral, sustained release | 2.5-9mg two to four times a day |
| | Ointment | 1-2 in. to skin every 4-8 hours |
| | Transdermal | 1 disc (2.5-15mg) for 12-24 hours daily |
| Isosorbide dinitrate | Sublingual | 2.5-10mg every 2-3 hours |
| | Oral | 5-40mg every 6 hours |
| | Oral, sustained release | 40-80mg every 8-12 hours |
| Isosorbide mononitrate | Oral | Tablet: 10-40mg BID<br>Cap: 60-120mg QD |
| Amyl nitrite | Inhalant | 2-6 inhalations |

Contraindications[9]

Amyl nitrite:
- Patients with glaucoma, recent head trauma, cerebral hemorrhage, and pregnancy

Isosorbide dinitrate:
- Allergic reactions to isosorbide dinitrate or any of its ingredients

Isosorbide mononitrate:
- Hypersensitivity or idiosyncratic reactions to other nitrates or nitrites

Nitroglycerin:

- Allergic reactions to organic nitrates
- Patients who take phosphodiesterase inhibitors for erectile dysfunction
- Allergy to the adhesives used in the transdermal patches
- Patients with early MI, severe anemia, increased intracranial pressure, known hypersensitivity to nitroglycerin
- Patients with pericardial tamponade, restrictive cardiomyopathy, constrictive pericarditis, solutions containing dextrose in patients with known allergy to corn or corn products (IV)

## VIII. Effectiveness

**Table 7. Outcomes Evidence for the Nitrates and Nitrites**

| Study | Sample | Results |
|---|---|---|
| Stable Angina | | |
| Parker JO[10] | n=214, ISMN 5,10,20 mg BID arms plus placebo, duration: 3 weeks | Fewer episodes of angina with the 20mg dose, without tolerance |
| Thadani U, et al.[11] | n=116, ISMN 20mg BID plus placebo | ISMN was well tolerated & improved exercise performance, no rebound increase in anginal attacks |
| Chrysant SG, et al.[12] | n=313, ISMN ER 30,60,120,240 mg qAM plus placebo | ISMN ER 120 & 240mg QD prolonged exercise time to development of moderate effort-induced angina 4-12 hours post dose with no tolerance |
| Demots H, et al.[13] | n=206, TD NTG intermittent plus placebo, duration: 4 weeks | Intermittent TD NTG was well tolerated with absolute response |
| Unstable Angina | | |
| Kaplan, et al.[14] | n=35, unresponsive to standard therapy, given IV-NTG 10 mcg/min | IV-NTG appears effective for angina refractory to standard medications |
| Heart Failure | | |
| VHEFT-1[15] | n=642, ISDN + Hydralazine (n=186), Prazosin (n=183), placebo | Combination of vasodilators had the most significant benefit in all cause mortality (p=0.046) |
| A-HeFT[16] | n=518, ISDN + Hydralazine N=532, placebo | Combination of vasodilators in addition to standard therapy had significant mortality benefit (p=0.02) |

**Additional Evidence**

Dose Simplification

In the COMPASS (Compliance with Oral Mononitrates in Angina Pectoris Study) study comparing once-daily isosorbide mononitrate (60mg) with twice-daily isosorbide mononitrate (20mg BID) the once-daily dose was shown to have significantly better overall compliance than the twice-daily dose ($p<0.001$). The once daily dose also resulted in decreased mean number of chest pain episodes versus the twice daily dose ($p<0.0001$).[16] Long-acting forms of nitrates (i.e. nitroglycerin patch, once-daily isosorbide mononitrate) have been shown to have anti-anginal activity for up to 12 hours of the day.[17] However, there has been no direct comparison of different nitrates in therapy for angina.

Stable Therapy

Tolerance to the anti-anginal activity of nitrates has been known to be a common problem since they were first used. The use of long-acting nitrates or erratically split dosing (every 7 hours instead of every 12 hours) has led to decreased tolerance and sustained anti-anginal activity. A nitrate-free period of 12 to 14 hours seems necessary to avoid tolerance.[16,17]

Impact on Physician Visits
A search of Medline and Ovid 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 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-$25 per Rx |
| $$ | $26-$50 per Rx |
| $$$ | $51-$75 per Rx |
| $$$$ | $76-$100 per Rx |
| $$$$$ | Over $100 per Rx |

RX=prescription

**Table 8. Relative Cost of Nitrates and Nitrites**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Amyl nitrite | inhalant | N/A | N/A | $ |
| Isosorbide dinitrate | chewable tablet, sublingual tablet, sustained-release capsule, sustained-release tablet, tablet | Dilatrate-SR®, Isordil®* | $$-$$$ | $ |
| Isosorbide mononitrate | sustained-release tablet, tablet | Imdur®*, Ismo®*, Monoket®* | $$-$$$ | $ |
| Nitroglycerin | controlled-release tablet, injection, ointment, spray, sublingual tablet, sustained-release capsule, transdermal patch | Minitran®*, Nitrek®*, Nitro-Bid®, Nitro-Dur®*, Nitroglyn®*, Nitrolingual®, Nitroquick®, Nitrostat®*, Nitrotab®, Nitro-Time® | $-$$$ | $ |

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

## X. Conclusions

Overwhelming evidence supports the beneficial effects of nitrates for the management of chronic stable angina and acute angina attacks. Since nitrates have the same pharmacologic effects, the product selection is based on desired onset and duration of action. Nitrate tolerance is minimized by ensuring a 14 hour nitrate-free period. Oral isosorbide mononitrate has the advantage of once or twice-daily dosing over isosorbide dinitrate, which is typically dosed thrice-daily. Isosorbide mononitrate was shown to have improved efficacy and adherence at once-daily dosing. Both isosorbide mononitrate and isosorbide dinitrate are available generically. Nitroglycerin extended-release capsules, injection, ointment, sublingual tablets, and transdermal patches are available generically.

Nitroglycerin sublingual tablets have long demonstrated their utility as an invaluable treatment of acute angina due to their rapid onset of action. The nitroglycerin sublingual spray possesses no known clinical advantage over the sublingual tablets.

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

## XI. Recommendations

No brand nitrates or nitrites are recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers of the nitrates and nitrites to determine cost effective products and possibly designate one or more preferred agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Antilipemic Agents**
**AHFS Class 240600**
**February 22, 2006**

# I. Overview

The Antilipemic Therapeutic Class consists of several types of drugs including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and nicotinic acid (niacin). These drugs differ in their 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.[1] 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 low-density lipoprotein cholesterol (LDL-C) lowering agents with LDL-C reductions ranging from 20-60%.[1-3] If goal 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 hypertriglyceridemia (TG) is the primary lipid abnormality, fibric acid derivatives are particularly effective. They are also effective for raising high-density lipoprotein cholesterol (HDL-C) levels. Niacin shares a similar lipid lowering capacity as the fibric acid derivatives; however, its use has been limited historically by poor tolerability.[1] Cholesterol absorption inhibitors 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 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.

# II. Evidence Based Medicine and Current Treatment Guidelines

**Hyperlipidemia**
The treatment of hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III[2] which was published in 2001. This guideline focuses primarily on designated LDL-C goals as LDL-C is considered the major atherogenic lipid component. LDL-C goals are calculated according to a coronary heart disease (CHD) risk factor assessment. The NCEP authors also published an update to the guideline in 2004, which outlined implications of five clinical trials that were published subsequent to the NCEP guidelines.[3] This publication expands and encourages intensified LDL-C goals for high risk individuals as well as moderately high risk individuals. The updated treatment goals are listed below and have been incorporated in Table 1.

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal remains <100mg/dL.
    - An LDL-C goal of <70mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
    - If LDL-C is ≥100mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.

- If baseline LDL-C is <100mg/dl, institution of an LDL-lowering drug to achieve an LDL-C level <70mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥200mg/dL, non-HDL-C is a secondary target of therapy, with a goal of 30mg/dL higher than the identified LDL-C goal.

- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130mg/dL; an LDL-C goal <100mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g. 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.
- 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 at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

Ultimately, LDL-C goals vary depending on the presence of particular CHD risk factors. The major risk factors for CHD, which are used to determine an LDL-C goal, are listed in Table 1.

**Table 1. Major Risk Factors that Modify LDL-C Goal[1-3]**

| Positive Risk Factors (increase the risk for CHD) | Negative Risk Factors* (decrease the risk for CHD) |
|---|---|
| • Age (men ≥ 45 years; women ≥ 55 years)<br>• Family history of premature CHD (first degree male relative < 55 years; first degree female relative < 65 years)<br>• Current cigarette smoking<br>• Hypertension (blood pressure ≥ 140/90 or the use of antihypertensives)<br>• Low HDL-C (< 40 mg/dL) | • High HDL-C (≥ 60 mg/dL) |

*Presence of a negative risk factor removes one positive risk factor from the total count of risk factors.

Diabetes, clinical CHD, symptomatic carotid artery disease, peripheral arterial disease, and aortic abdominal aneurysm are considered CHD risk equivalents. Once a patient's risk factors are assessed, it is possible to calculate 10-year CHD risk in patients with 2 or more risk factors (other than LDL-C) who do not have clinically manifested CHD or a CHD risk equivalent. Calculating this short-term risk helps identify individuals who may benefit from more intensive treatment. Estimated CHD risk is tabulated based on the patient's age, total cholesterol, HDL-C, systolic blood pressure, and smoking status. Risk is then assigned to one of three categories, which correlates with the risk of developing CHD or experiencing a coronary event in the next 10 years:

- High risk = > 20% CHD risk
- Intermediate risk = 10-20% CHD risk
- Low risk = < 10% CHD risk

Once CHD risk is determined, the LDL-C goal may be determined. Table 2 lists LDL-C goals along with recommendations for initiation of therapeutic lifestyle changes (TLC) versus pharmacotherapy.

**Table 2. LDL-C Categories and Cutpoints for TLC and Drug Therapy Per Risk Category[3]**

| Risk Category | LDL-C Goal | LDL-C Level at Which to Initiate (TLC) Changes | LDL-C Level at Which to Consider Drug Therapy |
|---|---|---|---|
| **High Risk**<br>CHD or<br>CHD Risk Equivalent<br>(10-year risk > 20%) | < 100 mg/dL<br>(optional goal < 70mg/dl)* | ≥ 100 mg/dL | ≥ 100mg/dL<br>(<100mg/dL, consider drug options)** |
| **Moderately High Risk**<br>2+ Risk Factors<br>(10-year risk 10-20%) | < 130 mg/dL<br><br>(optional goal < 100mg/dl) | ≥ 130 mg/dL | ≥ 130 mg/dL<br>(for 10-year risk 10-20%)<br><br>(100-129, consider drug options) |
| **Moderate Risk**<br>2+ Risk Factors<br>(10-year risk <10%) | < 130 mg/dL | ≥ 130 mg/dL | ≥160 mg/dL |
| **Lower Risk**<br>0-1 Risk Factor | < 160 mg/dL | ≥ 160 mg/dL | ≥ 190 mg/dL<br>(160-189 mg/dL,<br>drug optional)*** |

*****Very high risk favors the optional LDL-C goal of <70mg/dl, and in patients with high triglycerides, non-HDL-C <100mg/dl.
******When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
*******Factors that favor drug therapy after 3 months of TLC include a severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL-C), multiple life-habit risk factors and emerging risk factors, or 10-year risk approaching 10%.

**Table 3. Progression of Drug Therapy in Primary Prevention[2]**

| | |
|---|---|
| 1. Initiate LDL-lowering drug therapy. | • Start statin or<br>• Bile acid sequestrant or<br>• Nicotinic acid |
| 2. After 6 weeks, if LDL goal is not achieved, intensify LDL-lowering drug therapy. | • Consider higher dose of statin or<br>• Add bile acid sequestrant or nicotinic acid |
| 3. After an additional 6 weeks, if LDL goal is not achieved, intensify drug therapy or consider referral to a lipid specialist. If LDL goal is achieved, treat other lipid risk factors. | |
| 4. Every 4-6 months, monitor response and adherence to therapy. | |

**Hypertriglyceridemia**
The NCEP-ATP III guidelines focus primarily on attaining specific LDL-C goals. However, this treatment guideline also incorporates and classifies triglycerides as depicted in Table 4 below.

**Table 4. NCEP-ATP III Classification of Triglyceride Levels[2]**

| Triglycerides | Classification |
|---|---|
| < 150 mg/dL | Normal |
| 150-199 mg/dL | Borderline High |
| 200-499 mg/dL | High |
| ≥ 500 mg/dL | Very High |

Hypertriglyceridemia is also a significant risk factor for coronary heart disease (CHD) and treatment is recommended. In addition, very high triglycerides can increase the risk of pancreatitis. If triglycerides are >500 mg/dL, the primary goal of therapy is targeted towards lowering triglycerides as opposed to LDL-C lowering therapy. Once triglycerides are < 500 mg/dL, the primary focus should again shift back to LDL-lowering therapy. High triglycerides are often treated with weight reduction, a low fat/low cholesterol diet, regular exercise, smoking cessation, alcohol restriction, and pharmacotherapy with fibrates or nicotinic acid if needed. The NCEP guidelines also identify non-HDL as a secondary target of therapy in those with high triglycerides (> 200mg/dL). The goal for non-HDL should be set at 30mg/dL higher than the LDL-C goal. Non-HDL-C is calculated as total cholesterol minus HDL-C.[2]

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Bile Acid Sequestrants**
**AHFS Class 240604**
**February 22, 2006**

# I. Overview

Cholesterol is a major precursor of bile acids.[1] Bile acid sequestrants (BAS) bind bile acids in the intestine to form an insoluble complex that is excreted in the feces. The bile acid sequestrants can lower LDL-C by up to 20% and increase HDL-C; however, in patients with hypertriglyceridemia, triglycerides may increase.[2]

The Bile Acid Sequestrants (BAS) that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

**Table 1. Bile Acid Sequestrants Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| cholestyramine + aspartame | packet, powder | Prevalite®*, Questran Light®* | cholestyramine |
| cholestyramine + sucrose | packet, powder | Questran®* | cholestyramine |
| colesevelam | tablet | Welchol® | none |
| colestipol | granules, packet, tablet | Colestid® | none |

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

# II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under Antilipemic Agents. BAS are recommended by the NCEP expert panel as an alternative to HMG-CoA reductase inhibitors for the management of dyslipidemia and/or prevention of major acute coronary events in patients with concomitant coronary heart disease (CHD) risk factors or in those with established CHD.[3] Therapy that includes an HMG-CoA reductase inhibitor combined with a BAS or niacin, or addition or substitution of another antilipemic agent may be useful in hypercholesterolemic patients who have had an inadequate response or are not able to tolerate initial drug therapy. In patients without concurrent hypertriglyceridemia, combined therapy with a BAS plus niacin or a statin could potentially reduce LDL-cholesterol by 45-60%. Less pronounced reductions generally occur when a BAS is combined with a fibric acid derivative, but combined therapy may be useful in some patients.

# III. Indications

**Table 2. Indications for the Bile Acid Sequestrants[1,4,5]**

| Drug | Indication |
|---|---|
| Cholestyramine | • Monotherapy to reduce elevated LDL-C in primary hypercholesterolemia<br>• Combination with HMG-CoA reductase inhibitor to reduce elevated LDL-C in primary hypercholesterolemia<br>• Pruritus associated with biliary obstruction |

| Drug | Indication |
|---|---|
| Colesevelam | • Monotherapy to reduce elevated LDL-C in primary hypercholesterolemia<br>• Combination with HMG-CoA reductase inhibitor to reduce elevated LDL-C in primary hypercholesterolemia |
| Colestipol | • Monotherapy to reduce elevated LDL-C in primary hypercholesterolemia<br>• Combination with HMG-CoA reductase inhibitor to reduce elevated LDL-C in primary hypercholesterolemia |

## IV. Pharmacokinetics

The bile acid sequestrants are not absorbed and are not hydrolyzed by digestive enzymes.[1] They are hydrophilic and virtually water insoluble (99.75%). Cholestyramine is excreted about 100% in the feces, as an insoluble complex with bile acids.[6] After administration of 1.9 g of colesevelam twice daily for 28 days, an average of 0.05% of a single dose was excreted in the urine.[1] Less than 0.17% of colestipol was excreted in the urine following administration of 20 g per day for 60 days.

## V. Drug Interactions

Cholestyramine and colestipol may delay or reduce the absorption of concomitant oral medications.[1] To minimize this interaction, other drugs should be taken at least 1 hour before or 4-6 hours after these BAS. Colesevelam does not appear to interfere with the absorption of coadministered drugs. In human trials, colesevelam was shown to have no significant effect on the bioavailability of digoxin, warfarin, quinidine, valproic acid, metoprolol or lovastatin.[4] Colesevelam was noted to reduce the peak concentration and area under the curve (AUC) of sustained-release verapamil by 31% and 11%, respectively, although the clinical significance of this finding is not clear. It is not yet known if colesevelam interacts with other drugs that bind to cholestyramine or colestipol. Physicians should consider monitoring drug levels or effects when administering other drugs with colesevelam, for which alterations in blood levels could have clinically significant effects on safety or efficacy. Other significant drug interactions observed with the BAS are identified in Table 3.

**Table 3. Significant Drug-Drug Interactions for the Bile Acid Sequestrants[7]**

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Bile Acid Sequestrants (cholestyramine, colestipol) | 2 | HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) | The HMG-CoA reductase inhibitor may adsorb to the bile acid sequestrant, reducing the GI absorption of the HMG-CoA reductase inhibitor. |
| Bile Acid Sequestrants | 2 | Corticosteroids (hydrocortisone) | Cholestyramine and colestipol appear to interfere with the GI absorption of hydrocortisone. |
| Bile Acid Sequestrants | 2 | Troglitazone | Troglitazone probably binds to cholestyramine in the GI tract, decreasing troglitazone absorption. |
| Cholestyramine | 2 | Valproic acid (divalproex sodium, valproic acid) | Cholestyramine interferes with the GI absorption of valproic acid. |

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Cholestyramine | 2 | Thyroid hormones (levothyroxine, liothyronine, liotrix, thyroid) | Probable binding of thyroid hormone in the GI tract by cholestyramine, preventing absorption. |
| Cholestyramine | 2 | Digoxin | Cholestyramine may decrease the GI absorption of digoxin by physically binding to it. Cholestryramine may also interrupt the enterohepatic recycling of digoxin. |
| Cholestyramine | 2 | Anticoagulants (dicumarol, warfarin) | Reduced oral anticoagulant absorption and possibly increased elimination. |
| Cholestyramine | 2 | Loop diuretics (furosemide) | Cholestyramine (an anion exchange resin) binds furosemide. |

Level 1= major severity
Level 2=moderate severity

## VI. Adverse Drug Events

The adverse effects of colestipol and cholestyramine are similar.[2] Constipation occurs frequently and may be accompanied by heartburn, nausea, eructation and bloating. These symptoms may diminish over time or be relieved by increasing dietary fiber or adding a fiber supplement. Colesevelam appears to be better tolerated than cholestyramine or colestipol, with fewer gastrointestinal symptoms; however, there are no head-to-head trials comparing these agents. Cholestyramine and colestipol can decrease plasma folate levels, so supplementation should be considered in younger women and children. A summary of side effects with the BAS are listed in Table 4.

**Table 4. Adverse Events with the Bile Acid Sequestrants[6]**

| Drug | Adverse Event |
|---|---|
| Cholestyramine | • Gastrointestinal: abdominal discomfort, constipation, flatulence, nausea and vomiting<br>• Hematologic: clotting and bleeding disorders, due to hypoprothrombinemia |
| Colesevelam | • Gastrointestinal: constipation, dyspepsia, flatulence<br>• Musculoskeletal: myalgia<br>• Neurologic: asthenia |
| Colestipol | • Gastrointestinal: abdominal distension, abdominal pain, constipation, hemorrhoids, aggravation, nausea and vomiting<br>• Gastrointestinal: impaction of intestine (rare) |

## VII. Dosing and Administration

**Table 5. Dosing and Administration for the Bile Acid Sequestrants[1,4,5]**

| Drug | Dosage Forms | Usual Daily Dose | Maximum Daily Dose |
|---|---|---|---|
| Cholestyramine* | 4 g packet, powder | Adults:<br>Initial 4 g (1 packet or scoopful) 1 to 2 times daily<br>Maintenance: 8-16 g daily divided into 2 doses<br><br>Pediatric: 240 mg/kg/day in 2-3 divided doses | 24 g per day<br><br>8 g per day |
| Colesevelam | 625 mg tablet | 1875 mg bid or 3750 mg daily<br><br>Pediatric: safety and effectiveness not established | 4375 mg per day |
| Colestipol | 1 g tablet, 5 g/7.5 g granules for oral suspension | Initial: 2 g tablets once or twice a day; 5 g granules (1 packet or scoopful) once or twice daily<br><br>Pediatric: safety and effectiveness not established | Tablets: 16 g per day<br>Granules: 30 g (6 packets or scoopfuls) per day |

*Dose is based on anhydrous cholestyramine resin.

## VIII. Effectiveness

**Table 6. Outcomes Evidence for the Bile Acid Sequestrants**

| Study | Study Design | Results (Primary Outcomes of the Study) |
|---|---|---|
| **Cholestyramine** | | |
| The Lipid Research Clinics Coronary Primary Prevention Trial[7] | Large, placebo-controlled, multi-clinic | Compared to placebo, cholestyramine resulted in:<br>• 19% reduction in the combined rate of coronary heart disease death plus nonfatal MI relative to placebo |
| Rosuvastatin 80 mg daily vs rosuvastatin 80 mg daily & cholestyramine 8 g twice-daily[11] | Open-label, multicenter, parallel group trial<br>Rosuvastatin 80 mg (n=69)<br>Rosuvastatin 80 mg/cholestyramine (n=75) | Compared to rosuvastatin 80 mg, the combination cholestyramine and rosuvastatin 80 mg resulted in:<br>• 4.2% higher LDL-C<br>• 2.5% higher total cholesterol<br>• 1% lower HDL-C<br>• 2.7% higher triglycerides<br>• 0.8% higher Apo-B<br>• None of the results were significant between treatment groups (p>0.05) |
| Pravastatin vs pravastatin & cholestyramine[12] | Randomized, multicenter study<br><br>Cholestyramine 16 g (n=467)<br>Cholestyramine 8 g and pravastatin 20 mg (n=492)<br>Pravastatin 20 mg (n=528)<br>Pravastatin 40 mg (n=521) | Compared to the monotherapies in this study, the combination of cholestyramine and pravastatin 20 mg resulted in:<br>• 36% reduction in LDL-C vs 26% with cholestyramine, 27% with pravastatin 20 mg, and 32% with pravastatin 40 mg<br>• 24% reduction in total-C vs 15% with cholestyramine, 19% with pravastatin 20 mg, and 23% with pravastatin 40 mg<br>• 3% increase in HDL-C vs 1.4% with pravastatin 20 mg, 3.3% with pravastatin 40 mg, and a 0.2% decrease with cholestyramine<br>• 0.5% reduction in triglycerides vs 5.6% with pravastatin 20 mg, 9.5% with pravastatin 40 mg, and a 14% increase with cholestyramine<br>• 53% of patients completing study vs 44% with cholestyramine, 76% with pravastatin 20 mg, and 78% with pravastatin 40 mg<br>• Adverse drug reactions were the most common reason for leaving study, especially GI upset with cholestyramine groups |

| Study | Study Design | Results (Primary Outcomes of the Study) |
|---|---|---|
| **Colesevelam** | | |
| Colesevelam 24-Week Trial[6] | Colesevelam 3.8 g/day (n=88)<br>Colesevelam 4.5 g/day (n=95)<br>Placebo (n=88) | Compared to placebo, colesevelam 3.8 g (6 tablets) resulted in:<br>• 7% decrease in total-C ($p<0.05$)<br>• 15% decrease in LDL-C ($p<0.05$)<br>• 3% increase in HDL-C ($p<0.05$)<br>• 10% decrease in non-HDL-C ($p<0.05$)<br>• 10% increase in triglycerides<br>• 12% decrease in Apo-B compared to baseline ($p<0.05$)<br>Compared to placebo, colesevelam 4.5 g (7 tablets) resulted in:<br>• 10% decrease in total-C ($p<0.05$)<br>• 18% decrease in LDL-C ($p<0.05$)<br>• 3% increase in HDL-C ($p<0.05$)<br>• 13% decrease in non-HDL-C ($p<0.05$)<br>• 9% increase in triglycerides<br>• 12% decrease in Apo-B compared to baseline ($p<0.05$) |
| Colesevelam in combination with atorvastatin[6] | Placebo (n=19)<br>Atorvastatin 10 mg (n=18)<br>Colesevelam 3.8 g/atorvastatin 10 mg (n=18)<br>Atorvastatin 80 mg (n=20) | Compared to atorvastatin 10mg, the combination resulted in:<br>• 31% reduction in Total-C vs 27% with atorvastatin 10 mg alone*<br>• 48% reduction in LDL-C vs 38% with atorvastatin 10 mg alone**<br>• 11% increase in HDL-C vs 8% with atorvastatin 10 mg alone<br>• 40% reduction in non-HDL-C vs 35% with atorvastatin 10 mg alone*<br>• Atorvastatin 80 mg had numerically better results on all treatment measures except increase in HDL-C* |

| Study | Study Design | Results (Primary Outcomes of the Study) |
|---|---|---|
| Colesevelam in combination with simvastatin[6] | N=178<br>Placebo (n=33)<br>Simvastatin 10 mg (n=35)<br>WelChol® 3.8 g/simvastatin 10 mg (n=34)<br>Simvastatin 20 mg (n=39)<br>WelChol® 2.3 g/simvastatin 20 mg (n=37) | Compared to simvastatin 10 mg, the combination colesevelam 3.8 g & simvastatin 10 mg resulted in:<br>• 28% reduction in total cholesterol vs 19% with simvastatin 10 mg alone*<br>• 42% reduction in LDL-C vs 26% reduction with simvastatin 10 mg alone**<br>• 33% reduction in Apo-B vs 20% reduction with simvastatin 10 mg alone*<br>• 10% increase in HDL-C vs 3% increase with simvastatin 10 mg alone*<br>• 37% decrease in non-HDL-C vs 24% decrease with simvastatin 10 mg alone*<br>Compared to simvastatin 20mg, the combination colesevelam 2.3 g & simvastatin 20 mg resulted in:<br>• 29% reduction in total cholesterol vs 23% with simvastatin 20 mg alone*<br>• 42% reduction in LDL-C vs 34% reduction with simvastatin 20 mg alone**<br>• 32% reduction in Apo-B vs 26% reduction with simvastatin 20 mg alone*<br>• 4% increase in HDL-C vs 7% increase with simvastatin 20 mg alone*<br>• 37% reduction in non-HDL-C vs 30% reduction with simvastatin 20 mg alone* |
| Colesevelam in combination with lovastatin[6] | N=102<br>Placebo (n=26)<br>Lovastatin (n=26)<br>WelChol® 2.3 g/lovastatin 10 mg together (n=27)<br>WelChol® 2.3 g/lovastatin 10 mg apart (n=23) | Compared to lovastatin 10 mg , the combination of colesevelam 2.3 g & lovastatin together resulted in:<br>• 21% reduction in total cholesterol vs 14% reduction with lovastatin 10 mg alone*<br>• 34% reduction in LDL-C vs 22% reduction with lovastatin 10 mg alone**<br>• 24% reduction in Apo-B vs 16% reduction with lovastatin 10 mg alone*<br>• 4% increase in HDL-C vs 5% increase in HDL-C with lovastatin 10 mg alone<br>• 27% reduction in non-HDL-C vs 19% reduction with lovastatin 10 mg alone*<br>• There were no significant differences noted when taking the combination apart or together |

*Significant ($p<0.05$) compared to baseline
**Combination statistically more effective than HMG-CoA reductase inhibitor alone

Cholestyramine and colestipol have been shown to be equally effective in lowering serum cholesterol concentrations.[4,7] In placebo-controlled clinical trials, colestipol 15 gm/day in divided doses was comparable in efficacy to cholestyramine 12 g/day, with reductions in total cholesterol of 10-15%.[8, 10] A small increase in triglycerides was observed in some patients. Compliance was reported as better with colestipol; however, cholestyramine was rated as more palatable in another study.[8] There are no head-to-head trials comparing cholestyramine or colestipol to colesevelam.

The addition of BAS to other antilipidemic agents, particularly the HMG CoA-reductase inhibitors, results in further lowering of total cholesterol concentrations that could not be achieved with either agent alone.[6,7,10]

**Additional Evidence**

Dose Simplification
All bile acid sequestrants can be dosed once or twice a day. Therefore, no bile acid sequestrant has any intrinsic advantage over another in promoting adherence by its dosing schedule.

Stable Therapy
Colesevelam achieves maximum effect at 2 weeks and maintains its effect over long-term therapy.[6] Studies with cholestyramine have demonstrated efficacy for at least 7 years.[7] There is no information regarding switching therapy from one bile acid sequestrant to another.

Impact on Physician Visits
A search of Medline and Ovid 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 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-$25 per Rx |
| $$ | $26-$50 per Rx |
| $$$ | $51-$75 per Rx |
| $$$$ | $76-$100 per Rx |
| $$$$$ | over $101 per Rx |

Rx=prescription

**Table 7. Relative Cost of Bile Acid Sequestrants**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Cholestyramine + aspartame | packet, powder | Prevalite®*, Questran Light®* | $$$$$ | $$ |
| Cholestyramine + sucrose | packet, powder | Questran®* | $$$$$ | $$ |
| Colesevelam | tablet | Welchol® | $$$$$ | N/A |
| Colestipol | granules, packet, tablet | Colestid® | $$ | N/A |

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

## X. Conclusions

The bile acid sequestrants have shown to have modest efficacy in reducing LDL-C with slight increases in HDL-C. They all possess synergistic activity when added to the HMG-CoA reductase inhibitors (statins). The bile acid sequestrants may provide an alternative therapy to patients who require modest LDL-C reduction and who are refractory or intolerant to other lipid lowering agents, such as the HMG-CoA reductase inhibitors. They may also be useful as adjunctive therapy to statins to help patients reach their NCEP LDL-C goals when the statin alone is insufficient or there are safety issues related to increasing the dose of the statin.

Colestipol has been shown to be comparable in safety and efficacy to cholestyramine. The efficacy of colesevelam appears to be comparable to the other BAS; however, there are no head-to-head trials. Colesevelam has a more favorable adverse reaction profile, particularly in regard to gastrointestinal tolerability. Colesevelam may have a more favorable drug-interaction profile; however, potential drug interactions with BAS may be minimized by adjusting the timing of the doses.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC 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 agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Cholesterol Absorption Inhibitors**
**AHFS Class 240605**
**February 22, 2006**

## I. Overview

At the time of this review, ezetimibe is the only antilipemic agent that is classified as a cholesterol absorption inhibitor. 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.[1]

The cholesterol absorption inhibitors included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

**Table 1. Cholesterol Absorption Inhibitors Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| ezetimibe | tablet | Zetia® | none |

There are no generics or over-the-counter products in this class.

## II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under Antilipemic Agents. The HMG-CoA reductase inhibitors, or "statins" are the most effective antilipemic agents for decreasing LDL cholesterol.[2] They are considered drugs of choice by most specialists for prevention of coronary disease in high-risk patients. Clinical studies have demonstrated that ezetimibe produces relatively moderate LDL reductions in patients with primary hypercholesterolemia, with reductions of LDL-C by about 18%.[1] Ezetimibe's primary role is in combination with a statin in patients unable to achieve or sustain target LDL levels on a statin alone or to reduce the dose of a statin required to achieve target levels.[2] Ezetimibe monotherapy may be useful in patients who are unable to tolerate or are at risk of statin interactions, or those with only mild hypercholesterolemia.

## III. Indications

**Table 2. FDA-Approved Indications for the Cholesterol Absorption Inhibitors**

| Generic Name | Brand Name(s) | FDA Approved Indications |
|---|---|---|
| ezetimibe | Zetia® | • Administered alone or in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary hypercholesterolemia<br>• In combination with atorvastatin or simvastatin for the reduction of elevated total-C and LDL-C levels in patients with homozygous familial hyper-cholesterolemia as an adjunct to other lipid lowering treatments or if such treatments are unavailable<br>• Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia |

## IV. Pharmacokinetics

The bioavailability of ezetimibe is unknown.[2] Following oral absorption, ezetimibe is extensively metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion.[3] Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both parent and metabolite. About 78% and 11% of the dose was recovered in the feces and urine, respectively, over 10 days. Ezetimibe and its metabolite are highly protein bound (>90%). Preclinical studies suggest that ezetimibe has no significant effect on drug metabolizing enzymes and it appears to have minimal propensity to interact with cytochrome P450 substrates. Efficacy in reducing LDL cholesterol levels has been similar when given with or without food.[2]

## V. Drug Interactions

The following moderate drug interactions have been reported with ezetimibe. [2,3]

- Cholestyramine (established)
- Ciprofibrate (probable)
- Clofibrate (probable)
- Colesevelam (probable)
- Colestipol (probable)
- Cyclosporine (probable)
- Fenofibrate (probable)
- Gemfibrozil (probable)
- Warfarin (post-marketing reports)

Cholestyramine appears to significantly reduce the absorption of ezetimibe.[2] Coadministration of ezetimibe with fibric acid derivatives is not recommended because of a potential increased risk of cholelithiasis. Concomitant use of ezetimibe with cyclosporine may increase the plasma concentrations of either drug. Caution should be used when using ezetimibe with cyclosporine and cyclosporine concentrations should be monitored. [3] The International Normalized Ratio should be monitored if ezetimibe is added to warfarin.

## VI. Adverse Drug Events

The most frequent side effect of ezetimibe is flatulence.[1] Other common side effects include abdominal pain, diarrhea, arthralgia, back pain, myalgia, headache, cough, sinusitis and fatigue.[2] More serious side effects include hepatitis, increased liver function test, drug-induced myopathy (very rarely) and rhabdomyolysis (very rarely).

## VII. Dosing and Administration

The recommended dose of ezetimibe is 10 mg once daily.[3] Ezetimibe may be taken at the same time as a HMG-CoA reductase inhibitor. No dosage adjustment 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 in children less than 10 years of age.

## VIII. Effectiveness

**Table 3. Outcomes Evidence for the Cholesterol Absorption Inhibitors**

| Study | Study Design | Efficacy Variables | Results (Primary Outcomes of the Study) |
|---|---|---|---|
| Efficacy and safety of ezetimibe in patients with primary hypercholesterolemia[4] | Multicenter, double-blind, randomized, placebo-controlled study<br><br>Ezetimibe (n=666)<br>Placebo (n=226) | Percent-change from baseline to endpoint in plasma concentration of direct LDL<br><br>Secondary: % change from baseline of LDL (calculated), total-C, HDL, triglycerides | Compared to placebo, ezetimibe resulted in:<br>• 17% decrease in direct LDL vs 0.4% increase with placebo ($p<0.01$) |
| Efficacy and safety of ezetimibe added to ongoing statin therapy in primary hypercholesterolemia<br><br>Statins included are: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin[5] | Multicenter, double-blind, randomized, placebo-controlled study<br><br>15 weeks<br><br>Statin and placebo (n=390)<br>Statin and ezetimibe (n=379) | Mean percent-change in LDL-C from baseline to endpoint | Compared to continued statin therapy, the addition of ezetimibe resulted in:<br>• 25% decrease in LDL-C from baseline compared with 3.7% decrease with continued statin monotherapy |
| Ezetimibe (EZE) coadministered with atorvastatin (ATV) in patients with primary hypercholesterolemia[6] | Randomized, double-blind, placebo-controlled, balanced-parallel group trial<br><br>Placebo (n=60)<br>Ezetimibe (n=65)<br>Atorvastatin 10, 20, 40, or 80mg (n=248)<br>Ezetimibe + atorvastatin 10, 20, 40, or 80mg (n=255) | Percentage reduction in LDL-C for pooled ezetimibe plus atorvastatin vs pooled atorvastatin plus placebo groups | Compared to atorvastatin or ezetimibe alone, the combination of atorvastatin and ezetimibe resulted in:<br>• 54.5% reduction in direct LDL-C vs 42.4% for ATV and 18.4% for EZE[a]<br>• 41.1% reduction in total-C vs 32.1% for ATV and 13.5% for EZE[a]<br>• 32.8% reduction in triglycerides vs 24.5% for ATV and 5.1% for EZE[a]<br>• 7.3% increase in HDL-C vs 4.2% increase with ATV and 4.2% increase for EZE[b]<br>• 45.4% decrease in Apo B vs 36.1% for ATV and 15.4% for EZE[a] |
| Efficacy and safety of ezetimibe (EZE) and lovastatin (LOV) coadministration[7] | Multicenter, randomized, double-blind, placebo-controlled study<br><br>Placebo (n=64)<br>Ezetimibe 10mg (n=72)<br>Lovastatin 10, 20, or 40mg (n=220)<br>Ezetimibe 10mg + lovastatin 10, 20, or 40mg (n=192) | Percent reduction in LDL | Compared with ezetimibe 10 mg or lovastatin all doses pooled, the combination of ezetimibe 10 mg and all lovastatin doses resulted in:<br>• 39% reduction in direct LDL-C vs 19% for EZE and 25% for LOV[c]<br>• 29% reduction in total-C vs 13% for EZE and 18% for LOV[c]<br>• 22% reduction in triglycerides vs 3% for EZE and 11% for LOV[c]<br>• 9% increase in HDL-C vs 3% for EZE and 4% for LOV[c]<br>• 33% reduction in Apo B vs 14% for EZE and 21% for LOV[c] |

| Study | Study Design | Efficacy Variables | Results (Primary Outcomes of the Study) |
|---|---|---|---|
| Pravastatin (PRV) and ezetimibe (EZE) coadministration in primary hypercholesterolemia[8] | Multicenter, double-blind, randomized, placebo-controlled, balanced-parallel – group, 2x4 factorial study<br><br>Placebo (n=65)<br>Ezetimibe (n=64)<br>Pravastatin 10, 20, or 40mg (n=205)<br>Ezetimibe and pravastatin 10, 20, or 40mg (n=204) | Percent-change in LDL-C from baseline | Compared with ezetimibe or pooled pravastatin alone, the pooled combination of pravastatin and ezetimibe resulted in:<br>• 37.7% decrease in direct LDL-C vs 18.7% for EZE and 24.3% for PRV[d]<br>• 27.1% decrease in total-C vs 13.2% for EZE and 17.2% for PRV[d]<br>• 17.6% decrease in triglycerides vs 2.1% for EZE and 7.6% for PRV[d]<br>• 8.1% increase in HDL-C vs 4.1% for EZE and 6.7% for PRV[e]<br>• 30.2% decrease in Apo B vs 14.8% for EZE and 20% for PRV[d] |
| Ezetimibe (EZE) and simvastatin (SIM) combination tablet vs either therapy alone[9] | Randomized, multicenter, double-blind, placebo-controlled, factorial design study<br><br>Placebo (n=148)<br>Ezetimibe 10mg (n=149)<br>Simvastatin 10, 20, 40, or 80mg (n=622)<br>Ezetimibe 10mg and simvastatin 10, 20, 40, or 80mg (n=609) | Mean percent-change in LDL-C from baseline<br><br>Secondary endpoints include other lipid measures | Compared with ezetimibe or pooled simvastatin alone, the pooled combination of simvastatin and ezetimibe resulted in:<br>• 53% mean reduction in LDL-C vs 18.9% for EZE and 39% for SIM[f]<br>• 24.3% decrease in triglycerides vs 10.7% for EZE and 20.8% for SIM[f]<br>• 37.6% decrease in total-C vs 13.3% for EZE and 27.7% for SIM[f]<br>• 7.2% increase in HDL-C vs 5% for EZE and 6.8% for SIM[g]<br>• 42.3% decrease in Apo B vs 14.8% for EZE and 31.6% for SIM[f] |

a. $p<0.01$ for ATV + EZE vs ATV and for ATV + EZE vs EZE
b. $p<0.01$ for ATV + EZE vs ATV only
c. $p<0.01$ for EZE + LOV vs EZE and for EZE + LOV vs LOV
d. $p<0.01$ for PRV + EZE vs PRV and for PRV + EZE vs EZE
e. $p=0.02$ for PRV + EZE vs PRV but was not significant for PRV + EZE vs EZE
f. $p<0.001$ for SIM + EZE vs SIM
g. Not significant for SIM + EZE vs SIM

**Additional Evidence**

Dose Simplification
Ezetimibe can be administered at the same time as most medications, with the exception of bile acid sequestrants.

Stable Therapy
Ezetimibe reaches its maximal response after about 2 weeks of administration and maintains efficacy after long-term therapy.[2]

Impact on Physician Visits
A search of Medline and Ovid 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 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 | |
|---|---|
| $ | $0-25 per Rx |
| $$ | $26-$50 per Rx |
| $$$ | $51-$75 per Rx |
| $$$$ | $76-$100 per Rx |
| $$$$$ | over $101 per Rx |

Rx = prescription

**Table 4. Relative Cost of Cholesterol Absorption Inhibitors**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Ezetimibe | tablet | Zetia® | $$$-$$$$ | N/A |

There are no generics or over-the-counter products 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 LDL-C. Additional data is necessary to determine its effects on HDL-C and triglycerides. HMG-CoA reductase inhibitors 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 LDL 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 an HMG-CoA reductase inhibitor. Additional studies are necessary to determine if the combination of ezetimibe plus a statin is associated with fewer side effects in comparison with increasing the dose of the statin. No trial has yet evaluated clinical outcomes with ezetimibe alone or in combination therapy. Compared to other lipid-lowering adjunctive therapies within alternative drug classes, ezetimibe offers a level of LDL-C reduction which appears to be comparable, although head-to-head comparisons are currently lacking.

Therefore, all brand products within the class appear to 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 most 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**
**February 22, 2006**

# I. Overview

Fibric acid derivatives work by increasing lipoprotein lipase activity and triglyceride clearance. These agents also increase hepatic oxidation of fatty acids, which decreases the secretion of triglyceride rich lipoproteins and enhances the breakdown of very low-density lipoprotein (VLDL). Finally, fibric acid derivatives may increase secretion of cholesterol into the bile.[1,2]

Gemfibrozil has been available generically for many years. This review encompasses all dosage forms and strengths.

**Table 1. Fibric Acid Derivatives Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| fenofibrate | tablet | Triglide® | none |
| fenofibrate micronized | capsule | Antara®, Lofibra® | none |
| fenofibrate nanocrystal | 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

Please refer to this section under Antilipemic Agents. Fibric acid derivatives are the most effective pharmacotherapeutic option for lowering triglycerides (TG). Their main clinical use is for treating hypertriglyceridemia and for increasing low levels of high-density lipoprotein cholesterol (HDL-C). However, fibric acid derivatives can also be used to treat primary hypercholesterolemia but are not as widely used as HMG-CoA reductase inhibitors ("statins") because of a reduced low-density lipoprotein cholesterol (LDL-C) lowering capacity compared to statins. Fibric acid derivatives can also be used to help raise HDL-C. This is important, as there is an inverse relationship between HDL-C and the risk for developing CHD. Every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[3]

# III. Indications

The Food and Drug Administration (FDA) has approved fibric acid derivatives as an adjunct to diet for hyperlipidemias. The following table summarizes the FDA-approved specific indications for each of the fibric acid derivatives in this review.

**Table 2. FDA-Approved Indications for the Single Entity Fibric Acid Derivatives[1,2]**

| Indication | Fenofibrate | Gemfibrozil |
|---|---|---|
| Treatment of primary hypercholesterolemia or mixed dyslipidemia | ✔ | ✔ * |
| Hypertriglyceridemia | ✔ | ✔ |

* To reduce the risk of developing CHD in patients specifically with type II b lipoprotein disorder who do not have a history or symptoms of CHD and who have low HDL-C in addition to increased LDL-C and TG levels.

Two main factors are typically considered when assessing efficacy of fibric acid derivatives: 1) the capacity to reduce lipids, especially triglycerides as this is where the fibric acid derivatives are most effective (along with secondarily modifying TC, LDL-C, and HDL-C) and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention of CHD) and mortality. Table 3 compares the cholesterol modifying effects of the fibric acid derivatives.

**Table 3. Fibric Acid Derivatives' Effects on Cholesterol[1,2]**

| Agent | TG | LDL-C | HDL-C | TC |
|---|---|---|---|---|
| Fenofibrate all formulations | ↓ 29-55% | ↓ 20%* | ↑ 11-23 | ↓ 9-19 |
| Gemfibrozil | ↓ 20-50% | ↓ 0-15%* | ↑ 15-20% | ↓ 15% |

* LDL-C may actually increase

## IV. Pharmacokinetics

Pharmacokinetic studies have shown that Lofibra® 200 mg capsule, Tricor® 160 mg tablet, Tricor® 145 mg nanocrystal tablet, Antara® 130 mg capsule, and Triglide® 160 mg tablet all produce comparable serum fenofibrate levels. Peak plasma concentrations with fenofibrate and fenofibrate micronized occur 6-8 hours after administration and the extent of absorption of the micronized product is increased by 35% when taken with food. Serum protein binding is approximately 99% and steady state is reached within 5 days for both fenofibrate products. Both products are mainly excreted via the urine. The half-life for both fenofibrate and fenofibrate micronized is 20 hours, allowing for once daily dosing for either product.[1,2]

Gemfibrozil reaches peak plasma concentration at 1-2 hours after administration. Rate and extent of gemfibrozil absorption are significantly increased if taken 30 minutes prior to a meal. Gemfibrozil is highly protein bound and approximately 70% is excreted via the urine. Half-life for gemfibrozil (1.5 hours) is shorter than fenofibrate products and thus twice daily dosing is needed.[1,2]

## V. Drug Interactions

Gemfibrozil and fenofibrate should be administered cautiously with HMG-CoA reductase inhibitors due to increased risk for myopathy and rhabdomyolysis.[1] Glucuronidation is an important pathway for renal excretion of lipophilic statins, which appears to be significantly inhibited by gemfibrozil but not by fenofibrate.[4] In clinical studies, serum levels of statins increased 1.9- to 5.7-fold in gemfibrozil-treated subjects but were unchanged in fenofibrate-treated subjects.[5] Thus, fenofibrate may be a more preferential fibric acid derivative when used in combination with a statin due to a reduced potential for a significant drug interaction. All of the fibric acid derivatives may interact with warfarin and proper anticoagulation monitoring is recommended if these agents are used concomitantly.[1,2] Also, fenofibrate should be used cautiously with cyclosporine as cyclosporine levels may be reduced, which may result in decreased effectiveness. Appropriate management requires monitoring and adjustment of the cyclosporine dose if needed.[1,2]

## 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. Table 4 below lists adverse effects reported with the fibric acid derivatives. Incidences of adverse effects are listed as percentages with the placebo incidence listed in parentheses.

**Table 4. Adverse Reactions (%) Reported with the Fibric Acid Derivatives[1,2]**

| Adverse Effect | Fenofibrate* (placebo) | Gemfibrozil (placebo) |
|---|---|---|
| Abdominal pain | 4.6% (4.4%) | 19.6% (11.9%) |
| Headache | 3.2% (2.7%) | 1.2% (1.1%) |
| Abnormal liver function test | 7.5% (1.4%) | R# |
| Diarrhea | 2.3% (4.1%) | 7.2% (6.5%) |
| Nausea | 2.3% (1.9%) | 2.5% (2.1%) |
| Constipation | 2.1% (1.4%) | 1.4% (1.3%) |
| CPK increase | 3.0% (1.4%) | R# |

* Dosage equivalent to 200 mg of each product
# Reported but no incidence provided

## VII. Dosing and Administration

Table 5 summarizes the dosing and administration of each fibric acid derivative.

**Table 5. Dosing and Administration for the Fibric Acid Derivatives[1,2]**

| Agent | Formulation | Dosing & Administration |
|---|---|---|
| Fenofibrate micronized | 43, 130 mg capsules (Antara®) | • primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 130mg daily<br>hypertriglyceridemia, initial dose is 43-130 mg daily |
| | 67, 134, 200 mg capsules (Lofibra®) | • primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 200mg daily<br>hypertriglyceridemia, initial dose is 67-200 mg daily |
| Fenofibrate | 48, 145 mg tablets (Tricor®) | • primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 145 mg daily<br>• hypertriglyceridemia, initial dose is 48 or 145 mg daily |
| | 50, 160 mg tablets (Triglide®) | • primary hypercholesterolemia or mixed hyperlipidemia, initial dose is 160mg daily<br>• hypertriglyceridemia, initial dose is 50-160 mg daily |
| Gemfibrozil | 600 mg tablet (Lopid®) | • initiated and maintained at 600 mg twice daily (maximum dose 1,200 mg/day) |

## VIII. Effectiveness

**Table 6. Outcomes Evidence for the Fibric Acid Derivatives**

| Study | Study Design | Duration | Efficacy Variables | Results |
|---|---|---|---|---|
| Insua et al[6] | Randomized, double-blind, crossover trial<br><br>21 participants with type IIa and IIb hyperlipidemia were randomized to receive gemfibrozil 600 mg daily or micronized fenofibrate 200 mg daily | 6 weeks | To compare the hypolipidemic effects of gemfibrozil and micronized fenofibrate | Results demonstrated:<br><br>• Similar reductions in TG (54% and 46.5%, respectively; $p > 0.05$) and increases in HDL-C (9% and 9%, respectively; $p > 0.05$)<br>• Reductions in LDL-C and TC were greater with fenofibrate micronized compared to gemfibrozil (LDL-C: 27% versus 16%, respectively; $p = 0.0117$) and (TC: 22% versus 15%, respectively; $p = 0.0148$)<br><br>This trial is limited by the fact that the maximum dose of fenofibrate micronized was compared to a subtherapeutic dose of gemfibrozil. The recommended dose of gemfibrozil is 600 mg twice daily. |
| HHS[7] | Randomized, double-blind, placebo-controlled trial<br><br>4,081 men age 40-55 years with a baseline TC of 290 mg/dL and a non-HDL-C $\geq$ 200 mg/dL were randomized to receive gemfibrozil 1200 mg daily or placebo | 5 years | Primary endpoint: risk of coronary heart disease measured by incidence of cardiac events<br><br>Secondary endpoint: total mortality | Compared to placebo, gemfibrozil daily resulted in:<br>• 34% ↓ in coronary heart disease*<br>• No significant difference between groups in total mortality<br><br>A post-trial evaluation done 3.5 years after the HHS showed[8]:<br>• No difference in cardiovascular or total mortality (total mortality was slightly higher in the gemfibrozil group, but this was not statistically significant)<br><br>An ancillary study (Helsinki II)[9] conducted in patients with CHD demonstrated a non-significant ↑ in nonfatal MI, cardiac deaths and non-cardiac deaths with gemfibrozil. |

| Study | Study Design | Duration | Efficacy Variables | Results |
|---|---|---|---|---|
| VA-HIT[10] | Randomized, double-blind, placebo-controlled trial<br><br>2,531 men age < 74 years with CHD and a baseline HDL-C ≤ 40 mg/dL and LDL-C ≤ 140 mg/dL were randomized to receive gemfibrozil 1200 mg daily or placebo | 5.1 years | Primary endpoint:<br>nonfatal MI or death from coronary causes | Compared to placebo, gemfibrozil resulted in:<br>• 22% ↓ risk of nonfatal MI or death due to CHD (17.3% vs placebo = 21.7%) p = 0.006*<br>• 24% ↓ risk for nonfatal MI, death due to CHD, or confirmed stroke (placebo = 26%, tx = 20.4%; p < 0.001)<br>• A non-significant difference was seen in all-cause mortality (placebo = 17.4%, tx = 15.7%; p = 0.23)<br><br>A post-trial analysis[12] showed that gemfibrozil 600 mg twice daily resulted in:<br>• 11% ↓ risk for CHD events for every 5 mg/dL increase in HDL-C (p = 0.02) |
| DAIS[11] | Randomized, placebo-controlled trial<br><br>731 type 2 diabetics with at least one coronary lesion were randomized to receive fenofibrate 200 mg daily or placebo | 3 years | Primary endpoint:<br>mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter | Compared to placebo, fenofibrate resulted in:<br><br>• A smaller increase in percentage of diameter stenosis (mean 2.11 vs 3.65) p = 0.02*<br>• A smaller decrease in minimum lumen diameter (-0.06 vs -0.10mm) p= 0.029*<br>• A non-significant smaller decrease in mean segment diameter (-0.06 vs – 0.08mm) p =0.171*<br>• A significant change in all lipid parameters (total cholesterol, HDL,LDL, and TG) vs placebo p ≤ 0.001<br><br>The trial was not powered to examine clinical endpoints. |
| FIELD[12] | Randomized, double-blind, placebo-controlled trial<br><br>9975 participants (2131 with CVD) with type 2 diabetes were assigned to receive fenofibrate 200 mg daily of placebo | 5 years | Primary endpoint:<br>coronary events (CHD death or non-fatal MI)<br><br>Other endpoints:<br>total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization | Compared to placebo, fenofibrate resulted in:<br><br>• A non-significant ↓ in coronary events 5.9% vs 5.2% placebo p = 0.16*<br>• A corresponding 24% ↓ in non-fatal MI p = 0.010<br>• A non-significant ↑ in CHD mortality p = 0.22<br>• A ↓ in total cardiovascular events from 13.9% to 12.5%. p = 0.035<br>• This included a 21% ↓ in coronary revascularization p= 0.003<br>• There was a non-significant ↑ in total mortality with fenofibrate 7.3% vs 6.6% with placebo p =0.18 |

CHD = Coronary heart disease; CVD = Cardiovascular disease; MI = myocardial infarction
* = primary endpoint

**Additional Evidence**

Dose Simplification:
The half-life of fenofibrate (20 hours) is substantially longer compared to gemfibrozil (1.5 hours)[1,2] This allows for once daily dosing of fenofibrate versus twice daily dosing of gemfibrozil. There are no studies to support differences in compliance or clinical outcomes between QD and BID dosing schedules for this drug class.

Stable Therapy:
A study was conducted to determine lipid effects from a conversion of gemfibrozil to fenofibrate in patients on stable statin therapy.[13] Subjects (n= 98) were converted from gemfibrozil (mean dose 1200 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, patients showed statistically significant improvements in mean total cholesterol, triglycerides, HDL, and non-HDL ($p < 0.005$) Specifically, more patients achieved a TG goal < 200mg/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:
A search of Medline and Ovid 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 medication within this 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 costs 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 dosing 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-$25 per Rx |
| $$ | $26-$50 per Rx |
| $$$ | $51-$75 per Rx |
| $$$$ | $76-$100 per Rx |
| $$$$$ | Over $100 per Rx |

Rx=prescription

**Table 7. Relative Cost of Fibric Acid Derivatives**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Fenofibrate | tablet | Triglide® | $$$ | N/A |
| Fenofibrate micronized | capsule | Antara®, Lofibra®, | $$$$ | N/A |
| Fenofibrate nanocrystal | tablet | Tricor® | $$$$ | N/A |
| Gemfibrozil | tablet | Lopid®* | $$$$ | $ |

*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 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 should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C despite LDL-C goal attainment.

Fibric acid derivatives are used less frequently than HMG-CoA reductase inhibitors, primarily because of a reduced LDL-C lowering capacity compared to these "statins." The main place in therapy for fibric acid derivatives is for the treatment of hypertriglyceridemia, in which they have a greater capacity to reduce triglycerides compared to statins.

Gemfibrozil is available generically. There are numerous formulations of fenofibrate of which no particular product offers a distinct clinical advantage. There are no major clinically relevant differences between gemfibrozil and fenofibrate with regard to triglyceride lowering efficacy, tolerability and safety. Notably, both gemfibrozil and fenofibrate are supported by clinical trials that show reduction in patient-oriented outcomes (CHD morbidity and/or mortality)[7-10,12] However, neither product has demonstrated a decrease in all cause mortality as has been shown with the HMG-CoA reductase inhibitors. Both gemfibrozil and fenofibrate should be administered cautiously with concomitant HMG-CoA reductase inhibitors; 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 OTC 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 of the fibric acid derivatives to determine cost effective products and possibly designate one or more preferred agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of HMG-COA Reductase Inhibitors–Single Entity**
**AHFS Class 240608**
**February 22, 2006**

# I. Overview

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. The inhibition of this enzyme decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein (LDL) cholesterol receptors and enhanced clearance of circulating LDL cholesterol (LDL-C).

Lowering total cholesterol and LDL-C and raising high-density lipoprotein cholesterol (HDL-C) are important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD). Every 1% reduction in LDL-C results in a 1.7% decrease in the risk of a major coronary event. An inverse relationship exists between HDL-C and the risk for developing CHD—every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[1] Thus, pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is beneficial. In the US in 2003, 865,000 adults experienced a new or recurrent myocardial infarction (MI) and up to 20% of those resulted in death.[2] Given that CHD is the leading cause of death in the U.S. for both men and women and that approximately 100 million Americans have total cholesterol levels greater than or equal to 200mg/dL (with 33.5 million American adults having levels of 240mg/dL or above),[2] it seems prudent to screen for and aggressively treat patients with hyperlipidemia.

HMG-CoA reductase inhibitors are considered first-line agents for treating hyperlipidemia due to their ability to lower total cholesterol and LDL-C.[3,4] These agents also have the ability to moderately raise HDL-C. Table 1 lists the HMG-CoA reductase inhibitors included in this review. 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 Agents |
|---|---|---|---|
| atorvastatin | Tablets | Lipitor® | none |
| fluvastatin | Capsules<br>Extended-release tablets | Lescol®<br>Lescol XL® | Lescol®<br>Lescol XL® |
| lovastatin | Extended-release tablets, tablets | Mevacor®*<br>Altoprev® | lovastatin, Altoprev®<br>(Altocor®) |
| pravastatin | Tablets | Pravachol® | none |
| rosuvastatin | Tablets | Crestor® | Crestor® |
| simvastatin | Tablets | Zocor® | Zocor® |

* Generic available in at least one dosage form or strength

# II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under Antilipemic Agents. As noted above, the HMG-CoA reductase inhibitors are considered first-line agents for treating hyperlipidemia due to their ability to favorably impact multiple lipid parameters.

## III. Indications

The Food and Drug Administration (FDA) approved all HMG-CoA reductase inhibitors for use in adjunct to diet for the reduction of total cholesterol and LDL-C in patients with primary hypercholesterolemia. Table 2 summarizes the FDA-approved indications for each of the statins in this review.

**Table 2. FDA-Approved Indications for the Single Entity HMG-CoA Reductase Inhibitors [5,6]**

| Indication | Atorvastatin | Fluvastatin/ Fluvastatin XL | Lovastatin/ Lovastatin ER | Pravastatin | Rosuvastatin | Simvastatin |
|---|---|---|---|---|---|---|
| Primary Prevention of Cardiovascular Events | ✔ | | ✔ | ✔ | | ✔ * |
| Secondary Prevention of Cardiovascular Events | | ✔ ** | | ✔ | | ✔ * |
| Primary Hypercholesterolemia/ Mixed Dyslipidemia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Homozygous Familial Hyperlipidemia | ✔ | | | | ✔ | ✔ |
| Primary Dysbetalipoproteinemia | ✔ | | | ✔ | | ✔ |
| Regression of Coronary Atherosclerosis | | ✔ | ✔ | ✔ | | |
| Heterozygous Familial Hypercholesterolemia in Adolescents | ✔ | | ✔ | ✔ | | ✔ |
| Hypertriglyceridemia | ✔ | | | ✔ | ✔ | ✔ |

*Approved for patients at high-risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease to reduce mortality by reducing CHD deaths, to reduce the risk of non-fatal MI and stroke, and to reduce the need for coronary and non-coronary revascularization procedures.
** To reduce risk of undergoing coronary revascularization procedures in patients with CHD.

## IV. Pharmacokinetics

Minor differences exist between the statins in regards to pharmacokinetic parameters. Half-life is one parameter that separates some statins from others. In particular, atorvastatin and rosuvastatin are the only two statins within this class that have half-lives over 15 hours, allowing for more flexible dose scheduling. 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. Table 3 summarizes various pharmacokinetic parameters of the statins.

**Table 3. Pharmacokinetic Parameters of the Single Entity HMG-CoA Reductase Inhibitors[5,6]**

| Parameters | Atorvastatin | Fluvastatin/ Fluvastatin XL | Lovastatin/ Lovastatin ER | Pravastatin | Rosuvastatin | Simvastatin |
|---|---|---|---|---|---|---|
| Systemic Bioavailability | 30% | 24%<br>XL: 29% | < 5%<br>ER: 190% compared to lovastatin | 17% | 20% | < 5% |
| Protein Binding | ≥ 98% | 98% | > 95% | 50% | 88% | 95% |
| Lipid Solubility | Hydrophilic | Hydrophilic | Lipophilic | Hydrophilic | Hydrophilic | Lipophilic |
| Crosses Blood-brain Barrier | No | No | Yes | No | No | Yes |
| Main Metabolizing Enzyme | CYP3A4 | CYP2C9 | CYP3A4 | None | CYP2C9 | CYP3A4 |
| T ½ Elimination, Hours | 15-30 | 0.5-2.3<br>XL: Not given | 2.9<br>ER: Not given | 1.3-2.8 | 19 | 2-3 |
| Active Metabolites | Yes | No | Yes | No | No | Yes |

## V. Drug Interactions

Clinically important drug interactions exist for the 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 CYP34A, they share similar drug interactions. Fluvastatin and rosuvastatin are 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. Specific drug interaction studies have not been performed with lovastatin ER; however, the drug interactions listed in the package insert for lovastatin ER are similar to those seen with immediate release lovastatin.

**Table 4. Significant Drug-Drug Interactions for the Single Entity HMG-CoA Reductase Inhibitors**[7]

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin | 1 | Azole antifungals (fluconazole, itraconazole, ketoconazole, voriconazole) | Azole antifungal agents may inhibit the first-pass hepatic metabolism of HMG-CoA reductase inhibitors. |
| Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin | 2 | Bile acid sequestrants (cholestyramine, colestipol) | The HMG-CoA reductase inhibitors may adsorb to the bile acid sequestrant, reducing the GI absorption of the HMG-CoA reductase inhibitors. |
| Atorvastatin, lovastatin, simvastatin | 2 | Carbamazepine | Increased metabolism (CYP3A4) of the HMG-CoA reductase inhibitors by carbamazepine is suspected. |
| Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin | 1 | Cyclosporine | Decreased metabolism of certain HMG-CoA reductase inhibitors is suspected. |
| Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin | 1 | Fibric acid derivatives (fenofibrate, gemfibrozil) | Severe myopathy or rhabdomyolysis may occur. |
| Atorvastatin, lovastatin, simvastatin | 1 | Macrolides (azithromycin, clarithromycin, erythromycin and telithromycin) | Inhibition of metabolism (CYP3A4) is suspected. |
| Atorvastatin, lovastatin, simvastatin | 1 | Nefazadone | Possible nefazadone inhibition of metabolism of HMG-CoA Reductase inhibitors by the cytochrome P450 3A4 isozyme. |
| Atorvastatin, lovastatin, simvastatin | 2 | Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) | Possible inhibition of first-pass metabolism (CYP3A4) of the HMG-CoA reductase inhibitors. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 2 | Protease inhibitors (indinavir, ritonavir, amprenavir, nelfinavir, saquinavir, atazanavir, lopinavir) | Inhibition of first-pass metabolism (CYP3A4) in the GI tract is suspected. |
| Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin | 2 | Rifamycins (rifabutin, rifampin, rifapentine) | Inhibition of first-pass metabolism (CYP3A4) in the GI tract is suspected. |
| Fluvastatin, lovastatin, rosuvastatin, simvastatin | 2 | Warfarin | Inhibition of warfarin hepatic metabolism is suspected. |

Significance level 1= major severity
Significance level 2 = moderate severity

Most of the drug interactions listed above can be managed with appropriate dosing modifications and monitoring. Atorvastatin, lovastatin, and simvastatin should not be used concomitantly with nefazodone and protease inhibitors unless benefits of therapy outweigh the risks for potential side effects. Nefazodone and protease inhibitors are used in specific patient populations and not the general population for which we are evaluating the use of statins. The use of a particular statin in the general population should take into consideration other comorbid conditions and medications in order to select the most suitable therapy.

## VI. Adverse Effects

Statins are generally well tolerated with minor common side effects such as abdominal pain, constipation, gas/flatulence, and headache. More serious but rare side effects of statins include increases in liver enzymes and myopathy accompanied by elevations in creatinine kinase, which can progress to rhabdomyolysis and acute renal failure. Routine liver function monitoring is recommended with each statin. It is suggested that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation or elevation in dose and periodically thereafter.[5,6] Increases in hepatic transaminases > 3x the upper limit of normal (ULN) have been reported with each statin (0.5%-2.0%) and appear to be dose-dependent (risk increases as the statin dose increases).[7,8] Elevations in hepatic transaminases frequently reverse with a reduction in dose or suspension of therapy. Upon re-challenge or initiation of another statin, elevations in liver enzymes do not often occur.[8] Myositis (defined as elevated creatinine kinase—generally > 10 times the ULN—plus muscle aches/weakness) has also been reported with each statin (0.1- 0.5%), as has rhabdomyolysis when statins are used as monotherapy (0.04-0.2%).[9] However, no clear differences exist between the statins in the rates of these rare but serious adverse reactions.[8]

Additionally, in regard to the minor adverse reactions, no clear differences seem to exist between the drugs in this class. Patients that do not tolerate one statin generally may tolerate another (tolerability differences between statins exist for unknown reasons).

Beginning in 2004, Public Citizen, a consumer advocacy group, stated that the incidence of rhabdomyolysis is increased with rosuvastatin. The FDA has responded to this group, and the most recent FDA statement from March 2005 is listed below:

> "Rhabdomyolysis (serious muscle damage) has been reported in patients taking Crestor as well as other statin drugs. To date, it does not appear that the risk is greater with Crestor than with other marketed statins. However, the labeling for Crestor is being revised to highlight important information on the safe use of Crestor to reduce the risk for serious muscle damage, especially at the highest approved dose of 40 mg. In addition, a study has found that the amount of drug in the blood of a diverse group of Asian patients taking Crestor was two times higher than for Caucasian patients in the study. Therefore, the labeling for Crestor will now recommend a lower starting dose of 5 mg for Asian patients. Kidney failure of various types has also been reported in patients treated with Crestor as well as other statins. FDA has determined that there is not enough evidence to conclude that kidney damage is a direct result of Crestor therapy. If you are currently taking Crestor or any statin and develop signs and symptoms of muscle pain and weakness, fever, dark urine, nausea or vomiting, you should contact your healthcare professional right away."[10]

**Table 5. Adverse Reactions (%) Reported with the Single Entity HMG-CoA Reductase Inhibitors [5,6]**

| Adverse Effects | Atorvastatin | Fluvastatin/ Fluvastatin XL | Lovastatin/ Lovastatin ER | Pravastatin | Rosuvastatin | Simvastatin |
|---|---|---|---|---|---|---|
| Abdominal Pain | 0 - 3.8 (0.7) | 2.1 – 3.8 (2.0) / 3.7 (3.8) | 2.0 – 2.5 (1.6) | 5.4 (6.9) | >2* | 3.2 (3.2) |
| Asthenia | 0 – 3.8 (1.9) | N/A / N/A | 1.2 – 1.7 (1.4) | N/A | 2.7 (2.6) | 1.6 (2.5) |
| Constipation | 0 – 2.5 (1.8) | 1.8 – 2.8 (2.5) / 2.3 (3.3) | 2.0 – 3.5 (1.9) | 4.0 (7.1) | >2* | 2.3 (1.3) |
| Diarrhea | 0 – 5.3 (1.5) | 1.5 – 2.5 (2.1) / 3.3 (4.2) | 2.2 – 2.6 (2.3) | 6.2 (5.6) | 3.4 (2.9) | 1.9 (2.5) |
| Dizziness | ≥ 2* | 0.5 – 1.1 (1.8) / 1.9 (2.5) | 0.5 – 1.2 (0.7) | 3.3 (3.2) | >2* | N/A |
| Dyspepsia | 1.3 – 2.8 (4.1) | 4.7 – 7.3 (2.3) / 3.5 (3.2) | 1.0 – 1.6 (1.9) | N/A | 3.4 (3.1) | 1.1 (N/A) |
| Flatulence | 1.1 – 2.8 (3.3) | 1.6 – 2.5 (2.2) / 1.4 (2.5) | 3.7 -4.5 (4.2) | 2.7 (3.4) | N/A | 1.9 (1.3) |
| Headache | 2.5 – 16.7 (7.0) | 1.9 – 3.8 (3.0) / 4.7 (7.8) | 2.1 – 3.2 (2.7) | 6.2 (3.9) | 5.5 (5.0) | 3.5 (5.1) |
| Myalgia | 0 – 5.6 (1.1) | 1.7 – 2.7 (2.3) / 3.8 (4.5) | 1.8 – 3.0 (1.7) | 2.7 (1.0) | 2.8 (1.3) | 1.2 (1.3) |
| Nausea | ≥ 2* | 0.8 – 2.0 (1.4) / 2.5 (2.0) | 1.9 – 2.5 (2.5) | 7.3 (7.1) | 3.4 (3.1) | 1.3 (1.9) |

Number in parentheses is the incidence in percent reported for placebo
N/A = Not available

**Precautions**

Rosuvastatin: The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients.[5,6] Rosuvastatin is the only agent in the statin class that has precautionary statements that are specific to a particular ethnic group.

## VII. Dosing and Administration

All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin non extended-release products, which should be divided into twice daily dosing. Minor differences in administration exist between the statins but none of these are considered clinically relevant enough to provide advantages of one statin over another.

**Table 6. Dosing and Administration for the Single Entity HMG-CoA Reductase Inhibitors [5,6]**

| | Atorvastatin | Fluvastatin/ Fluvastatin XL | Lovastatin/ Lovastatin ER | Pravastatin | Rosuvastatin | Simvastatin |
|---|---|---|---|---|---|---|
| Initial Dose | 10-20 mg QD | 20-80 mg QD | 20 mg QD | 40 mg QD | 5-20 mg QD | 20-40 mg QD |
| Dosing Range | 10-80 mg QD | 20-80 mg* QD | 10-80 mg# QD | 10-80 mg QD | 5-40 mgQD | 5-80 mg QD |
| Maximum Dose | 80 mg QD | 80 mg QD | 80 mg QD | 80 mg QD | 40 mgQD | 80 mg QD |
| Administration | Can be taken anytime of the day with or without food | Should be taken at bedtime | Should be taken with evening meal (morning and evening if BID) | Should be taken on an empty stomach or at bedtime | Can be taken anytime of the day with or without food | Should be taken in the evening |
| Special considerations for initiating therapy | LDL-C reduction ≥ 45%, initiate at 40 mg QD | LDL-C reduction < 25%, initiate at 20 mg QD; LDL-C reduction > 25%, initiated based on needed reduction | LDL-C < 20%, initiate at 10 mg/day | Initiate at 10 mg/day in patients with significant renal or hepatic dysfunction | In Asian patients initiate at 5 mg once a day | LDL-C reduction ≥ 45% or is deemed at high risk for a CHD event, initiate at 40 mg QD |

* 80mg dose of non-extended-release formulation should be given as 40 mg BID.
# Non extended release formulations can be given QD or BID.

## VIII. Effectiveness

Two main factors are typically considered when assessing efficacy of statins: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the target of NCEP-ATP III guidelines; and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality. HMG-CoA Reductase Inhibitors reduce total cholesterol, LDL-C, and triglycerides while raising HDL-C in a dose-dependent manner.[5,6] Differences do exist however, between the statins and their cholesterol-lowering capacity (including LDL-C lowering capacity). Table 7 below compares the cholesterol-lowering effects of each statin.

**Table 7. Single Entity HMG-CoA Reductase Inhibitors' Effects on Cholesterol Levels[5,6]**

| Statin | Daily Dosage Range | Effect On: | | | |
|---|---|---|---|---|---|
| | | TC | LDL-C | TG | HDL-C |
| Atorvastatin | 10 mg – 80 mg | ↓ 29-45% | ↓ 39-60% | ↓ 19-37% | ↑ 5-9% |
| Fluvastatin/ Fluvastatin XL | 20 mg – 80 mg | ↓ 17-27% / ↓ 25% | ↓ 22-36% / ↓ 35% | ↓ 12-23% / ↓ 19% | ↑ 3-9% / ↑ 7% |
| Lovastatin/ Lovastatin ER | 10 mg – 80 mg | ↓ 16-34% | ↓ 21-42% | ↓ 6-27% | ↑ 2-9% |
| Pravastatin | 10 mg – 80 mg | ↓ 16-27% | ↓ 22-37% | ↓ 11-24% | ↑ 2-12% |
| Rosuvastatin | 5 mg-40 mg | ↓ 24-40% | ↓ 28-43% | ↓ 45-60% | ↑ 3-17% |
| Simvastatin | 5 mg – 80 mg | ↓ 19-36% | ↓ 26-47% | ↓ 12-33% | ↑ 8-16% |

TC = Total Cholesterol LDL-C = Low-density Lipoprotein Cholesterol TG = Triglycerides HDL-C = High-density Lipoprotein Cholesterol

Since LDL-C reduction is the focus of the NCEP-ATP III[3,4] treatment guidelines, Table 8 below provides a dose-based comparison of the statins and their ability to lower LDL-C.

**Table 8. Single Entity HMG-CoA Reductase Inhibitor Dose Related LDL-C Reductions[11]**

| Statin | Usual Daily Dose | LDL-C Reduction |
|---|---|---|
| Atorvastatin | Initial: 10 mg once<br>Maximum:80 mg once | 35%-40%<br>50%-60% |
| Fluvastatin/ Fluvastatin XL | Initial: 20 mg once<br>Maximum IR: 40 mg BID<br>Maximum XL: 80 mg once | 20%-25%<br>30%-35%<br>35%-38% |
| Lovastatin/ Lovastatin ER | Initial: 10 mg once<br>Maximum: 80 mg once<br>Initial ER: 20 mg once<br>Maximum ER: 60 mg once | 25%-50%<br>35%-40%<br>20-25%<br>40%-45% |
| Pravastatin | Initial: 40 mg once<br>Maximum: 80 mg once | 30%-35%<br>35%-40% |
| Rosuvastatin | Initial: 10 mg once<br>Maximum: 40 mg once | 45%-50%<br>50%-60% |
| Simvastatin | Initial: 20 mg once<br>Maximum: 80 mg once | 35%-40%<br>45%-50% |

Randomized controlled trials (RCTs) that measured patient-oriented outcomes (morbidity parameters and mortality) exist for each of the statins, with the exception of fluvastatin XL, lovastatin ER, and rosuvastatin. Major RCTs that measured patient-oriented outcomes are summarized on the following pages for each drug in this class.

**Table 9. Outcomes Evidence for the Single Entity HMG-CoA Reductase Inhibitors**

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| **Atorvastatin** | | | |
| AVERT[12]<br><br>80 mg/day atorvastatin vs percutaneous coronary transluminal angioplasty in ischemic events and revascularization | Randomized, multicentered study<br><br>n = 341<br><br>1.5 years | Number of ischemic events and/or need for revascularization | Compared to revascularization procedure, atorvastatin 80 mg/day resulted in:<br>• 13% of patients receiving atorvastatin compared to 21% of patients receiving revascularization experienced an ischemic event (p = 0.048) |
| MIRACL[13]<br><br>80 mg/day atorvastatin vs placebo initiated 24-96 hrs after acute coronary syndromes and the reduction of death and non-fatal ischemic events | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 3,086<br><br>16 weeks | **Primary endpoint** defined as death, non-fatal acute MI, cardiac arrest with resuscitation and recurrent symptomatic myocardial ischemia requiring hospitalization | Compared to placebo, atorvastatin 80 mg/day resulted in:<br>• 16% ↓ risk of a composite of death, nonfatal acute MI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia requiring hospitalization (placebo =17.4%, tx =14.8%; p = 0.048)*<br>• no statistically significant differences were found in the individual components of the above primary outcome with the exception of recurrent ischemia requiring hospitalization 26%↓ risk with atorvastatin; p = 0.02)<br>• 50% ↓ risk of fatal and nonfatal stroke (placebo = 1.6%, tx = 0.8%; p = 0.045) |
| GREACE[14]<br><br>Atorvastatin 10 mg/day vs atorvastatin 80 mg/day in clinical outcomes and lipid levels | Randomized, single centered study<br><br>n = 1,600<br><br>3 years | Correlation of lipid levels with coronary mortality and MI | Compared to placebo (termed 'usual care'), atorvastatin 10 mg titrated to 80 mg/day (mean dose 24 mg/day) resulted in:<br>• 51% ↓ risk in CHD recurrent event or death (placebo =24.5%, tx =12%; p < 0.0001)*<br>• 43% ↓ risk in total mortality (placebo =5%, tx =2.9%; p = 0.0021)*<br>• 47% ↓ risk of stroke (placebo = 2.1%, tx = 1.1%; p = 0.034)*<br>• 47% ↓ risk of coronary mortality (placebo =4.8%, tx =2.5%; p = 0.0017)<br>• 54% ↓ risk of coronary morbidity (p < 0.0001) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| ASCOT-LLA[15]<br><br>Atorvastatin 10 mg/day vs placebo in the primary prevention of CHD | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 10,305<br><br>3.3 years | **Primary endpoint** defined as nonfatal MI and fatal CHD<br>**Secondary endpoint** defined as all cause mortality, cardiovascular death, total cardiovascular events, revascularization and fatal/non-fatal stroke | Compared to placebo, atorvastatin 10 mg/day resulted in:<br>• 36% ↓ risk of a composite nonfatal MI and fatal CHD (placebo = 3.0%, tx = 1.9%; p = 0.0005)*<br>• 21% ↓ risk in total CV events and procedures (placebo = 9.5%, tx = 7.5%; p = 0.0005)<br>• 29% ↓ risk for total coronary events (placebo = 4.8%%, tx = 3.4%; p = 0.0005)<br>• Differences in ↓ risk in all cause mortality was not significant; p = 0.1649<br>• 27% ↓ risk of fatal or nonfatal stroke (placebo = 2.4%, tx = 1.7%; p = 0.0236) |
| CARDS[16]<br><br>Atorvastatin 10 mg/day vs placebo in primary prevention of major cardiovascular events | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 2835<br><br>4 years, termination of trial (2 years early) | **Primary outcome** defined as any acute coronary heart event, revascularizations and stroke<br>**Secondary outcomes** included total mortality and any acute hospital verified CV endpoint | Compared to placebo, atorvastatin 10 mg/day resulted in:<br>• 37% ↓ risk of major cardiovascular event (placebo = 9.0%, tx = 8.8%; p=0.001)*<br>• 36% ↓ risk of acute coronary events (placebo = 5.5% tx = 3.6%)*<br>• 31% ↓ risk of coronary revascularizations (placebo = 2.4%, tx = 1.7%)*<br>• 48% ↓ risk of stroke (placebo = 2.8%, tx = 1.5%)*<br>• 27% ↓ in death rate ( placebo = 5.8%, tx = 4.3%; p = 0.059) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| TNT[17]<br><br>Atorvastatin 10 mg/day vs atorvastatin 80 mg/day in secondary prevention of cardiovascular events | Randomized, double blinded, placebo controlled, multicentered, parallel group study<br><br>n = 10,003<br><br>5 years | **Primary endpoint** defined as time to CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke **Secondary endpoints** included any occurrence of a major coronary event, cerebrovascular event, and all cause mortality | Compared 10 mg to 80 mg atorvastatin resulting in:<br>• 22%↓ (HR 0.78) in the primary composite efficacy including death from CHD, non-fatal non-procedural related MI, resuscitation after cardiac arrest, fatal or non-fatal stroke (10 mg = 8.7%, 80 mg = 10.9%; p = 0.001)*<br>• 22% ↓ (HR 0.77) risk of cerebrovascular events (10 mg = 5.0%, 80 mg = 3.9%; p = 0.007)<br>• 16% ↓ (HR 0.81) risk of having any cardiovascular events (10 mg = 33.5%, 80 mg = 28.1%; p = <0.001)<br>• 19%↓ (HR 0.79) risk of having any coronary event (10 mg = 26.5%, 80 mg = 21.6%; p = <0.001) |
| IDEAL[18]<br><br>Atorvastatin 80 mg vs 20 mg simvastatin and secondary prevention of cardiovascular events | Randomized, blinded, open label, prospective study<br><br>n = 8,888<br><br>6 years | **Primary endpoint**: occurrence of a major coronary event, defined as coronary death, confirmed non-fatal acute MI, or cardiac arrest with resuscitation | Compared atorvastatin 80 mg vs simvastatin 20 mg resulting in:<br>• A major coronary event* 9.3% of atorvastatin group versus 10.4% of simvastatin group (HR 0.89; p = 0.07) but results were not significant<br>• Non-fatal MI: 6% with atorvastatin versus 7.2% with simvastatin (HR 0.83; p = 0.020)<br>• Major cardiovascular events (primary outcome + stroke:12% with atorvastatin versus 13.7% with simvastatin (HR 0.87; p = 0.02)<br>• Occurrence of any coronary event: in 20.2% with atorvastatin versus 23.8% with simvastatin (HR 0.84;p < 0.001)<br>• There were no differences between the 2 groups in risk of all cause mortality.<br>• There was a higher rate of drug discontinuation with atorvastatin 1% versus 0.1% simvastatin due to transaminase elevations. (p < 0.001) |
| REVERSAL[19]<br><br>Atorvastatin 80 mg vs 40 mg pravastatin and intensive lipid lowering on coronary artery atheroma burden and progression. | Randomized, double blinded, active control, multicentered study<br><br>n = 654<br><br>3 years | **Primary endpoint:** the percentage change in atheroma volume (follow up minus baseline) | Compared atorvastatin 80mg vs pravastatin 40mg resulting in:<br>• Significant lower progression rate in the atorvastatin group (p = 0.02)<br>• Similar differences between groups, including change in total atheroma volume (p = 0.02), change in percentage in atheroma volume (p < 0.001) and change in atheroma volume in the most severely diseased 10-mm vessel sub segment (p < 0.01)<br>• Progression of coronary atherosclerosis occurred in the 2.7% of the pravastatin group (2.7%; p = 0.001 compared with baseline)<br>• Progression did not occur in the atorvastatin group (-0.4%; p = 0.98) compared with baseline. |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| PROVE-IT[20]<br><br>Atorvastatin 80 mg vs pravastatin 40 mg in secondary prevention of death from any cause or cardiovascular outcome. | Randomized, double blinded, double dummy, multicentered study<br><br>n = 4162<br><br>3 years | **Primary endpoint**: composite death from any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization and stroke | Compared atorvastatin 80 mg to pravastatin 40 mg and resulted in:<br>• 16%↓ with atorvastatin in composite death from any cause, myocardial infarction, unstable angina requiring hospitalization, revascularization and stroke. p = 0.005<br>• Median LDL-C levels achieved during treatment was 95mg/dl with 40mg pravastatin and 62mg/dl with 80mg atorvastatin (p<0.001) |
| **Fluvastatin** | | | |
| LIPS[21]<br><br>Fluvastatin 40 mg/day vs placebo in secondary prevention | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 1,677<br><br>3.9 years | **Primary outcome** defined as survival time free of cardiac death, non-fatal MI or reinterventional procedures | Compared to placebo, fluvastatin 40 mg BID resulted in:<br>• 22% ↓ risk of a composite of cardiac death, nonfatal MI, or reinterventional procedure (placebo =26.7%, tx =21.4%; p = 0.01)*<br>• Nonsignificant trends towards ↓ cardiac death (p = 0.07), and combined cardiac death + nonfatal MI (p = 0.07) |
| FLORIDA[22]<br><br>Fluvastatin 80 mg vs placebo and effect on ischemia and secondary prevention following an acute myocardial infarction | Randomized, placebo controlled, double blinded, parallel study<br><br>n = 540<br><br>1 year | **Primary endpoint:** composite endpoint, consisting of the presence of either ischemia on ambulatory electrocardiograph monitoring at 12 months or the occurrence of a major clinical event during the study | Compared fluvastatin 80 mg to placebo and resulted in:<br>• After 12 months the total cholesterol (TC) level was reduced by 13% and LDL-C by 21% in the fluvastatin treatment group. Both TC and LDL-C increased by 9% in the placebo group (p < 0.001 between groups)<br>• At baseline, ischemia on ambulatory electrocardiograph was only present in 11% of the patients, while absent in the remaining 77%. At 6 weeks and 12 months, the patients with ischemia no longer showed signs of ischemia (no p value)<br>• Fluvastatin treatment did not affect ischemia on ambulatory electrocardiograph, nor the occurrence of any major clinical events as compared to placebo ( no p value)<br>• Post hoc analysis in patients with the most pronounced ischemia at baseline showed a trend for a beneficial effect of Fluvastatin on major clinical events (p = 0.084) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| **Lovastatin** | | | |
| ACAPS[23]<br><br>Lovastatin 20-40 mg/day vs placebo in primary prevention of cardiovascular events | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 919<br><br>2.8 years | **Primary objective** was to assess the effects of treatment on the average 3 year progression **Secondary objective** determined treatment effects on the incidence of major atherosclerotic events | Compared to placebo, lovastatin 20-40 mg/day resulted in:<br>• ↓ risk in total mortality (placebo =8, tx =1; p =0.02)<br>• ↓ risk for major CV events (placebo =14, tx =5; p = 0.04) |
| AFCAPS/TexCAPS[24]<br><br>Lovastatin 20-40 mg/day vs placebo in primary prevention of the first acute major coronary event | Randomized, double blinded, placebo controlled study<br><br>n = 6,605<br><br>5.2 years | **Primary outcome** defined as a first acute major coronary event (fatal or non-fatal MI, unstable angina, and sudden cardiac death) | Compared to placebo, lovastatin 20-40 mg/day resulted in:<br>• 37% ↓ in risk of first acute major coronary event (placebo =183, tx =116; p < 0.001)*<br>• 40% ↓ in risk of fatal or nonfatal MI (placebo =95, tx =57; p = 0.002)<br>• 33% ↓ in risk coronary revascularization procedures (placebo =157, tx =106; p = 0.001)<br>• 32% ↓ in risk of unstable angina (placebo =87, tx =60; p = 0.02)<br>• 25% ↓ in risk of CV events (placebo =255, tx =194; p =0.003)<br>• 25% ↓ risk for coronary events (placebo =215, tx =163; p =0.006) |
| Pravastatin | | | |
| PMS-CRP[25]<br><br>Pravastatin 20-40 mg/day vs placebo in primary prevention of cardiovascular events | Randomized, double-blinded, multicentered, placebo controlled study<br><br>n =1,062<br><br>26 weeks | Correlation of lipid levels with coronary mortality and MI | Compared to placebo, pravastatin 20-40 mg/day resulted in:<br>• Serious CV events (MI, unstable angina, acute CHF, sudden cardiac death) occurred less in the pravastatin group (placebo =13, tx =1; p < 0.001) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| WOSCOPS[26]<br><br>Pravastatin 40 mg/day vs placebo in primary prevention of nonfatal MI and death from CHD | Randomized, double blinded, placebo controlled, single centered study<br><br>n = 6,595<br><br>4.9 years | **Primary endpoint** defined as occurrence of non-fatal MI or death from CHD<br>**Secondary endpoints** include: death from cardiovascular disease and death from any cause | Compared to placebo, pravastatin 40 mg/day resulted in:<br>• 31% ↓ in risk for nonfatal MI or death from CHD (placebo = 248, tx =174; p = 0.001)*<br>• 31% ↓ in risk of definite nonfatal MI (placebo =204, tx =143; p < 0.001)<br>• A trend towards decreased death from definite CHD (placebo =52, tx =38; p = 0.13)<br>• 33% ↓ in death from definite + suspected CHD (placebo =61, tx =41; p= 0.042)<br>• 32% ↓ in death from all CV causes (placebo =73, tx =50; p = 0.033)<br>• A trend towards decreased all cause mortality (placebo =135, tx =106; p = 0.051) |
| PLAC-II[27]<br><br>Pravastatin vs placebo in progression of extra cranial carotid IMP | Randomized, double blinded, placebo controlled, single centered study<br><br>n = 151<br><br>3 years | **Primary outcome** was the change in the mean of the maximum intimal media measurement over time; effects on individual carotid artery segments and clinical events | Compared to placebo, pravastatin resulted in:<br>• 60% nonsignificant reduction of nonfatal MI plus death caused by coronary artery disease (p = 0.09)<br>• 61% reduction of any fatal events plus any nonfatal MI (p = 0.04)<br>• 80% reduction of fatal plus any nonfatal MI (p = 0.03) |
| CARE[28]<br><br>Pravastatin 40 mg/day vs placebo in secondary prevention of a coronary event | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 4,159<br><br>5 years | **Primary endpoint** of the trial was death from coronary heart disease (including fatal MI, either definite or probable; sudden death; death during a coronary intervention and death from other coronary causes) or a symptomatic non-fatal MI confirmed by serum CK | Compared to placebo, pravastatin 40 mg/day resulted in:<br>• 24% ↓ risk of death from CHD or nonfatal MI (placebo =13.2%, tx =10.2%; p = 0.003)*<br>• A trend towards a decreased risk of death from CHD (placebo =5.7%, tx =4.6%; p =0.10)<br>• 23% ↓ risk of nonfatal MI (placebo =8.3%, tx =6.5%; p = 0.02)<br>• A trend towards a decreased risk of fatal MI (placebo =1.8%, tx =1.2%; p= 0.07)<br>• 31% ↓ risk of stroke (placebo =3.8%, tx =2.6%; p =0.03) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| LIPID[29]<br><br>Pravastatin 40 mg/day vs placebo in secondary prevention of death from CHD | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 9,014<br><br>6.1 years | **Primary outcome**: death from CHD, i.e. fatal MI, sudden death, death in the hospital after possible MI, or death due to heart failure or another coronary cause<br>**Secondary outcomes**: death from any cause; death from cardiovascular causes, CHD, nonfatal MI, MI, hemorrhagic and non-hemorrhagic stroke, coronary revascularization | Compared to placebo, pravastatin 40 mg/day resulted in:<br>• 24%↓ risk of death due to CHD (placebo =8.3%, tx =6.4%; p < 0.001)*<br>• 25% ↓ risk of death due to CV disease (placebo =9.6%, tx =7.3%; p < 0.001)<br>• 22% ↓ risk of death from any cause (placebo =14.1%, tx =11%; p < 0.001)<br>• 24% ↓ risk of death due to CHD or nonfatal MI (placebo =15.9%, tx =12.3%; p <=0.001)<br>• 29% ↓ risk for any MI (placebo =10.3%, tx = 7.4%; p < 0.001)<br>• 19% ↓ risk for any stroke (placebo 4.5%, tx =3.7%; p = 0.048) |
| PROSPER[30]<br><br>Pravastatin 40 mg/day vs placebo in primary prevention of cardiovascular disease or stroke | Randomized, single blinded, placebo controlled, multicentered study<br><br>n = 5,804<br><br>3.2 years | **Primary outcome** was the combined endpoint of definite or suspected death from coronary heart disease, non-fatal MI and fatal or non-fatal stroke<br>**Secondary outcomes** included examinations of the coronary and cerebrovascular components separately | Compared to placebo, pravastatin 40 mg/day resulted in:<br>• 15% ↓ risk for the combined endpoint of death from CHD, nonfatal MI, and fatal or nonfatal stroke (placebo =16.2%, tx =14.1%; p = 0.014)*<br>• 19% ↓ risk for CHD or nonfatal MI (placebo =12.2%, tx = 10.1%; p = 0.006)<br>• 24% ↓ risk for CHD death (placebo = 4.2%, tx = 3.3%; p = 0.043)<br>• No difference was found for incidence of fatal or nonfatal stroke (p = 0.81)<br>• There were no differences in all-cause death p = 0.74) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| ALLHAT-LLT[31]<br><br>Pravastatin 40 mg/day vs placebo in the primary prevention of all cause mortality | Randomized, non-blinded, multicentered study<br><br>n = 10, 355<br><br>4.8 years | **Primary outcome** was all-cause mortality, with follow-up for up to 8 years<br>**Secondary outcomes** included nonfatal MI or fatal CHD combined, cause specific mortality, and cancer | Compared to 'usual care, pravastatin 40 mg/day resulted in:<br>• no statistically significant difference was found between groups in all-cause mortality (RR 0.99, 95%CI 0.89-1.11; p = 0.88)*<br>• no statistically significant difference was found between groups in CV disease deaths (RR 0.99, 95%CI 0.84-1.16; p = 0.91)<br>• no statistically significant difference was found between groups in fatal or nonfatal strokes (RR 0.91, 95%CI 0.75-1.09; p = 0.31) |
| PACT[32]<br><br>Pravastatin 20-40 mg vs placebo initiated 24 hours after acute myocardial infarction and the secondary prevention of cardiovascular events | Randomized, double blinded, placebo controlled, multicentered study | **Primary endpoint**: composite of death, recurrence of myocardial infarction, or readmission to hospital for unstable angina within 30 days of random assignment | Compared pravastatin 20-40 mg to placebo and resulted in:<br>• 6.4% (95% CI; -13.2-27.6% p = 0.48) ↓ in the composite primary endpoint composite of death, recurrence of myocardial infarction and unstable angina.<br>• The early initiation of a statin did not improve outcome in the early months following an acute coronary event. No evidence of harm was seen also. |
| PREVEND-IT[33]<br><br>Pravastatin 40 mg vs placebo in primary and secondary prevention of cardiovascular events in those with microalbuminuria | Randomized, double blinded, placebo controlled, single centered study<br><br>n = 864<br><br>Approx. 4 years | **Primary endpoint**: combined incidence of cardiovascular mortality and hospitalization (non-fatal or myocardial ischemia, heart failure, peripheral vascular disease and cerebrovascular accident | Compared pravastatin 40 mg vs placebo and resulted in:<br>• Pravastatin showed a non significant trend (13%) of lower incidence of the primary endpoint than subjects in the placebo group; p = 0.649 |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Rosuvastatin | | | |
| COMETS Study[34]<br><br>Atorvastatin 10/20 mg vs rosuvastatin 10/20 mg/day in safety and efficacy | Randomized, double blinded, double dummy, multinational, three arm, parallel group study<br><br>n = 401<br>12 weeks | **Primary endpoint** was the percentage change from baseline in LDL-C levels after 6 weeks of treatment | In the overall study sample, compared to atorvastatin 10/20mg, rosuvastatin 10/20mg/day resulted in:<br>• 42.7% (rosuvastatin 10mg) vs 36.6% (atorvastatin 10 mg) ↓ in LDL-C, (p<0.001) after 6 weeks of treatment*<br>• 42.7% (rosuvastatin 10 mg) vs 0.03% (placebo) ↓ in LDL-C, (p<0.001) after 6 weeks of treatment<br>• 48.9% (rosuvastatin combined 10/20mg) vs 42.5% (atorvastatin combined 10/20 mg) ↓ in LDL-C, ( p<0.001) after 12 weeks of treatment<br>• At 12 weeks, HDL-C ↑10.4% (rosuvastatin) vs 5.8% (atorvastatin) (p<0.01)<br>• TG reduction similar in both groups |
| STELLAR Trial[35]<br><br>Rosuvastatin vs atorvastatin, pravastatin and simvastatin at all dosage ranges in LDL-C reducing efficacy | Randomized, parallel group, open label, comparator controlled trial<br><br>n = 2431<br><br>6 weeks | **Primary endpoint** was percent change in LDL-C from baseline to 6 weeks. | In overall study sample, compared rosuvastatin to atorvastatin, pravastatin and simvastatin at all dosage ranges. The results showed:<br>• At 6 weeks, rosuvastatin 10 to 80mg reduced LDL-C by a mean of 8.2% more than atorvastatin 10 to 80mg, 26% more than pravastatin 10 to 40mg and 12% to 18% more than simvastatin 10 to 80mg (all p <0.001)*<br>• Mean increases of HDL-C in rosuvastatin 10 to 40mg was 7.7% to 9.6% compared with 2.1% to 6.8% in other groups<br>• NCEP ATP III LDL-C goals were achieved by 82% to 89% of the patients treated with rosuvastatin 10mg to 40mg compared with 69% to 85% treated with atorvastatin 10mg to 80mg, 82.2% to 50.9% with simvastatin 10 to 80mg and 43.9% to 54.7% with pravastatin 10 to 40mg<br>• The European cholesterol goal was achieved by 79% to 92% in rosuvastatin groups compared with 52% to 81% in the atorvastatin group. The simvastatin group was 26.1% to 77.3%, while the pravastatin group was 5% to 26.7%. |
| Simvastatin | | | |
| 4S[36]<br><br>Simvastatin 20-40 mg/day vs placebo in secondary prevention of morbidity in patients with coronary heart disease | Randomized, double blinded, placebo controlled study<br><br>n =4,444<br><br>5.4 years | **Primary outcome** was morbidity and mortality related to CHD | Compared to placebo, simvastatin 20-40 mg/day resulted in:<br>• 30% ↓ risk in total mortality (placebo =11.5%, tx =8.2%; p= 0.0003)*<br>• 42% ↓ risk for coronary death (placebo =8.5%, tx =5.0%; p value not provided in study)<br>• 34% ↓ risk for a major coronary event (placebo =28%, tx =19%; p < 0.00001)<br>• 37% ↓ risk for myocardial revascularization procedure (placebo =17.2%, tx =11.3%; p < 0.00001) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| HPS[37,38]<br><br>Simvastatin 40 mg/day vs placebo in primary and secondary prevention of vascular morbidity and mortality | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 20,536<br><br>5 years | **Primary endpoint** variable was defined as first major coronary event (non-fatal MI or coronary death) and first major vascular event (major coronary event, stroke or revascularization) | In the overall study sample, compared to placebo, simvastatin 40 mg/day resulted in:<br>• 13% ↓ risk in all-cause mortality (placebo =14.7%, tx = 12.9%; p = 0.0003)<br>• 17% ↓ risk for death from any vascular causes (placebo = 9.1%, tx = 7.6%; p < 0.0001)*<br>• 27% ↓ in first nonfatal MI or coronary death (placebo = 11.8%, tx =8.7%; p < 0.0001)*<br>• 24% ↓ in composite major coronary events, strokes, and revascularizations (placebo = 25.2%, tx =19.8%; p < 0.0001)<br>• 25% ↓ in first nonfatal or fatal stroke (placebo =5.7%, tx =4.3%; p < 0.0001)<br>• 24% ↓ in first revascularization procedure (placebo =11.7%, tx =9.1%; p < 0.0001)<br>• In 6,793 patients with baseline LDL-C < 116mg/dL, major vascular events risk was decreased with simvastatin (placebo = 22.2%, tx = 17.6%; p < 0.0001)<br>• In 3,421 patients with baseline LDL-C < 100mg/dL, major vascular events risk was decreased with simvastatin (placebo = 21%, tx = 16.4%; p = 0.0006)<br><br>In subjects with diabetes, simvastatin 40 mg/day resulted in:<br>• 27% ↓ in first nonfatal MI or coronary death (placebo =12.6%, tx =9.4%; p < 0.0001)*<br>• 22% ↓ in composite major coronary events, strokes, and revascularizations (placebo = 25.1%, tx = 20.2%; p < 0.0001)<br>• 24% ↓ in first nonfatal or fatal stroke (placebo =6.5%, tx =5.0%; p = 0.01)<br>• 17% ↓ in first revascularization procedure (placebo =10.4%, tx =8.7%; p = 0.02)<br>• 27% ↓ risk in major vascular events in the 2,426 diabetic patients with baseline LDL-C < 116mg/dL (placebo = 20.9%, tx = 15.7%; p < 0.0007) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| A to Z (phase Z)[39]<br><br>Patients with acute coronary syndrome (ACS) received 40 mg/day of simvastatin for 1 month then 80 mg/day thereafter compared with ACS patients that received placebo for 4 months then 20 mg/day of simvastatin | Randomized, double blinded, placebo controlled, multicentered study<br><br>n = 4497 | **Primary endpoint** composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke | • 343 patients (16.7%) in the placebo plus simvastatin group experienced the primary endpoint vs 309 (14.4%) in the simvastatin only group (40 mg/80 mg) (HR 0.89; p =.14).<br>• Cardiovascular death occurred in 109 (5.4%) and 83 (4.1%) patients in the 2 groups (HR, 0.75P =.05) but no differences were observed in other individual components of the primary endpoint.<br>• No difference were evident during the first 4 months between the groups for the primary endpoint (HR 1.01; P =.89), but from 4 months through the end of the study the primary endpoint was significantly reduced in the simvastatin only group (HR, 0.75; P =.02).<br>• Myopathy (creatinine kinase >10 times the ULN) occurred in 0.4% of those receiving simvastatin 80 mg/d, in no patients receiving lower doses of simvastatin, and in 1 patient receiving placebo (P =.02).<br><br>• The prespecified endpoint was not met; however, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of major cardiovascular events. |

tx= treatment group HR = hazard ratio

ASAP[20] and ARBITER[21] trials were not included due to lack of patient-oriented outcomes in these trials (studies primarily focused on the disease-oriented outcome of carotid intima medial thickness).

The Beltline et al. study[23] was not included in this review due to lack of patient-oriented outcomes (study primarily designed to compare cholesterol lowering capacity and side effects between atorvastatin and pravastatin). The CURVES study[24] was not included in this review due to lack of patient-oriented outcomes (study primarily designed to compare dose efficacy of atorvastatin to simvastatin, pravastatin, lovastatin, and fluvastatin).

EXCEL[28] trial not included due to lack of patient-oriented outcomes studied in this trial (study primarily designed to measure cholesterol lowering and safety).

PLAC-I trial[36]was not included in this review due to lack of patient-oriented outcomes (the trial was primarily designed to measure changes in minimum lumen diameter to predict progression of CAD).

KAPS trial[37] was not included in this review due to lack of patient-oriented outcomes (the trial was primarily designed to measure maximum carotid IMT; researchers reported clinical cardiovascular events to be lower in the pravastatin group although the difference was not statistically significant). REGRESS trial[38] was not included in this review due to lack of specific patient- oriented outcomes reporting (this trial was primarily designed to detect differences in angiographic restenosis as measured by diameter stenosis in patients post- PTCA; researchers also reported a 58% relative risk reduction in clinical endpoints with pravastatin compared to placebo with most of these events consisting of additional PTCA procedures. Incidence of MI, stroke and death not reported in the trial).

**Additional Evidence**

Dose Simplification: Administration of HMG-CoA reductase inhibitors is once a day. Given that most of the body's cholesterol is synthesized at night and most of the statins have a t ½ just long enough to cover the night time period, theoretically, dosing should be given at bedtime. Two drugs that are exempt from this dosing schedule that can be taken anytime are atorvastatin and rosuvastatin.[5,6]

Stable Therapy: In one study, the conversion from brand name simvastatin to generic lovastatin was evaluated according to relative safety and efficacy. This study was conducted to determine the feasibility of selecting the more cost effective generic lovastatin for formulary inclusion. With more than 33,000 patients, this study demonstrated successful conversion of simvastatin to lovastatin with relatively few adverse effects, while maintaining efficacy. In a comparison of preconversion and postconversion values, average lipid tests resulted in decreased LDL-C, an increase in HDL-C and a decrease in triglycerides. Rates of ALT and CK elevations were not found to be significantly different before and after conversion.[40]

Impact On Physician Visits: A search of Medline and Ovid 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 medication within this 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 costs 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 dosing 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-$50 per Rx |
| $$ | $51-$75 per Rx |
| $$$ | $76-$100 per Rx |
| $$$$ | $101-$150 per Rx |
| $$$$$ | over $150 per Rx |

Rx = prescription

**Table 10. Relative Cost of Single Entity HMG-COA Reductase Inhibitors**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Atorvastatin calcium | tablet | Lipitor® | $$$ | N/A |
| Fluvastatin | capsule, sustained-release tablet | Lescol®, Lescol XL® | $$ | N/A |
| Lovastatin | sustained-release tablet, tablet | Altoprev®^, Mevacor®* | $$$-$$$$$ | $$ |
| Pravastatin | tablet | Pravachol® | $$$$ | N/A |
| Rosuvastatin | tablet | Crestor® | $$$ | N/A |
| Simvastatin | tablet | Zocor® | $$$$ | N/A |

*Generic is available in at least one dosage form or strength.
^Product previously named Altocor®.
N/A = not available

## X. Conclusions

Three main issues require consideration when selecting a statin for preferred drug status: safety, patient outcomes data, and LDL-C lowering capacity. As previously discussed, no clear differences seem to exist amongst the statins in terms of safety.[5-9] They are all effective for lowering cholesterol (including LDL-C); although differences do exist between the statins in terms of their lipid-lowering capacities. However, all statins exert a dose-dependent cholesterol lowering capacity.[11]

Whether patient specific outcomes including morbidity and mortality are a class effect or product - specific, remains controversial. Notably, each statin with the exception of rosuvastatin, has demonstrated a reduction in cardiovascular morbidity and mortality.[12-39] In addition to the positive impact on cardiovascular outcomes; atorvastatin, lovastatin, pravastatin, and simvastatin have demonstrated reduction in all-cause mortality, although the strength of evidence on this outcome differs between these statins. It should be mentioned that the long-acting formulations of fluvastatin and lovastatin, are not supported by patient-oriented evidence from randomized controlled trials.

LDL-C lowering capacity has become especially important in the last few years. The impact of varying degrees of LDL-C lowering has been evaluated in four large outcomes trials involving in upwards of 27,548 patients.[41] The overwhelming and consistent finding from these trials is that "lower is better" when targeting LDL-C. There is now considerable evidence that aggressive lipid lowering results in additional cardiovascular morbidity and mortality benefit.[17,18,20,39] Amongst the statin class, the agents with the most potent LDL-C lowering capacity include atorvastatin, rosuvastatin and simvastatin. However, it must be kept in mind that amongst the three aforementioned statins, rosuvastatin has not demonstrated clinical utility in terms of impacting patient-oriented outcomes (morbidity and mortality parameters).[34,35]

## XI. Recommendations

Alabama Medicaid should work with the manufacturers on cost proposals so that at least one HMG CoA-reductase inhibitor (atorvastatin, lovastatin, pravastatin or simvastatin) that has demonstrated positive morbidity and mortality outcomes is selected as a preferred agent.

Alabama Medicaid should also work with manufacturers of atorvastatin, rosuvastatin and simvastatin on cost proposals so that at least one high-potency HMG CoA-reductase inhibitor is selected as a preferred agent.

Alabama Medicaid should accept proposals from the remaining manufacturers to determine cost effective products and possibly designate additional preferred agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of HMG-COA Reductase Inhibitors–Combination**
**AHFS Class 240608**
**February 22, 2006**

# I. Overview

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. The inhibition of this enzyme decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein cholesterol receptors and enhanced clearance of circulating LDL-C.

The mechanism of the lipid lowering effects of niacin is not completely understood. The primary mechanism of action seems to be inhibition of mobilization of free fatty acids from adipose tissues. Niacin also reduces hepatic synthesis of triglycerides (TG) and very low-density lipoprotein (VLDL), which in turn leads to decreased synthesis of low-density lipoprotein. Finally, niacin also increases high-density lipoprotein by reducing its catabolism.

The cholesterol absorption inhibitor, ezetimibe, exerts its mechanism of action by blocking both dietary and biliary cholesterol absorption by the small intestine. It is capable of reducing LDL-C by about 18% either on its own or as adjunctive therapy to statins, while also having small increases in HDL-C.

HMG-CoA reductase inhibitors are generally considered first-line agents for treating hyperlipidemia due to their ability to effectively lower total cholesterol and LDL-C. These agents also have the ability to moderately raise HDL-C. Niacin is not as widely used as HMG-CoA reductase inhibitors, but it may be a useful treatment option for combined hyperlipidemias (increased triglycerides and LDL-C with decreased HDL-C). Since niacin has a greater capacity than statins to raise HDL-C and lower TG, combining a statin and niacin may offer further benefit for modifying these cholesterol levels. Ezetimibe is useful as an adjunctive therapy to statins to help patients reach their NCEP LDL-C goal or in patients who are intolerant to statins.

Statins are also available as a fixed-dose combination product with a long-acting dihydropyridine (DHP) calcium-channel blocker (CCB) and aspirin to treat other diseases in addition to hyperlipidemias.

Table 1 lists the products included in this review. 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 Agents |
|---|---|---|---|
| atorvastatin/amlodipine | Tablet | Caduet® | none |
| lovastatin/niacin | Tablet | Advicor® | none |
| pravastatin /ASA (otherwise known as buffered aspirin and pravastatin sodium) | Extended-release tablet | Pravigard PAC® | none |
| simvastatin/ezetimibe | Tablet | Vytorin® | none |

There are no generic or over-the-counter products in this class.

## II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under Antilipemic Agents. 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.[4] Because LDL-C is the major atherogenic lipid component, NCEP-ATP III[4] focuses primarily on attaining goal LDL-C levels. While 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 LDL-C goal is already reached.[4]

## III. Indications

According to package insert information, combined niacin extended-release and lovastatin is indicated for the treatment of primary hypercholesterolemia and mixed dyslipidemias. This product should not be used as initial therapy but instead is best utilized in patients who are already taking monotherapy lovastatin but require further TG-lowering or HDL-raising and would benefit from the addition of niacin; or in patients currently taking niacin monotherapy but would benefit from addition of lovastatin to further reduce LDL-C.[1] Indications for the HMG-CoA Reductase Inhibitor Combination products are listed in Table 2.

**Table 2. FDA-Approved Indications for the Combination HMG-CoA Reductase Inhibitors[1-5]**

| Indication | Atorvastatin/ Amlodipine** | Lovastatin/ Niacin | Pravastatin/ ASA* | Simvastatin/ Ezetimibe |
|---|---|---|---|---|
| Primary hypercholesterolemia/ mixed dyslipidemia | ✔ | ✔ | ✔ | ✔ |
| Familial hypercholesterolemia - homozygous | ✔ | | | ✔ |
| Hypertension | ✔ | | | |
| Stable angina, chronic | ✔ | | ✔ | |
| Variant angina | ✔ | | ✔ | |
| Primary prevention of cardiovascular events | ✔ | | ✔ | |
| Secondary prevention of cardiovascular events | | | ✔ | |
| Primary dysbetalipoproteinemia | ✔ | | ✔ | |
| Regression of coronary atherosclerosis | | | ✔ | |
| Hypertriglyceridemia | ✔ | | ✔ | |

*According to package insert information, this product is approved for use in patients for whom treatment with both aspirin and pravastatin are appropriate.[5]

**According to package insert information, this product is approved for use in patients for whom treatment with both amlodipine and atorvastatin are appropriate.[2]

## IV. Pharmacokinetics

**Table 3. Pharmacokinetic Parameters of the Combination HMG-CoA Reductase Inhibitors [1-5]**

| Individual Component | Atorvastatin | Amlodipine | Lovastatin | Niacin | Pravastatin | ASA | Simvastatin | Ezetimibe |
|---|---|---|---|---|---|---|---|---|
| Systemic Bioavailability | 30% | 64%-90% | < 5% | 72%% | 17% | 50%-75% | < 5% | Variable |
| Protein Binding | ≥ 98% | 93%-98% | > 95% | <20% | 50% | - | 95% | >90% |
| Lipid Solubility | Hydrophilic | - | Lipophilic | - | Hydrophilic | - | Lipophilic | - |
| Crosses Blood-brain Barrier | No | - | Yes | - | No | - | Yes | - |
| Main Metabolizing Enzyme | CYP3A4 | CYP3A4 | CYP3A4 | None | None | None | CYP3A4 | None |
| $T_{½}$ Elimination, Hours | 15-30 | 30-50 | 2.9 | 45 m. | 1.3-2.8 | 3-10 | 2-3 | 22 |
| Active Metabolite | Yes | No | Yes | No | No | Yes | Yes | Yes |

## V. Drug Interactions

Clinically important drug interactions exist mainly for the statins and ASA components. All other non-statin components found within these combination products appear to be relatively benign and do not exhibit any major adverse drug interactions. Since atorvastatin, lovastatin and simvastatin are metabolized via CYP34A, they share similar drug interactions, whereas pravastatin is not appreciably metabolized by the CYP system.

Niacin[1]

- Antihypertensive therapy: Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension
- Aspirin: Concomitant aspirin may decrease the metabolic clearance of niacin. The clinical relevance of this finding is unclear.
- Bile acid sequestrants: In vitro studies investigating niacin binding capacity of colestipol and cholestyramine suggest that 4-6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of lovastatin/niacin extended-release.
- Other: Vitamins or other nutritional supplements containing large amounts of niacin or related compounds (e.g., nicotinamide) may potentiate the adverse effects of lovastatin/niacin extended-release.

Lovastatin[1]

- Serious skeletal muscle disorders, such as rhabdomyolysis, have been reported during concomitant therapy of lovastatin or other HMG-CoA reductase inhibitors with cyclosporine, itraconazole, ketoconazole, gemfibrozil, niacin, erythromycin, clarithromycin, nefazodone or HIV protease inhibitors.

Clinically significant [rated as 1 (major) or 2 (moderate)] drug interactions are listed below.

**Table 4. Significant Drug-Drug Interactions for the Combination HMG-CoA Reductase Inhibitors[6]**

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Atorvastatin, lovastatin, pravastatin, simvastatin | 1 | Azole antifungals (fluconazole, itraconazole, ketoconazole, voriconazole) | Azole antifungal agents may inhibit the first-pass hepatic metabolism of HMG-CoA reductase inhibitors. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 2 | Bile acid sequestrants (cholestyramine, colestipol) | The HMG-CoA reductase inhibitors may adsorb to the bile acid sequestrant, reducing the GI absorption of the HMG-CoA reductase inhibitors. |
| Atorvastatin, lovastatin, simvastatin | 2 | Carbamazepine | Increased metabolism (CYP3A4) of the HMG-CoA reductase inhibitors by carbamazepine is suspected. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 1 | Cyclosporine | Decreased metabolism of certain HMG-CoA reductase inhibitors is suspected. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 1 | Fibric acid derivatives (fenofibrate, gemfibrozil) | Severe myopathy or rhabdomyolysis may occur. |
| Atorvastatin, lovastatin, simvastatin | 1 | Macrolides (azithromycin, clarithromycin, erythromycin and telithromycin) | Inhibition of metabolism (CYP3A4) is suspected. |

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Atorvastatin, lovastatin, simvastatin | 1 | Nefazadone | Possible nefazadone inhibition of metabolism of HMG-CoA Reductase inhibitors by the cytochrome P450 3A4 isozyme. |
| Atorvastatin, lovastatin, simvastatin | 2 | Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) | Possible inhibition of first-pass metabolism (CYP3A4) of the HMG-CoA reductase inhibitors. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 2 | Protease inhibitors (indinavir, ritonavir, amprenavir, nelfinavir, saquinavir, atazanavir, lopinavir) | Inhibition of first-pass metabolism (CYP3A4) in the GI tract is suspected. |
| Atorvastatin, lovastatin, pravastatin, simvastatin | 2 | Rifamycins (rifabutin, rifampin, rifapentine) | Inhibition of first-pass metabolism (CYP3A4) in the GI tract is suspected. |
| Lovastatin, simvastatin | 2 | Warfarin | Inhibition of warfarin hepatic metabolism is suspected. |
| ASA | 2 | ACE Inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril) | The hypotensive and vasodilator effects of the ACEI may be reduced. |
| ASA | 2 | Beta Blockers (acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, metoprolol, nadalol, penbutolol, pindolol, propranolol and timolol) | Salicylates may inhibit biosynthesis of prostaglandins involved in the antihypertensive activity of beta blockers. |
| ASA | 2 | Carbonic Anhydrase Inhibitors (acetazolamide, dichlorphenamide and methazolamide) | ASA displaces acetazolamide from plasma protein binding sites and inhibits renal clearance. CAI-induced acidosis may allow increased CNS penetration by salicylates. |
| ASA | 1 | Clopidogrel | The effects of aspirin on the GI mucosa may be a risk factor. |
| ASA | 2 | Corticosteroids (betamethasone, cortisone, desoxycorticosterone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, and triamcinolone) | Corticosteroids probably stimulate liver metabolism of salicylates and may also increase renal elimination. |
| ASA | 1 | Heparin | Aspirin can inhibit platelet aggregation and has caused bleeding, which may be additive to heparin anticoagulation. |

| Drugs | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| ASA | 2 | Insulin | Basal insulin concentrations are increased, and the acute insulin response to a glucose load is enhanced. |
| ASA | 1 | Ketorolac | Salicylates may displace ketorolac from protein binding sites. |
| ASA | 1 | Methotrexate | Salicylates may decrease methotrexate renal clearance and plasma protein binding. |
| ASA | 2 | Probenecid | Possibly due to an alteration in the renal filtration of uric acid. |
| ASA | 2 | Sulfinpyrazone | Sulfinapyrazone is displaced from plasma protein binding sites by salicylates which results in a fall in plasma concentration of total sulfinapyrazone in the absence of increased excretion which implies an expansion of sulfinpyrazone distribution. Salicylate also blocks the inhibitory effect of sulfinapyrazone on tubular reabsorption of uric acid. |
| ASA | 2 | Sulfonylureas (acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide and tolbutamide) | Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose. Displaced sulfonylurea protein binding has been suggested. |
| ASA | 2 | Valproic acid | Displacement of valproic acid from protein binding sites by aspirin. Aspirin may also alter the metabolic pathways of valproic acid. |
| ASA | 1 | Warfarin | Anticoagulant activity may be enhanced. |

## VI. Adverse Drug Events

**Table 5. Adverse Reactions of the Combination HMG-CoA Reductase Inhibitors[1-5]**

| Individual Component | Atorvastatin | Amlodipine | Lovastatin | Niacin | Pravastatin | ASA | Simvastatin | Ezetimibe |
|---|---|---|---|---|---|---|---|---|
| Abdominal Pain | 0 - 3.8 (0.7) | 1.6 (0.3) | 2.0 – 2.5 (1.6) | 1* | 5.4 (6.9) | N/A# | 3.2 (3.2) | 2.7 (2.3) |
| Asthenia | 0 – 3.8 (1.9) | 0.1 – 1* | 1.2 – 1.7 (1.4) | 7* | N/A# | N/A# | 1.6 (2.5) | N/A# |
| Constipation | 0 – 2.5 (1.8) | 0.1 - 1* | 2.0 – 3.5 (1.9) | N/A# | 4.0 (7.1) | N/A# | 2.3 (1.3) | N/A# |
| Diarrhea | 0 – 5.3 (1.5) | 0.1 - 1* | 2.2 – 2.6 (2.3) | 9* | 6.2 (5.6) | Dose related | 1.9 (2.5) | 3.4 (1.5) |
| Dizziness | ≥ 2* | 0.1 - 1* | 0.5 – 1.2 (0.7) | N/A# | 3.3 (3.2) | Dose related | N/A# | 2.7 (1.2) |
| Dyspepsia | 1.3 – 2.8 (4.1) | 0.1 - 1* | 1.0 – 1.6 (1.9) | 5* | N/A# | Dose related | 1.1* | N/A# |
| Flatulence | 1.1 – 2.8 (3.3) | 0.1 - 1* | 3.7 -4.5 (4.2) | N/A# | 2.7 (3.4) | N/A# | 1.9 (1.3) | N/A# |
| Headache | 2.5 – 16.7 (7.0) | 7.3 (7.8) | 2.1 – 3.2 (2.7) | 13* | 6.2 (3.9) | Dose related | 3.5 (5.1) | 8.0 (5.4) |
| Myalgia | 0 – 5.6 (1.1) | 1-2* | 1.8 – 3.0 (1.7) | 5* | 2.7 (1.0) | Dose related | 1.2 (1.3) | 5.0 (4.6) |
| Nausea | ≥ 2* | 2.9 (1.9) | 1.9 – 2.5 (2.5) | 12* | 7.3 (7.1) | Dose related | 1.3 (1.9) | N/A# |

* Placebo incidence not provided
() designates rates in the placebo group
# Incidence not available

**Table 6. Side Effects of Niacin Combination Products[1]**

| Side Effect | Lovastatin/Niacin-extended release | Niacin extended-release | Lovastatin |
|---|---|---|---|
| **Cardiovascular** | 76% | 72% | 26% |
| Flushing | 71% | 65% | 18% |
| **Body as a Whole** | 49% | 54% | 45% |
| Asthenia | 5% | 7% | 5% |
| Flu Syndrome | 6% | 8% | 4% |
| Headache | 9% | 13% | 5% |
| Infection | 20% | 15% | 20% |
| Pain | 8% | 3% | 10% |
| Abdominal pain | 4% | 1% | 6% |
| Back pain | 5% | 5% | 5% |
| **Digestive System** | 24% | 28% | 17% |
| Diarrhea | 6% | 9% | 2% |
| Dyspepsia | 3% | 5% | 4% |
| Nausea | 7% | 12% | 2% |
| Vomiting | 3% | 5% | 0% |
| **Metabolic and Nutritional System** | 17% | 20% | 14% |
| Hyperglycemia | 4% | 7% | 6% |
| **Musculoskeletal System** | 9% | 10% | 18% |
| Myalgia | 3% | 5% | 9% |
| **Skin and Appendages** | 2% | 21% | 12% |
| Pruritus | 7% | 8% | 3% |
| Rash | 5% | 12% | 3% |

## VII. Dosing and Administration

All of the combination products are taken once a day with slight differences in administration scheduling. Table 7 below details dosing and administration guidelines for these combination products.

**Table 7: Dosing and Administration of HMG-CoA Reductase Inhibitor Combinations[1-5]**

| | Atorvastatin/ Amlodipine | Lovastatin/Niacin | Pravastatin/ASA | Simvastatin/Ezetimibe |
|---|---|---|---|---|
| Initial Dose | 10 mg/5.0-10 mg | 20 mg/500 mg | 40 mg/81 mg | 10 mg/10 mg |
| Dosage Strengths | 10,20,40 mg/2.5 mg<br>10,20,40,80 mg/5.0 mg<br>10,20,40,80 mg/10 mg | 20 mg/500 mg<br>20 mg/750 mg<br>20 mg/1000 mg | 40 mg/81 mg | 10 mg/10 mg<br>20 mg/10 mg<br>40 mg/10 mg<br>80 mg/10 mg |
| Maximum Dose | 80 mg/10 mg | 20 mg/1000 mg | 40 mg/81 mg | 80 mg/10 mg |
| Administration | Can be taken any time of the day with or without food | Should be taken at bedtime with a low fat meal and should not be crushed or chewed | Should be taken on an empty stomach or at bedtime | Should be taken in the evening |
| Special Considerations for Initiating Therapy | Small, fragile or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg amlodipine QD | Equivalent doses of Lovastatin/Niacin can be substituted for Niaspan® but should not be substituted for other modified release niacin products | - | Should not be started in those with severe renal insufficiency unless the patient has already tolerated treatment with simvastatin of 5 mg or higher |

Warnings

Lovastatin/niacin: Equivalent doses of lovastatin/niacin may be substituted for equivalent doses of Niaspan® but should not be substituted for other modified release (sustained release or time release) niacin preparations or immediate release (crystalline) niacin preparations. The usual recommended initial dose of extended-release niacin is 500 mg/day (given at bedtime). The typical recommended starting dose of lovastatin is 20 mg/day. Extended-release niacin can be titrated by 500 mg every 4 weeks to a maximum of 2,000 mg/day. Lovastatin can be titrated every 4 weeks to a maximum of 80 mg/day. However, the product in this review only contains 20 mg of lovastatin per tablet. Dosing of lovastatin/niacin extended-release product should not exceed 40 mg/2,000mg daily. The fixed-dose product can be titrated every 4 weeks according to patient response and tolerance based on the extended release niacin ingredient. This product should be taken at bedtime following a low-fat snack. [1]

## VIII. Effectiveness

Two main factors are typically considered when assessing efficacy of antilipemic agents: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the target of NCEP-ATP III[6] guidelines (and secondarily to reduce TG and raise HDL-C); and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality.

All of the combination products contain statin components aimed at lowering cholesterol levels. Other drug products contained within these combinations, offer added benefit for those with indications for both constituents.

**Table 8. HMG-CoA Reductase Inhibitors' Combinations Effects on Cholesterol Levels[1, 2, 3, 5]**

| Statin | Daily Dosage | Effect On: | | | |
|---|---|---|---|---|---|
| | | TC | LDL-C | TG | HDL-C |
| Atorvastatin/ Amlodipine | 10 mg – 80 mg* | ↓ 29-45% | ↓ 39-60% | ↓ 19-37% | ↑ 5-6% |
| Lovastatin/Niacin | 20 mg/1000 mg** | - | ↓ 30% | ↓ 32% | ↑20% |
| Pravastatin/ASA | 40 mg/81 mg | ↓ 25% | ↓ 34% | ↓ 24% | ↑ 12% |
| Simvastatin/ Ezetimibe | 10 mg/10 mg – 80 mg/10 mg | ↓ 31-43% | ↓ 45-60% | ↓ 23-31% | ↑ 6-8% |

TC = Total Cholesterol LDL-C = Low-density Lipoprotein Cholesterol TG = Triglycerides HDL-C = High-density Lipoprotein Cholesterol

* The LDL-C lowering effect found in the atorvastatin/amlodipine package insert was only attributed to atorvastatin as a single entity.

** Based on the package insert, the information given was only available for the maximum dosage formulation.

Even though there is an abundance of data with the statin products found in these combinations, there are very few studies available for the combination products as a whole. In Table 9 are listed some trials for these products.

**Table 9: Outcomes Evidence for the HMG-CoA Reductase Inhibitor Combinations**

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Atorvastatin/Amlodipine | | | |
| Caduet Package Insert Study[2]<br><br>Identified the effects of atorvastatin/ amlodipine combination on SBP, DBP & LDL-C | Double blind, placebo controlled study<br><br>n = 1660<br><br>8 weeks | Primary endpoints defined as mean change of SBP, DBP and reduction of LDL-C | • Atorvastatin/Amlodipine 10 mg/5 mg: mean change SBP -13.7%, DBP -8.2% & LDL-C -38.7% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 20 mg/5 mg: mean change SBP -15.3%, DBP -9.4% & LDL-C -42.3% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 40 mg/5 mg: mean change SBP -12.7%, DBP -7.3% & LDL-C -44.9% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 80 mg/5 mg: mean change SBP -12.2%, DBP -8.4% & LDL-C -48.4% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 10 mg/10 mg: mean change SBP -15.9%, DBP -9.1% & LDL-C -36.6% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 20 mg/10 mg: mean change SBP -16.1%, DBP -10.6% & LDL-C -38.6% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 40 mg/10 mg: mean change SBP -16.3%, DBP -9.8% & LDL-C -43.2% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given)<br>• Atorvastatin/Amlodipine 80 mg/10 mg: mean change SBP -17.6%, DBP -11.1% & LDL-C -49.1% (placebo SBP -3.0%, DBP -3.3% & LDL-C -1.1%; no p value given) |
| Lovastatin/Niacin | | | |
| ADVOCATE[8]<br><br>Compared lipid altering efficacy of lovastatin/ niacin ER 40 mg/1000 mg vs standard doses of simvastatin 40 mg and atorvastatin 40 mg | Randomized, open-label, multicentered, dose comparison study<br><br>n = 315<br><br>16 weeks | Primary efficacy: percent change from baseline in LDL-C and HDL-C<br><br>Secondary endpoint: mean percent change from baseline in total cholesterol, apolipoprotein B, apolipoprotein A-1, HDL subfractions, $HDL_2$ and $HDL_3$ and median percent change in triglycerides and lipoprotein (a) | • Lovastatin/Niacin ER 40 mg/1000 mg LDL-C -39% vs simvastatin 40mg -39% vs atorvastatin 10mg -49% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg HDL-C +17% vs simvastatin 40mg +7% vs atorvastatin 10mg +6% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg triglycerides -29% vs simvastatin 40mg -19% vs atorvastatin 10mg -31% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg lipoprotein (a) -19% vs simvastatin 40mg -2% vs atorvastatin 10mg -0% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg apolipoprotein B -33% vs simvastatin 40mg -31% vs atorvastatin 10mg -40% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg apolipoprotein A-1 +7% vs simvastatin 40mg +6% vs atorvastatin 10mg +2% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg $HDL_2$ +113% vs simvastatin 40mg +42% vs atorvastatin 10mg +30% ($p < 0.05$)<br>• Lovastatin/Niacin ER 40 mg/1000 mg $HDL_3$ +8% vs simvastatin 40mg +4% vs atorvastatin 10mg +4% ($p < 0.05$) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Lovastatin/ extended-release (ER) niacin vs either alone[1] | Multicenter, randomized, double-blind, parallel, 28-week, active comparator study<br><br>n=179 | Primary efficacy variable was mean percent change from baseline in LDL-C | Compared with ER-niacin 1000 mg or lovastatin 20mg, the combination of 20mg lovastatin and 1000mg ER-niacin resulted in:<br>• 30% decrease in LDL vs 3% for ER-niacin and 29% for lovastatin<br>• 20% increase in HDL vs 14% for ER-niacin and 3% for lovastatin<br>• 32% decrease in triglycerides vs 23% for ER-niacin and 17% for lovastatin<br><br>Compared with ER-niacin 1000 mg or lovastatin 40 mg, the combination of 1000 mg ER-niacin and 40mg of lovastatin resulted in:<br>• 36% decrease in LDL vs 6% for ER-niacin and 31% for lovastatin<br>• 20% increase in HDL vs 15% for ER-niacin and 5% for lovastatin<br>• 39% decrease in triglycerides vs 23% for ER-niacin and 17% for lovastatin<br><br>Compared with ER-niacin 1500 mg or lovastatin 40 mg, the combination of 1500 mg ER-niacin and 40 mg lovastatin resulted in:<br>• 37% decrease in LDL vs 12% for ER-niacin and 34% for lovastatin<br>• 27% increase in HDL vs 22% for ER-niacin and 6% for lovastatin<br>• 44% decrease in triglycerides vs 31% for ER0niacin and 21% for lovastatin<br><br>Compared with ER-niacin 2000 mg or lovastatin 40 mg, the combination of 2000 mg ER-niacin and 40mg lovastatin resulted in:<br>• 42% decrease in LDL vs 14% for ER-niacin and 32% for lovastatin<br>• 30% increase in HDL vs 24% for ER-niacin and 6% for lovastatin<br>• 44% decrease in triglycerides vs 31% for ER-niacin and 20% for lovastatin |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Simvastatin/Ezetimibe | | | |
| VYVA[22]<br><br>simvastatin/ ezetimibe (10-80 mg/10 mg ) vs atorvastatin (10 mg-80 mg) and percentage change in LDL-C | Randomized, double blind, active controlled, multicentered, eight arm parallel group study<br><br>n = 1640<br><br>10 weeks | **Primary Endpoint**: percent change from baseline to the end of the 6-week treatment period in LDL-C<br><br>Secondary efficacy endpoint: 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 goal | • 20mg/10mg simvastatin/ezetimibe -50.6% LDL-C vs -36.1% 10mg atorvastatin (95% CI -17.2 to -11.9 treatment difference, p < 0.001), -43.7% LDL-C for 20mg atorvastatin (95% CI -9.5 to -4.3, p < 0.001)<br>• 40mg/10 mg simvastatin/ezetimibe -57.4% LDL-C vs -48.3% 40mg atorvastatin (95% CI -11.7 to -6.5 treatment difference, p < 0.001)<br>• 80mg/10 mg simvastatin/ezetimibe -58.6% LDL-C vs -52.9% 80mg atorvastatin (95% CI -8.4 to -3.0 treatment difference, p < 0.001),<br>• 10 mg/10 mg simvastatin/ezetimibe +7.7% HDL-C vs +6.9% 10mg atorvastatin (no p value)<br>• 20 mg/10 mg simvastatin/ezetimibe +7.2% HDL-C vs +5.1% 20mg atorvastatin (no p value)<br>• 40 mg/10 mg simvastatin/ezetimibe +9.0% HDL-C vs +3.8% 40mg atorvastatin ( p < 0.001)<br>• 80 mg/10 mg simvastatin/ezetimibe +7.5% HDL-C vs +1.4% 80mg atorvastatin ( p < 0.001)<br>• When averaged across dose ranges, the percentage of patients that reached the NCEP ATP II LDL-C goal was significantly greater with the combination product; 89.7% vs 81.1% (p < 0.001) |
| Bays[23]<br><br>Ten different treatments: ezetimibe 10mg, simvastatin 10mg, 20mg, 40mg, 80mg,or Vytorin® 10/10, 10/20, 10/40, or 10/80 | Randomized, double-blind, placebo-controlled, multicentered trial<br><br>n = 1528<br>12 weeks | **Primary Endpoint**: percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/ simvastatin vs simvastatin alone | • When patients receiving Vytorin® were compared to those receiving all doses of simvastatin (monotherapy), Vytorin® significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C.<br>• Vytorin® also produced significantly greater reductions in LDL-C compared to simvastatin monotherapy at each individual dose comparison (p<0.001).<br>• The LDL-C reduction observed with Vytorin® was significantly greater compared to each next highest dose of simvastatin (p<0.001).<br>• Pooled Vytorin® therapy significantly reduced the following other lipid parameters compared to pooled simvastatin: non-HDL-C (-49% vs –36%, p<0.001); apolipoprotein B (-42% vs –32%, p<0.001); TG (-24 vs –21%, p<0.001).<br>• The effects of Vytorin® on HDL-C were similar to the effects with simvastatin but were significantly greater compared with placebo.<br>• Overall safety was similar across all treatment groups. |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Ballantyne[25]<br><br>Three treatment groups: atorvastatin 10, 20, 40, or 80mg or Vytorin® 10/10, 10/20, 10/40 or 10/80 (Group 3 started at 10/20 instead of 10/10) | Randomized, double-blind, forced titration multicenter study<br><br>After four weeks of diet/placebo, patients who had not attained NCEP LDL-C goal, were randomized to one of three treatment groups for four 6-week periods<br><br>n = 788<br>24 weeks | **Primary Endpoint:** percent change in LDL-C and HDL-C from baseline to end of treatment period | • At the end of Period 1, the mean LDL cholesterol reduction was significantly greater with Vytorin® 10/10mg/day (46%) and Vytorin® 10/20mg/day (50%) than with atorvastatin 10mg/day (37%; both $p \leq 0.05\%$), and the mean HDL cholesterol increase was greater (8.0% and 10% vs 5%; both $p \leq 0.05$).<br>• At the end of Week 4, when max doses of the drugs were administered, Vytorin® 10/80mg/day caused a greater mean LDL cholesterol reduction than did atorvastatin 80mg/day (59% vs 53%) and a greater mean increase in HDL cholesterol (12% vs 6%; both $p \leq 0.005$).<br>• Vytorin® was superior to atorvastatin in decreasing LDL-C at each dose. Table 10 in the study further describes the lipid parameters from baseline for all treatment periods.<br>• The safety of Vytorin® was observed to be similar to that of atorvastatin monotherapy. |
| Goldberg[26]<br><br>Co-administered ezetimibe and simvastatin equivalent to Vytorin®, with simvastatin monotherapy | Randomized, double-blind, placebo-controlled, multicentered trial<br><br>Patients with primary hyperlipidemia<br><br>n = 887<br>12 week | **Primary Endpoint:** percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/ simvastatin vs simvastatin alone | • Coadministration of ezetimibe/simvastatin (pooled data) led to a mean percent reduction in LDL-C levels from baseline to study endpoint of –53% compared with a reduction of –38% with simvastatin alone (pooled).<br>• The incremental mean percent LDL-C reduction for pooled ezetimibe/simvastatin vs pooled simvastatin alone was 14.8% ($p<0.001$).<br>• The percent reduction in LDL-C with ezetimibe/simvastatin at any given simvastatin dose was significantly greater than that seen with the next higher dose of simvastatin alone ($p<0.001$ for all between-group comparisons).<br>• The mean percent reduction from baseline in LDL-C levels at study endpoint obtained with ezetimibe/simvastatin at 10/10mg was numerically similar to that with simvastatin 80mg alone.<br>• A greater number of patients in the ezetimibe plus simvastatin treatment group reached LDL-C goal of <100mg/dL compared to simvastatin monotherapy (82% vs 43%, $p<0.001$).<br>• Coadministration of ezetimibe and simvastatin also resulted in significant improvements in TC, non-HDL-C, TG, Apo B, LDL-C:HDL-C, and TC:HDL-C ($p<0.001$ for between group comparisons). |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Davidson[27]<br><br>Ezetimibe coadministered with simvastatin (equivalent to Vytorin® 10/10, 10/20, 10/40, 10/80) with simvastatin monotherapy | Randomized, double-blind, placebo-controlled, multicentered trial<br><br>Patients with primary hyperlipidemia<br><br>n = 668<br>12 week | **Primary Endpoint**: percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/ simvastatin vs simvastatin alone | • Ezetimibe coadministered with simvastatin was significantly more effective than simvastatin monotherapy in reducing plasma LDL-C levels from baseline to endpoint (-49.9% vs 36.1%).<br>• The combination resulted in a significant 13.8% LDL-C reduction compared with pooled simvastatin alone ($p<0.01$).<br>• Mean percentage changes in direct LDL-C from baseline to endpoint ranged from approximately –44% to –57% for coadministration versus –27% to –44% for simvastatin monotherapy.<br>• NCEP ATP III goal was reached by 77% of patients receiving coadministration therapy (pooled data) versus 64% who received simvastatin monotherapy ($p<0.01$).<br>• Tolerability of the combination was similar to that of simvastatin and placebo.<br>• Eight patients, six receiving coadministration therapy and two receiving simvastatin monotherapy, had consecutive elevations ≥ 3X ULN for ALT and/or AST levels. However, activity was asymptomatic and no cases of hepatitis, jaundice, or signs of liver dysfunction were reported. |
| Gaudiani[28]<br><br>Six weeks of simvastatin 20mg/day then patients received the addition of either ezetimibe 10mg/day or simvastatin 20mg/day, for 24 weeks. | Randomized, double-blind, parallel group multicenter trial<br><br>diabetic patients stable on a thiazolidine-dione, with hyperlipidemia<br><br>n = 214<br>30 weeks | **Primary Endpoint**: percent change in LDL-C and HDL-C from baseline to end of treatment period | • Coadministered ezetimibe plus simvastatin was significantly more effective than doubling the dose of simvastatin to 40mg.<br>• Median changes from baseline for the combination were: LDL-C:25% and –5%; total-C:16% and –5%; Apo B: -19% and –5%, and non-HDL-C: -23% and –5%. Results for the HDL-C and TG between the two treatment groups were not significantly different.<br>• 33% of patients were above goal for LDL-C at randomization. Of these, 75.7% in the ezetimibe + simvastatin 20mg group versus 39.4% in the simvastatin 40mg only group had LDL-C <100mg/dL at the end of the study.<br>• 2.7% of the simvastatin monotherapy patients and 1.0% of the ezetimibe + simvastatin patients discontinued therapy due to treatment-related adverse events. |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| Gagne[29]<br><br>Co-administration of ezetimibe plus a statin (atorvastatin or simvastatin) | Randomized, double-blind trial<br><br>patients with homozygous familial hypercholester-olemia already receiving statin treatment plus NCEP or stricter diet<br><br>n = 50<br>12 weeks | **Primary Endpoint**: percent change in LDL-C from baseline to end of treatment period | • Ezetimibe plus statin significantly reduced LDL-C levels compared with the 80mg statin dose alone (-20.7% vs –6.7%, p=0.007).<br>• In high-dose statin cohorts, ezetimibe plus statin 80mg reduced LDL-C by an additional 20.5% (p=0.0001).<br>• Increasing the dose of simvastatin from 40mg to 80mg produced a reduction of LDL-C of 13% from baseline on simvastatin 40mg.<br>• Coadministration of ezetimibe and simvastatin (equivalent to Vytorin® 10/40 and 10/80 pooled), produced a reduction of LDL-C of 23% from baseline on simvastatin 40mg.<br>• In patients previously on baseline simvastatin 40mg, coadministered ezetimibe and simvastatin (10/80), produced a reduction in LDL-C of 29%.<br>• One patient in the statin 80mg group and one patient in the ezetimibe plus statin group had asymptomatic single transient increases in serum ALT and/or AST >3 X ULN.<br>• There were no episodes of myopathy or rhabdomyolysis. |

**Additional Evidence**

Dose Simplification:
A literature search revealed no peer reviewed studies comparing adherence rates in patients given HMG-CoA Reductase Inhibitors combination products versus patients receiving therapy with each agent separately.

Studies have shown improved efficacy when the agents in these combination products are taken together, but no studies have evaluated patient adherence or observed differences in outcomes with the combination products as compared to coadministration of their individual components.

Additionally, all of the agents under discussion are administered once daily, so the combination products offer patients only the opportunity to take one versus two tablets per day

Stable Therapy:
A search of Medline and Ovid did not reveal data pertinent to this topic.

Impact on Physician Visits:
A search of Medline and Ovid 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 medication within this 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 costs 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 dosing 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-$50 per Rx |
| $$ | $51-$75 per Rx |
| $$$ | $76-$100 per Rx |
| $$$$ | $101-$150 per Rx |
| $$$$$ | Over $150 per Rx |

Rx = prescription

**Table 10. Relative Cost of Combination HMG-CoA Reductase Inhibitors**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Atorvastatin/amlodipine | tablet | Caduet® | $$$$ | N/A |
| Ezetimibe/simvastatin | tablet | Vytorin® | $$$ | N/A |
| Lovastatin/niacin | extended-release tablet | Advicor® | $$$ | N/A |
| Pravastatin/aspirin | tablet | Pravigard PAC® | $$$$$ | N/A |

There are no generics available.
N/A = not available

## X. Conclusions

Studies have shown positive benefits when another agent is added to a HMG CoA-reductase inhibitor. The combination products are considered equivalent to the individual components, and no studies have directly compared the efficacy of different dosing regimens. Studies confirm that the efficacy and safety of the combination products are similar to the individual agents when administered separately. The combination products demonstrate no clinical advantage over the individual components when coadministered.

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

## XI. Recommendations

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

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Review of Miscellaneous Antilipemic Agents**
**AHFS Class 240692**
**February 22, 2006**

# I. Overview

The mechanism of the lipid lowering effects of niacin is not completely understood. The primary mechanism of action seems to be inhibition of mobilization of free fatty acids from adipose tissues. Niacin also reduces hepatic synthesis of triglycerides (TG) and very low-density lipoprotein (VLDL), which in turn leads to decreased synthesis of low-density lipoprotein. Finally, niacin also increases high-density lipoprotein by reducing its catabolism.[1]

Lowering total cholesterol and low-density lipoprotein cholesterol (LDL-C) and raising high-density lipoprotein cholesterol (HDL-C) are important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD).[2] Every 1% reduction in LDL-C results in a 1.7% decrease in the risk of a major coronary event. An inverse relationship exists between HDL-C and the risk for developing CHD: every 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.[1] Thus, pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is worthwhile. Hypertriglyceridemia (triglycerides > 150mg/dL) is also a risk factor for CHD and should be treated.

Niacin is not as widely used as HMG-CoA Reductase Inhibitors ("statins"), but it may be a useful treatment option for combined hyperlipidemias (increased triglycerides and LDL-C with decreased HDL-C). Niacin is available in three different formulations; immediate-release (IR), extended-release (ER), and sustained-release (SR). Prescription products include immediate-release niacin and extended-release niacin. Additionally, the immediate-release and sustained-release products are available over-the-counter (OTC) and all of these products are labeled as "dietary supplements." The OTC formulations of Niacin are not regulated by the Food and Drug Administration (FDA) in the same way as prescription niacin. In fact, OTC niacin may contain variable amounts of niacin other than stated on the product labeling. The American Heart Association states that OTC dietary supplement niacin must not be used as a substitute for prescription niacin.[3]

This review encompasses all niacin dosage forms and strengths. These products are listed in Table 1. In accordance with Preferred Drug Legislation, this review does not include information on the antilipemic Omacor® (omega-3-acid ethyl esters) because it has not been on the market for at least 6 months. This medication will be reviewed at a future time.

**Table 1. Niacin Single Entity Agents Included in this Review**

| Generic Name | Formulations | Example Brand Name(s) | Current PDL Agents |
|---|---|---|---|
| niacin | Elixir | Niacels®^ | niacin |
| | Immediate-Release | Niacor® | niacin |
| | Extended-Release | Niaspan® | none |
| | Sustained-Release | Slo-Niacin®^ , Niadelay®^ | niacin |

^Product is available over-the-counter.

# II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under Antilipemic Agents. 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.[2] The NCEP guidelines focus primarily on attaining goal LDL-C levels, since LDL-C is the major atherogenic lipid component. However, 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.[2]

## III. Indications

The Food and Drug Administration (FDA) approved niacin for use as an adjunct to diet for the reduction of total cholesterol and LDL-C in patients with primary hypercholesterolemia. Niacin is also indicated to reduce the risk of recurrent nonfatal myocardial infarction (MI) in patients with a history of MI and hypercholesterolemia. Table 2 summarizes the FDA-approved indications for single entity niacin products.

**Table 2. FDA Approved Indications for Single Entity Niacin Agents[4,5]**

| Indication | Extended-release Niacin (Niaspan®) | Immediate-release Niacin (Niacor®) |
|---|---|---|
| As an adjunct to diet for the reduction of elevated TC and LDL-C in patients with primary hypercholesterolemia | | ✔ |
| Hypertriglyceridemia | ✔ | ✔ |
| As an adjunct to diet for the reduction of TC, LDL-C, Apo B, TG, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia | ✔ | |
| In combination with lovastatin for the treatment of primary hypercholesterolemia* | ✔ | |
| In combination with a bile acid binding resin for reduction of elevated TC and LDL-C | ✔ | |

* Not indicated for initial therapy

In general, niacin, when compared to statins or fibric acid derivatives, is the most effective agent for increasing HDL-C. Niacin also effectively lowers LDL-C and triglycerides, although to a lesser extent than statins and fibric acid derivatives. Table 3 details the cholesterol-modifying effects of the agents in this review.

**Table 3. Comparative Cholesterol Modifying Effects for Single Entity Niacin Agents[4,5]**

| Agent | TC | LDL-C | TG | HDL-C |
|---|---|---|---|---|
| Extended-release Niacin | ↓ 5-12% | ↓ 7-16% | ↓ 16-38% | ↑ 14-22% |
| Immediate-release Niacin | ↓ 10-20% | ↓ 10-20% | ↓ 30-70% | ↑ 20-35% |

## IV. Pharmacokinetics

The main difference between the various niacin products are half-life and absorption. Niacin (extended-release and immediate-release) is rapidly and extensively absorbed from the gastrointestinal (GI) tract. Niacin extended-release at a 1 to 2 gram dose is absorbed over 8-12 hours whereas immediate-release niacin at a 1 gram dose reaches peak plasma concentration within 30-60 minutes.[4,5] Sustained-release niacin has the slowest absorption rate of > 12 hours.

## V. Drug Interactions

Major clinical drug interactions for the single entity niacin agents have not been reported.[4,5] However, all niacin products should be used cautiously when administered concomitantly with HMG-CoA Reductase Inhibitors or fibric acid derivatives due to increased risk for rhabdomyolysis. While this does not preclude use of niacin with a statin or fibric acid derivative, additional care should be exercised to closely monitor the patient for any signs or symptoms of myopathy.

## VI. Adverse Drug Events

Patient intolerance tends to limit niacin use, particularly prostaglandin mediated vasodilatory (flushing of the neck and face, postural hypotension, tingling and itching) and GI side effects (nausea, vomiting, dyspepsia, and aggravation of peptic ulcer disease). Vasodilatory effects tend to be dose related and typically subside after several weeks of niacin therapy. [4,5] Pre-medicating with aspirin 325 mg or a non-steroidal anti-inflammatory drug 30 minutes prior to niacin administration may help to minimize flushing. It is also advisable to avoid hot beverages or alcohol around the time of niacin administration to minimize flushing. Extended-release niacin is typically taken at bedtime so flushing may be less bothersome because it occurs during sleep. However, care must be taken on the part of the patient if he/she is awakened by the flushing—the patient should get up slowly especially if feeling dizzy, faint, or taking antihypertensive medications. [4,5]

Increases in hepatic enzymes have been reported with niacin and thus periodic monitoring of liver function tests is recommended. The risk of liver toxicity is significantly greater with some sustained-release formulations of niacin.[3] In fact, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at equivalent doses. Therefore, caution is warranted when switching from an immediate-release product to a sustained-release or extended-release product. In addition, such conversions should be initiated at low doses then titrated slowly according to tolerability. Niacin may also increase glucose levels and serum uric acid, so it should be used cautiously in patients with diabetes or gout.

Large head-to-head trials that compare tolerance of extended-release niacin to immediate-release niacin have not been published. However, one small study of 223 men and women with hypercholesterolemia compared extended-release niacin 1.5 grams/day to immediate-release niacin 1.5 grams/day (given as 500 mg three times daily) for 8 weeks.[6] Both formulations demonstrated comparable increases liver enzymes (AST increased 5% versus 4.8% for ER niacin and IR niacin, respectively; $p > 0.05$) and increasing fasting plasma glucose levels (4.8% versus 4.5% for, ER niacin and IR niacin, respectively; $p > 0.05$). Statistically significant differences were seen for increases in uric acid (6% versus 16% for, ER niacin and IR niacin, respectively; $p = 0.0001$) and for flushing events (576 versus 1,905 for ER niacin and IR niacin, respectively; $p < 0.001$). Flushing severity was reported by study participants to be slightly greater with ER niacin.[6]

Conversely, studies comparing IR niacin and SR niacin have reported an incidence of hepatotoxicity of up to 52% with SR niacin. [7]

In placebo-controlled trials of ER niacin, flushing was reported by as many as 88% of patients.[4,5] In comparison to IR niacin, the proportion of patients who experienced flushing was similar; however, patients who took ER niacin reported fewer flushing episodes.

Regarding the adverse event potential of OTC "dietary supplement" niacin, the American Heart Association has issued the following statement:

> "Niacin (nicotinic acid) comes in prescription form and as "dietary supplements." Dietary supplement niacin is not regulated by the U.S. 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.

"Dietary supplement (OTC) niacin must not be used as a substitute for prescription niacin. It should not be used for cholesterol lowering because of potentially very serious side effects."3

## VII. Dosing and Administration

Both ER niacin and IR niacin should be initiated at a low dose and titrated slowly according to patient tolerance and response. In general, immediate-release niacin is dosed twice daily or three times daily; extended-release niacin can be dosed once daily (recommended at bedtime). No studies have been conducted to compare patient compliance with immediate-release versus extended-release niacin. Table 4 details the dosing guidelines for the niacin products included in this review.

**Table 4. Dosing and Administration of Single Entity Niacin Agents[4,5]**

| Agent | Dosing & Administration |
|---|---|
| Extended-release Niacin (Niaspan®) | Initiate at 500 mg/day (given as a single dose at bedtime after a low-fat snack) and continue for 4 weeks. Titrate to 1 gram/day (given as two 500 mg tablets at bedtime) for the next 4 weeks. After week 8, dosage should be titrated to patient response and tolerance. If patient LDL-C or TG not at goal, can titrate dose to 1.5 grams/day (single dose at bedtime). Daily dose should not be titrated by more than 500mg/day every 4 weeks. Maximum recommended dose is 2 grams/day (as a single dose at bedtime). |
| Immediate-release Niacin (Niacor®) | Initiate at 250mg/day (given as a single dose following the evening meal). Increase the frequency of dosing and the total daily dose every 4-7 days until goal LDL-C or TG is attained or if the therapeutic dose of 1.5-2 grams/day is reached (and if the patient tolerates). After 2 months of 1.5-2 grams/day, if goal LDL-C or TG is not reached, the dosage can be further titrated every 2-4 weeks to 1 gram three times daily. Usual adult dose is 1-2 grams two or three times daily. Higher doses are occasionally required but should not exceed 6 grams/day. |

Special Dosing Considerations

As stated previously, extended-release and sustained-release niacin are not interchangeable with immediate-release.[3] When switching from an immediate-release product to an extended-release product, start at a lower dose and titrate according to tolerance. Long-acting forms should not be crushed, broken, or chewed. Do not substitute long-acting forms for immediate-release ones.

Precautions

Niacin should be used cautiously in those taking concomitant anticoagulants or vasodilators and in those with diabetes, high alcohol consumption, history of liver disease, gout, renal disease or unstable angina.[4,5]

## VIII. Effectiveness

**Table 5. Outcomes Evidence for Niacin (Nicotinic Acid)**

<table>
<tr><th>Study</th><th>Study Design</th><th>Duration</th><th>Efficacy Variables</th><th>Results</th></tr>
<tr>
<td>Knopp[6]</td>
<td>Randomized, double-blind, parallel trial<br><br>223 men and women with hypercholesterolemia compared ER niacin (Niaspan®) 1.5 grams/day to “plain niacin” 1.5 grams/day (given as 500 mg three times daily)</td>
<td>16 weeks</td>
<td>Primary Endpoint<br>efficacy and safety of a once daily ER niacin compared to plain niacin</td>
<td>• ER niacin provided comparable efficacy (a non-statistically and non-clinically significant difference) to plain niacin.<br>• Effects on lipid parameters included:<br><br>
<table>
<tr><th>Agent</th><th>TC</th><th>LDL-C</th><th>TG</th><th>HDL-C</th></tr>
<tr><td>ER niacin</td><td>8%</td><td>12%</td><td>16%</td><td>20%</td></tr>
<tr><td>IR Niacin</td><td>8%</td><td>12%</td><td>18%</td><td>17%</td></tr>
</table>
<br>• AST increases were similar (5.0% versus 4.8%) and not significant.<br>• Flushing events were more frequent with plain niacin versus ER niacin (1,905 vs 576), $p < .001$). Flushing severity was slightly greater with Niaspan®, but still well tolerated.</td>
</tr>
<tr>
<td>CDP[8]</td>
<td>Randomized, placebo controlled trial<br><br>8,341 men (aged 30-64 years) with previous MI; looked at both IR niacin and clofibrate compared to placebo<br><br>(n = 3,908 for niacin vs placebo)</td>
<td>9 years</td>
<td>Primary Endpoint<br>long-term efficacy and safety of lipid-influencing drugs</td>
<td>Compared to placebo, niacin 3 g/day resulted in:<br>• A reduced incidence of nonfatal MI (placebo= 12.2%, niacin = 8.9%; $p < 0.004$).<br>• A comparable total mortality incidence (placebo = 25.4%; niacin = 24.4%; p value was not-significant).<br>• No evidence of efficacy was found with clofibrate.<br><br>A follow up of subjects 9 years after study completion showed:[9]<br>• Niacin reduced risk of all-cause mortality by 11% (placebo = 58.2%, niacin = 52%; $p = 0.0004$).</td>
</tr>
</table>

| Study | Study Design | Duration | Efficacy Variables | Results |
|---|---|---|---|---|
| McKenney[7] | Randomized, double-blind, parallel trial<br><br>46 patients with LDL-C >160 mg/dL after 1 month on an NCEP-Step 1 diet received IR or SR niacin administered sequentially at 500, 1000, 1500, 2000, and 3000 mg/d, each for 6 weeks. | 6 weeks | **Primary Endpoint**<br>compare escalating doses of IR and SR niacin for effects on lipid parameters and for the occurrence of adverse reactions, especially hepatotoxicity | • SR niacin lowered LDL-C significantly more than IR niacin did at the dosage of 1500 mg/d and above.<br>• IR niacin increased HDL-C levels significantly more than SR niacin did at all dosage levels.<br>• TG levels were decreases were similar with IR and SR niacin.<br>• 39% of the IR niacin group withdrew before completing the 3000-mg daily dose.<br>  ○ The most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans.<br>• 78% of SR niacin group withdrew before completing the 3000-mg daily dose.<br>  ○ The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction.<br>  ○ None of the patients taking IR niacin developed hepatotoxic effects, while 52% of the patients taking SR niacin did. |
| Guyton[10] | Randomized, double blind placebo controlled trial<br><br>173 patients received ER niacin (Niaspan®) , titrated over 1-4 wk intervals up to 2000mg daily or gemfibrozil 1200 mg daily | 8 weeks | **Primary Endpoint**<br>effect on HDL level | • ER niacin 1500 mg and 2000 mg raised HDL by 21% and 26%, respectively) vs 13% with gemfibrozil p <0.02.<br>• Triglycerides decreased by 40% with gemfibrozil vs 16% with niacin 1000 mg and 30% with niacin 2000 mg. p<.001.<br>• Flu syndrome occurred more frequently with niacin vs gemfibrozil group (p=0.006).<br>• Dyspepsia was a more frequent occurrence with gemfibrozil (p=0.009). |

| Study | Study Design | Duration | Efficacy Variables | Results |
|---|---|---|---|---|
| Grundy[11] | Randomized, double blind placebo controlled trial<br><br>148 type 2 diabetics received ER niacin (Niaspan®) 1000mg/day, 1500 mg/day, or placebo.<br><br>47% were receiving concomitant statin therapy | 16 weeks | **Primary Endpoint**<br>efficacy and safety of once-daily ER niacin in type 2 diabetics with dyslipidemia | Compared to placebo, niacin resulted in:<br><br>• A dose-dependent ↑ in HDL-C +19% to +24% (p <.05) vs placebo.<br>• Reductions in TG levels –13% to –28% (p <.05) vs placebo for the 1500-mg ER niacin).<br>• Non-significant changes in hemoglobin A1C levels at baseline to week 16 with ER niacin 1000mg/day (7.28% and 7.35%) vs placebo (7.13% and 7.11%) p = .16.<br>• Significant changes in hemoglobin A1C levels at baseline to week 16 with ER niacin 1500mg/day (7.2% and 7.5%) vs placebo (p = 0.048).<br>• Four patients in the ER niacin group discontinued participation because of inadequate glucose control.<br>• Rates of adverse event rates other than flushing were similar for the niacin and placebo groups.<br>• No hepatotoxic effects or myopathy was observed. |
| ARBITER[12] | Randomized, double blind placebo controlled trial<br><br>167 patients (mean age 67 years) with known coronary heart disease and low levels of HDL-C (<45 mg/dL) received ER niacin (Niaspan®) 1000 mg daily or placebo in addition to background statin therapy | 1 year | **Primary Endpoint**<br>Change in common carotid intima-media thickness (CIMT) after 1 year | Compared to placebo, niacin resulted in:<br>• A 21% ↑ in HDL-C.<br>• An unchanged mean CIMT of 0.014mm (p=0.23) compared to an increased mean CIMT with placebo group (0.044mm) p<0.001.<br>• The overall difference in CIMT progression between the groups was not statistically 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).<br>• Clinical cardiovascular events occurred in 3 patients treated with niacin (3.8%) vs 7 patients with placebo (9.6%) P=0.20. |

**Additional Evidence**

Dose Simplification:
A search of Medline and Ovid did not reveal data pertinent to this topic.

Stable Therapy:
A search of Medline and Ovid revealed no peer reviewed studies evaluating the effects of changing from between various formulations of niacin. However, as mentioned previously, when switching from an immediate-release product to an extended-release product, niacin should be started at a lower dose and titrated. Different formulations (immediate-release, extended-release) of niacin should not be used interchangeably; severe hepatic toxicity (e.g., fulminant hepatic necrosis) has occurred in individuals who substituted certain extended-release niacin preparations for immediate-release niacin at equivalent dosages.

Impact on Physician Visits:
A search of Medline and Ovid 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 medication within this 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 costs 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 dosing 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 | |
|---|---|
| $ | $0-25 per Rx |
| $$ | $26-$50 per Rx |
| $$$ | $51-$75 per Rx |
| $$$$ | $76-$100 per Rx |
| $$$$$ | Over $100 per Rx |

Rx=prescription

**Table 6. Relative Cost of Miscellaneous Antilipemic Agents**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Niacin | elixir, extended-release tablet, sustained-release capsule, sustained-release tablet, tablet | Niacels®^, Niacor®, Niadelay®^, Niaspan®, Slo-Niacin®^ | $-$$$ | N/A |

^Product is available over-the-counter.
N/A = Not available

## X. Conclusions

Only once-daily, extended-release niacin has been shown to be as efficacious as immediate-release niacin.[13] While extended-release niacin may offer better tolerance than immediate-release niacin, extended-release niacin is still associated with tolerability problems.[4,5] Large randomized trials that definitively show improved tolerance of extended-release niacin compared to immediate-release niacin are lacking. Niacin has been shown to reduce the rates of fatal and nonfatal MI and cardiac surgical interventions.[8] However, there is a need for additional large randomized trials that firmly establish the role of niacin in reducing cardiovascular morbidity and mortality.

There are significant safety concerns with older forms of OTC-SR niacin as is evident from the American Heart Association (AHA) position statement, which 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.[3] Furthermore, the AHA states that OTC-SR niacin should not be used for cholesterol lowering because of potentially very serious side effects including hepatotoxicity. This narrows the choices to two products, prescription immediate-release or extended-release niacin.

Therefore, the prescription immediate-release and extended-release niacin products are comparable to each other but do appear to offer clinical advantage over OTC products in this class.

## XI. Recommendations

Prescription niacin is recommended for preferred status. Alabama Medicaid should negotiate with manufacturers of prescription niacin products and possibly designate at least one product for preferred status.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Class Review**
**Platelet-Aggregation Inhibitors AHFS Class 920000,**
**Aspirin AHFS Class 280804, and Dipyridamole AHFS Class 241292**
**Single Entity**
**February 22, 2006**

# I. Overview

Platelet-aggregation inhibitors, also known as antiplatelet agents, play a major role in the management of coronary artery disease, angina, stroke, transient ischemic attacks (TIAs), and myocardial infarction. In addition, antiplatelet drugs are used after angioplasty and heart bypass surgery, and to prevent the formation of blood clots in patients with atrial fibrillation. For over a century, aspirin has been used as a pain reliever and antipyretic agent via its inhibition of the cyclooxygenase (COX) enzyme. When this enzyme is blocked, platelets are less able to produce prostaglandins, chemicals that signal injury and trigger the pain response, namely thromboxane A-2. However, since the 1970s, and the emergence of new studies, aspirin has also been used to prevent and manage a variety of cardiac diseases and is currently the most commonly used antiplatelet drug. Since thromboxane A-2 can also trigger the platelet-aggregation cascade, aspirin inhibits clot formation to prevent stroke and the occurrence of a heart attack, or other cardiac complications.[1]

In addition to thromboxane A-2, 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. Dipyridamole inhibits adenosine uptake into erythrocytes, endothelial cells and platelets and is another medication that decreases platelet aggregation.[1]

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 Agents |
|---|---|---|---|
| aspirin | chewable tablet, delayed-release capsule, delayed-release tablet, enteric-coated tablet, packet, rectal suppository, sustained-release tablet, tablet | Arthritis Foundation®^, Aspir 81®^, Aspir-Low®^, Children's Aspirin®^, Children's Chewable Aspirin®^, Easprin®^, EC Aspirin®^, Eco-5®^, Ecotrin®^, Ecpirin®^ Empirin®^, Genacote®^, Genprin®^, St. Joseph Aspirin®^, Stanback Analgesic®^, Sureprin 81®^, ZORprin®^ | aspirin^ |
| cilostazol | oral tablet | Pletal®* | cilostazol |
| clopidogrel | oral tablet | Plavix® | none |
| dipyridamole | oral tablet, injection | Persantine®* | dipyridamole |
| ticlopidine | oral tablet | Ticlid®* | ticlopidine |

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

## II. Evidence Based Medicine and Current Treatment Guidelines

**Table 2. Treatment Guidelines Using the Platelet-Aggregation Inhibitors***

| Clinical Guideline | Recommendation |
|---|---|
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Ischemic Stroke**[2] | **Acute ischemic stroke:**, Early (within 48 hours of stroke onset) aspirin therapy, 160 to 325 mg/d is recommended for patients with ischemic stroke who are not receiving thrombolysis (Grade 1A).<br><br>**Noncardioembolic transient ischemic attack (TIA) or stroke:**<br>• To prevent cerebral ischemic events, an antiplatelet agent is recommended (Grade 1A) and acceptable options for initial therapy include aspirin 50 to 325 mg qd; the combination of aspirin 25mg and extended-release (ER) dipyridamole 200 mg bid; or clopidogrel 75mg qd.<br>• Low doses of aspirin, 50 to 100 mg/d, is recommended in patients receiving aspirin who are at moderate-to-high risk of bleeding complications (Grade 1C+).<br>• The authors suggest use of the combination of aspirin and ER dipyridamole 25/200 mg bid over aspirin (Grade 2A), and clopidogrel over aspirin (Grade 2B).<br>• Clopidogrel is recommended in patients who are allergic to aspirin (Grade 1C+).<br>• Antiplatelet agents are recommended over oral anticoagulation for most patients with noncardioembolic TIA or stroke (Grade 1A).<br>• Oral anticoagulation is suggested over antiplatelet agents in patients with well-documented prothrombotic disorders (Grade 2C).<br><br>**Carotid endarterectomy:** Aspirin 81 to 325 mg/d, prior to and following the procedure, is recommended to prevent cerebral ischemic events (Grade 1A).<br><br>**Stroke with underlying atrial fibrillation:**<br>• Long-term oral anticoagulation [target international normalized ratio (INR) 2.5; range 2.0 to 3.0] is recommended in patients with atrial fibrillation (AF) who have had a recent stroke or TIA (Grade 1A).<br>• Aspirin is recommended for patients with cardioembolic stroke who have contraindications to anticoagulant therapy (Grade 1A). |
| National Institute for Health and Clinical Excellence (NICE) 2005: **Clopidogrel and Modified-release Dipyridamole in the Prevention of Occlusive Vascular Events**[3] | 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 revascularisation or carotid artery procedures.<br><br>• As part of the prevention of occlusive vascular events:<br>  • The combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischaemic stroke or a transient ischaemic 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).<br>  • 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.<br>• For the purposes of this guidance, aspirin intolerance is defined as either of the following:<br>  • Proven hypersensitivity to aspirin-containing medicines.<br>  • History of severe dyspepsia induced by low-dose aspirin. |

| Clinical Guideline | Recommendation |
|---|---|
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Antithrombotic Therapy for Coronary Artery Disease**[2] | **Acute management of non-ST-elevation (NSTE) acute coronary syndrome (ACS):**<br>• Aspirin 75 to 325 mg orally and then daily 75 to 162 mg is recommended for all patients presenting with NSTE ACS without a clear allergy to aspirin (Grade 1A).<br>• Clopidogrel 300mg bolus orally, followed by 75 mg/d indefinitely is recommended for all NSTE ACS patients with an aspirin allergy (Grade 1A).<br>• In addition to aspirin, clopidogrel (bolus 300mg followed by 75mg/d for 9 to 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 (Grade 1A).<br>• In NSTE ACS patients in whom angiography will take place rapidly (≤ 24 h), the authors suggest beginning clopidogrel after the coronary anatomy has been determined (Grade 2A).<br>• 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 (Grade 2A).<br>• 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 patients presenting with NSTE ACS (not graded).<br>• Either eptifibatide or tirofiban is recommended for initial (early) treatment in addition to aspirin and heparin in moderate- to high-risk patients presenting with NSTE ACS (Grade 1A). In these moderate- to high-risk patients who are also receiving clopidogrel, eptifibatide or tirofiban is recommended as additional initial treatment (Grade 2A).<br><br>**Post myocardial infarction (MI) and post ACS:**<br>• Aspirin at initial doses from 160 to 325 mg, and then indefinite therapy, 75 to 162 mg/d is recommended in patients with ACSs with and without ST-segment elevation (Grade 1A).<br>• For patients with a history of aspirin-induced bleeding or with risk factors for bleeding, we recommend lower doses (≤ 100 mg) of aspirin (Grade 1C+).<br>• Long-term administration of clopidogrel 75mg/d is recommended for patients in whom aspirin is contraindicated or not tolerated (Grade 1A).<br>• In most health-care settings, for moderate- and low-risk patients with a myocardial infarction (MI), aspirin alone over oral vitamin K antagonists (VKAs) plus aspirin is recommended (Grade 2B).<br>• In health-care settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after MI, 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 (both Grade 2B).<br>• For high-risk patients with MI, including those with a large anterior MI, 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/d) for 3 months after the MI (Grade 2A).<br><br>**Chronic stable coronary artery disease (CAD):**<br>• Aspirin 75 to 162 mg po qd is recommended for all patients with chronic stable CAD (Grade 1A). The authors suggest that aspirin be continued indefinitely (Grade 2C).<br>• 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 |

| Clinical Guideline | Recommendation |
|---|---|
| | development of acute MI (Grade 2C).<br><br>**<u>Congestive heart failure (CHF) with and without CAD:</u>**<br>• In patients with CHF due to nonischemic etiology, the authors recommend against routine use of aspirin or oral VKAs (Grade 1B).<br>• The authors recommend that when otherwise indicated, patients receive aspirin whether or not they are receiving ACEIs (Grade 1C+).<br><br>**<u>Primary prevention:</u>**<br>• Aspirin 75 to 162 mg/d is recommended over either no antithrombotic therapy or 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%) (Grade 2A).<br>• 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 (Grade 2A). |
| ACC/AHA 2002: **Guideline Update for the Management of Patients with Unstable Angina and Non–ST-segment Elevation Myocardial Infarction**[4]<br><br>AHA 2005: **Practical Implementation of the Guidelines for Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction in the Emergency Department** [5] | **<u>Hospital care:</u>**<br>• Antiplatelet therapy should be initiated promptly. Aspirin should be administered as soon as possible after presentation and continued indefinitely (Level of Evidence A).<br>• Clopidogrel should be administered to hospitalized patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Level of Evidence A).<br>• In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to aspirin as soon as possible on admission and administered for at least 1 month (Level of Evidence A) and for up to 9 months (Level of Evidence B).<br>• In patients for whom a percutaneous coronary intervention is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (Level of Evidence A) and up to 9 months (Level of Evidence B).<br>• In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days (Level of Evidence B).<br>• Anticoagulation with subcutaneous low molecular weight heparin or intravenous unfractionated heparin should be added to antiplatelet therapy with aspirin and/or clopidogrel (Level of Evidence A).<br>• A platelet GP IIb/IIIa antagonist should be administered, in addition to aspirin and heparin, to patients in whom catheterization and percutaneous coronary intervention are planned. The GP IIb/IIIa antagonist may also be administered just prior to percutaneous coronary intervention (Level of Evidence A).<br><br>**<u>Long-term medical management:</u>**<br>• Aspirin 75 to 325 mg qd in the absence of contraindications (Level of Evidence A).<br>• Clopidogrel 75 mg daily (in the absence of contraindications) when aspirin is not tolerated because of hypersensitivity or gastrointestinal intolerance (Level of Evidence A).<br>• The combination of aspirin and clopidogrel for 9 months after UA/NSTEMI (Level of Evidence B). |

| Clinical Guideline | Recommendation |
|---|---|
| AHA 2005 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: **Stabilization of the Patient With Acute Coronary Syndromes**[6] | **Initial treatment ACS:**<br>• The early administration of a single chewed dose of aspirin (160 to 325 mg) is recommended in either the out-of-hospital or emergency department (ED) setting for patients with suspected ACS (Class I). Other formulations of ASA (soluble, IV) may be as effective as chewed tablets. Aspirin suppositories (300 mg) are safe and can be considered for patients with severe nausea, vomiting, or disorders of the upper gastrointestinal tract.<br><br>**Adjunctive treatment for ACS and AMI:**<br>• Clopidogrel 300-mg loading dose in addition to standard care (aspirin, UFH, or LMWH and GP IIb/IIIa inhibitors if indicated) to ED patients with ACS with elevated cardiac markers or new ECG changes consistent with ischemia (excluding STEMI) in whom a medical approach or PCI is planned (Class I).<br>• It is reasonable to administer a 300-mg oral dose of clopidogrel to ED patients with suspected ACS (without ECG or cardiac marker changes) who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Class IIa). Providers should administer a 300-mg oral dose of clopidogrel to ED patients up to 75 years of age with STEMI who receive aspirin, heparin, and fibrinolysis. |
| European Society of Cardiology 2002: **Acute Coronary Syndromes**[7] | • Acute treatment with aspirin is recommended in all patients with suspected acute coronary syndromes in the absence of contraindications (Level of Evidence A) and for long-term treatment thereafter (Level of Evidence A).<br>• In ACS patients, clopidogrel is recommended for acute treatment and for long term treatment, for at least 9-12 months (Level of Evidence B)<br>• Clopidogrel should be given to ACS patients scheduled for angiography unless there is a likelihood that the patients will proceed to urgent surgery (within 5 days) (no specified Level of Evidence).<br>• Clopidogrel may also be recommended for immediate and long-term therapy in patients who do not tolerate aspirin (CAPRIE), and is recommended in patients receiving a stent (Level of Evidence B). |
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Thrombolysis and Adjunctive Therapy in Acute Myocardial Infarction**[2] | **Adjunctive treatment with antithrombotic agents in patients receiving fibrinolysis for acute myocardial infarction (MI):**<br>• Aspirin, 160 to 325 mg orally, at initial evaluation by healthcare personnel followed by indefinite therapy, 75 to 162 mg/d orally is recommended for patients with acute ST elevation MI, whether or not they receive fibrinolytic therapy (both Grade 1A).<br>• Clopidogrel, 300 mg followed by a maintenance dose of 75 mg/d, is suggested as an alternative to aspirin in patients who are allergic to aspirin (Grade 2C). |

| Clinical Guideline | Recommendation |
|---|---|
| ACC/AHA: **Guidelines for the Management of Patients with ST-elevation Myocardial Infarction (STEMI)**[8] | **Hospital management Class I:**<br>• A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy (Level of Evidence: A). Aspirin should be given to the patient with suspected STEMI as early as possible and should be continued indefinitely, regardless of the strategy for reperfusion and regardless of whether additional antiplatelet agents are administered. True aspirin allergy is the only exception to this recommendation.<br>• Clopidogrel combined with aspirin is recommended for STEMI patients who undergo coronary stent implantation. In patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and for up to 12 months in patients who are not at high risk for bleeding (Level of Evidence: B).<br><br>**Secondary prevention Class I:**<br>• A daily dose of aspirin 75 to 162 mg orally should be given indefinitely to patients recovering from STEMI (Level of Evidence: A).<br>• If true aspirin allergy is present, preferably clopidogrel (75 mg orally per day) or alternatively, ticlopidine (250 mg orally twice daily) should be substituted (Level of Evidence: C).<br>• If true aspirin allergy is present, warfarin therapy with a target INR of 2.5 to 3.5 is a useful alternative to clopidogrel in patients less than 75 years of age who are at low risk for bleeding and who can be monitored adequately for dose adjustment to maintain a target INR range (Level of Evidence C).<br><br>**CABG surgery after STEMI Class I:**<br>• Aspirin should not be withheld before elective or nonelective CABG after STEMI (Level of Evidence C).<br>• Aspirin (75 to 325 mg daily) should be prescribed as soon as possible (within 24 hours) after CABG unless contraindicated (Level of Evidence B).<br>• In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of excess bleeding. (Level of Evidence: B) |
| European Society of Cardiology 2004: **Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease**[9] | **Major recommendations for individual antiplatelet agents:**<br><br>Aspirin<br>• Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favourable benefit/risk profile.<br>• Because of gastrointestinal (GI) 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.<br>• The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (i.e., $\geq$3% per annum).<br>• In clinical situations where an immediate antithrombotic effect is required (such as in acute coronary syndromes or in acute ischaemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane (TX)-A2-dependent platelet aggregation.<br>• No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. |

| Clinical Guideline | Recommendation |
|---|---|
| | • 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 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting.<br>• Nonsteroidal anti-inflammatory drugs (NSAIDs) 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.<br>• Because of potential pharmacodynamic interactions between traditional NSAIDs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring NSAID therapy may benefit from the use of selective cyclooxygenase-2 (COX-2) inhibitors.<br><br>**Ticlopidine**<br>• The role of ticlopidine in the present therapeutic armamentarium is uncertain. Now that ticlopidine is available as a generic drug in many countries, its lower cost as compared to clopidogrel is being emphasized within a broad cost-containment strategy.<br>• 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.<br>• In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction.<br><br>**Clopidogrel**<br>• 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.<br>• 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.<br>• The results of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial have led to 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 glycoprotein (GP) IIb/IIIa antagonists.<br><br>**Dipyridamole**<br>• 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 non-cardioembolic cerebral ischaemic events, there is no basis to recommend this combination in patients with ischaemic heart disease. |

| Clinical Guideline | Recommendation |
|---|---|
| American College of Cardiology Foundation 2005: **Coronary Artery Bypass Graft (CABG)**[10] | **Saphenous vein graft patency:**<br>• Aspirin significantly reduces vein graft closure during the first postoperative year.<br>• Aspirin should be started within 24 hours after surgery.<br>• Dosing regimens from 100 to 325 mg per day appear to be efficacious.<br>• Ticlopidine offers no advantage over aspirin but is an alternative in truly aspirin-allergic patients. Life-threatening neutropenia is a rare but recognized side effect.<br>• Clopidogrel has fewer side effects than ticlopidine as an alternative in aspirin-allergic patients. |
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Antithrombotic Therapy in Patients with Saphenous Vein and Internal Mammary Artery Bypass Grafts**[2] | **Prevention of saphenous vein graft occlusion following coronary artery bypass grafting (CABG):**<br>• Aspirin, 75 to 162 mg/d, is recommended indefinitely for all patients with coronary artery disease (CAD) (Grade 1A).<br>• Aspirin, 75 to 162 mg/d, starting 6 hours after CABG operation is recommended over preoperative aspirin (Grade 1A).<br>• 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 (Grade 1C).<br>• For patients undergoing CABG, the addition of dipyridamole to aspirin therapy is not recommended (Grade 1A).<br>• Clopidogrel, 300 mg orally 6 hours after operation followed by 75 mg/d, is recommended for patients with CAD undergoing CABG who are allergic to aspirin (Grade 1C+).<br>• Clopidogrel, 75 mg/d, for 9 to 12 months following CABG, in addition to aspirin, is recommended in patients who undergo CABG for non-ST-segment elevation ACS (Grade 1A).<br>• 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 (Grade 2A).<br><br>**Prevention of internal mammary bypass graft occlusion following CABG:**<br>• Aspirin, 75 to 162 mg/d, is recommended indefinitely for all patients with CAD who undergo internal mammary artery bypass grafting. |
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Antithrombotic Therapy in Valvular Heart Disease-Native and Prosthetic**[2] | **Prosthetic heart valves:**<br>• For all patients with mechanical prosthetic heart valves, VKAs are recommended (Grade 1C+). Administration of unfractionated heparin or LMWH until the INR is stable and at a therapeutic level for 2 consecutive days is also advised (Grade 2C).<br>• In patients who have mechanical valves and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction, a target INR of 3.0 (range 2.5 to 3.5), combined with low doses of aspirin, 75 to 100 mg/d, is recommended (Grade 1C+).<br>• For patients with caged ball or caged disk valves, a target INR of 3.0 (range 2.5 to 3.5) in combination with aspirin, 75 to 100 mg/d, is suggested (Grade 2A).<br>• For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, aspirin, 75 to 100 mg/d, in addition to VKAs, and maintenance of the INR at target of 3.0 (range 2.5 to 3.5) is recommended (Grade 1C+).<br>• In patients with prosthetic heart valves in whom VKAs must be discontinued, low molecular weight heparin (Grade 1C) or aspirin 80 to 100 mg/day is recommended (Grade 1C). |

| Clinical Guideline | Recommendation |
|---|---|
| | • VKAs with a target INR 2.5 (range 2.0 to 3.0) are recommended for patients with bioprosthetic valves in the mitral position for the first 3 months after valve insertion (Grace 1C+).<br>• VKAs with a target INR of 2.5 (range 2.0 to 3.0) for the first 3 months after valve insertion (Grade 2C) or aspirin 80 to 100 mg/d (Grade 1C) are suggested for patients with bioprosthetic valves in the aortic position.<br>• Long-term treatment with VKAs with a target INR of 2.5 (range 2.0 to 3.0) is recommended in patients with bioprosthetic valves who have AF (Grade 1C+).<br>• Long-term therapy with aspirin 75 to 100 mg/d is recommended for patients with bioprosthetic valves who are in sinus rhythm and do not have AF (Grace 1C+). |
| American College of Cardiology Foundation 2005: **Percutaneous Coronary Intervention (PCI)**[11] | **Class I:**<br>• Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed (Level of Evidence: A).<br>• Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed (Level of Evidence: C).<br>• After the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent (BMS) implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg (Level of Evidence: B).<br>• A loading dose of clopidogrel should be administered before PCI is performed (Level of Evidence: A). An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy (Level of Evidence: B).<br>• In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after BMS implantation (unless the patient is at increased risk for bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding (Level of Evidence: B).<br><br>**Class IIa:**<br>• If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial to facilitate earlier platelet inhibition than with clopidogrel alone (Level of Evidence: B).<br>• For patients with an absolute contraindication to aspirin, it is reasonable to give a 300 mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI (Level of Evidence: C).<br>• When a loading dose of clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared with a 300 mg loading dose are less established (Level of Evidence: C).<br>• It is reasonable that patients undergoing brachytherapy be given daily clopidogrel 75 mg indefinitely and daily aspirin 75 to 325 mg indefinitely unless there is significant risk for bleeding (Level of Evidence: C).<br><br>**Class IIb:**<br>• In patients in whom subacute thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated (Level of Evidence: C). |

| Clinical Guideline | Recommendation |
|---|---|
| Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy 2004: **Peripheral Arterial Occlusive Disease** [2] | **Chronic limb ischemia:**<br>• Lifelong aspirin therapy, 75 to 325 mg/d, is recommended in comparison to no antiplatelet therapy in patients with clinically manifest coronary or cerebrovascular disease (Grade 1A) and in those without clinically manifest coronary or cerebrovascular disease (Grade 1C+).<br>• Clopidogrel is recommended over ticlopidine (Grace 1C+).<br>• Clopidogrel is recommended in comparison to no antiplatelet therapy, but the authors suggest aspirin be used instead of clopidogrel (Grade 2A).<br>• 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 (Grade 2A). The authors suggest that clinicians not use cilostazol in those with less-disabling claudication (Grade 2A).<br><br>**Vascular grafts-prolonging the patency of grafts:**<br>• Aspirin is recommended in patients undergoing prosthetic infrainguinal bypass (Grade 1A).<br>• For routine patients undergoing infrainguinal bypass without special risk factors for occlusion, Vitamin K antagonists (VKAs) plus aspirin are not recommended (Grade 1A). VKAs plus aspirin are suggested for those at high risk of bypass occlusion and limb loss (Grade 2B).<br><br>**Carotid endarterectomy:**<br>• Aspirin, 75 to 325 mg/d, is recommended preoperatively and continued indefinitely in patients undergoing carotid endarterectomy (Grade 1A).<br><br>**Asymptomatic and recurrent carotid stenosis:**<br>• Lifelong aspirin, 75 to 162 mg/d is recommended in nonoperative patients with asymptomatic or recurrent carotid stenosis (Grade 1C+).<br><br>**Lower extremity endovascular procedures:**<br>• Long-term aspirin, 75 to 162 mg/d, is recommended for all patients undergoing lower-extremity balloon angioplasty (with or without stenting) (Grace 1C+). |

*See Table 3 for grade definitions.

**Table 3. Classification of Recommendations[2,4]**

| Grade of Recommendation | Clarity of Risk/Benefit | Methodologic Strength of Supporting Evidence |
|---|---|---|
| ACCP Grade Definitions | | |
| 1A | Clear | Randomized trials without important limitations |
| 1B | Clear | Randomized trials with important limitations (inconsistent results, methodological flaws) |
| 1C+ | Clear | No RCTs, but RCT results can be unequivocally extrapolated, or overwhelming evidence from observation studies |
| 1C | Clear | Observation studies |
| 2A | Unclear | Randomized trials without important limitations |
| 2B | Unclear | Randomized trials with important limitations (inconsistent results, methodological flaws) |
| 2C | Unclear | Observation studies |
| ACC/AHA/SCAI Definitions | | |
| Class I | | Conditions for which there is evidence of and/or general agreement that a given procedure or treatment is beneficial, useful and effective. |
| Class II | | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. |
| Class IIa | | Weight of evidence/opinion is in favor of usefulness/efficacy. |
| Class IIb | | Usefulness/efficacy is less well established by evidence/opinion. |
| Class III | | Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. |
| Level of Evidence A | | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of Evidence B | | Data derived from a single randomized trial or nonrandomized studies. |
| Level of Evidence C | | Only consensus opinion of experts, case studies, or standard-of-care. |

## III. Indications

**Table 4. FDA-Approved Indications for the Platelet-Aggregation Inhibitors[12]**

| Drug | FDA-Approved Indications |
|---|---|
| **Aspirin** | • Arthritis<br>• Cerebrovascular accident - transient ischemia<br>• Coronary artery bypass graft<br>• Disorder of joint of spine<br>• Fever<br>• Juvenile rheumatoid arthritis<br>• Myocardial infarction<br>• Myocardial infarction-prophylaxis<br>• Osteoarthritis<br>• Pain<br>• Percutaneous coronary intervention<br>• Pleurisy - systemic lupus erythematosus<br>• Rheumatoid arthritis<br>• Stable angina, chronic<br>• Unstable angina |
| **Dipyridamole** | • Myocardial imaging with thallium<br>• Prosthetic cardiac valve replacement-prophylaxis |
| **Cilostazol** | • Intermittent claudication-reduction of symptoms |
| **Clopidogrel** | • Acute coronary syndrome-prophylaxis<br>• Myocardial infarction-prophylaxis<br>• Peripheral arterial occlusive disease-prophylaxis<br>• Thromboembolic stroke-prophylaxis |
| **Ticlopidine** | • Thromboembolic stroke-prophylaxis<br>• Placement of stents in coronary artery, in combination with aspirin |

## IV. Pharmacokinetics

**Table 5. Pharmacokinetics of the Platelet-Aggregation Inhibitors[12]**

| **Drug** | Aspirin | Cilostazol | Clopidogrel | Dipyridamole | Ticlopidine |
|---|---|---|---|---|---|
| **Bio-availability** | 50% to 75% | 87 to 100% | N/A (well absorbed) | 37% to 66% | 80% to 90% |
| **Protein Binding** | 50% to 80% | 97% to 98% | 94% to 98% | 91% to 99% | 98% |
| **Metabolism** | Hepatic | Hepatic, primarily via CYP 3A4 | Hepatic; extensively hydrolyzed | Hepatic | Hepatic; extensively metabolized |
| **Active Metabolites** | Yes; salicylate | Yes | Yes (has not been isolated) | None | Yes |
| **Elimination** | Renal (5.6% to 35.6%) | Renal (74%); fecal (20%) | Renal (50%); fecal (46%) | Fecal | Renal (60%); fecal (23%) |
| **Half-Life** | 15-20 mins (parent compound) 3-10 hrs (metabolite) | 11-13 hrs | 8 hrs | 10-12 hrs | 12.6 hrs |

## V. Drug Interactions

Platelet-aggregation inhibitors may have pharmacodynamic interactions with other platelet function inhibitors. Cilostazol could have pharmacokinetic interactions because of effects on other drugs on its metabolism by CYP3A4 or CYP2C19. Cilostazol does not appear to inhibit CYP3A4. At high concentrations, clopidogrel inhibits CYP2C9 and may interfere with the metabolism of some drugs. There is no information on the concurrent use of cilostazol and clopidogrel. Significant drug interactions with the platelet-aggregation inhibitors are noted in Table 6.

**Table 6. Significant Drug Interactions with the Platelet-Aggregation Inhibitors[13]**

| Precipitant Drug | Object Drug | Description |
|---|---|---|
| Antacids | Ticlopidine | Ticlopidine plasma levels decreased by 18% when administered after antacids. |
| Aspirin | ACE Inhibitors<br>Beta Blockers<br>Diuretics | The effectiveness may be diminished by concomitant aspirin because of inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention. |
| Aspirin | Acetazolamide | Concomitant use may lead to high serum levels of acetazolamide due to competition at the renal tubule for secretion. |
| Aspirin | Anticoagulants | Because of aspirin's effects on platelets, patients on anticoagulation therapy are at increased risk of bleeding. Aspirin can displace warfarin from protein binding sites, leading to prolongation of PT and bleeding time. Aspirin can also increase the anticoagulant activity of heparin. |
| Aspirin | Anticonvulsants | Reports of increased free fraction of valproic acid, possibly leading to toxic effects of valproic acid. High doses of salicylates may increase the pharmacologic and toxic effects of hydantoins. |
| Aspirin | Cilostazol | Short-term ($\leq$ 4 days) coadministration with aspirin increased ADP-induced ex vivo platelet aggregation by 23-35% with no clinically significant impact on PT, aPTT, or bleeding time versus aspirin alone. Effects of long-term coadministration are unknown. Of 201 patients, the incidence of hemorrhagic adverse effects compared to aspirin alone was not greater. |
| Aspirin | Clopidogrel | Risk of life-threatening bleeding (e.g., intracranial and GI hemorrhage) may be increased in high-risk patients with transient ischemic attack or ischemic stroke. |
| Aspirin | Methotrexate | Salicylates can inhibit renal clearance of methotrexate. |
| Aspirin | NSAIDs | Concurrent use may increase bleeding or lead to decreased renal function. |
| Aspirin | Oral Hypoglycemics | Moderate aspirin doses may increase the hypoglycemic effects of these drugs. |
| Aspirin | Uricosuric Agents | Salicylates antagonize the uricosuric action of uricosuric agents. |
| Cimetidine | Ticlopidine | Chronic cimetidine reduced clearance of a single ticlopidine dose by 50%. |
| Diltiazem | Cilostazol | Diltiazem increased cilostazol plasma concentrations by about 53%. Initiate therapy at half the recommended dose. |
| Dipyridamole | Adenosine | Plasma levels and cardiovascular effects of adenosine were increased. |

| Precipitant Drug | Object Drug | Description |
|---|---|---|
| Dipyridamole | Cholinesterase Inhibitors | Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis. |
| Macrolides | Cilostazol | Erythromycin increased Cmax and AUC of cilostazol by 47% and 73%, respectively. Other macrolides would be expected to have similar effect. Initiate therapy at half the recommended dose. |
| NSAIDs | Clopidogrel | Coadministration of clopidogrel with naproxen was associated with increased occult GI blood loss. Administer with caution. |
| Omeprazole | Cilostazol | Coadministration of omeprazole increased systemic exposure to 3,4-dehydro-cilostazol by 69%. Initiate therapy at half the recommended dose. |
| Ticlopidine | Aspirin | Ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. Ticlopidine-mediated inhibition of ADP-induced platelet aggregation is not affected. Coadministration is not recommended. |
| Ticlopidine | Digoxin | Digoxin plasma levels may decrease slightly (about 15%). |
| Ticlopidine | Phenytoin | Coadministration resulted in elevated phenytoin plasma levels leading to somnolence and lethargy. Exercise caution with coadministration and suggest remeasuring phenytoin levels. |
| Ticlopidine | Theophylline | Theophylline elimination half-life increased from 8.6 to 12.2 hours with a comparable reduction in total plasma clearance. |
| Warfarin | Clopidogrel | Clopidogrel prolongs bleeding time. The safety of coadministration has not been established; therefore, administer concomitantly with caution. |

## VI. Adverse Drug Events

**Table 7. Adverse Drug Events (ADEs) Associated with Platelet-Aggregation Inhibitors[12]**

| Drug | Common ADEs (frequency %) | Serious ADRs (frequency %) |
|---|---|---|
| **Aspirin** | • Gastrointestinal: Dyspepsia, Nausea and vomiting | • Gastrointestinal: Gastrointestinal ulcer<br>• Hematologic: Bleeding<br>• Otic: Tinnitus<br>• Respiratory: Bronchospasm<br>• Other: Angioedema, Reye's syndrome |
| **Cilostazol** | • Cardiovascular: Edema, Palpitations, Tachyarrhythmia<br>• Gastrointestinal: Abdominal pain, Diarrhea, Dyspepsia, Flatulence, Nausea<br>• Musculoskeletal: Back pain, Myalgia<br>• Neurologic: Dizziness, Headache, Vertigo<br>• Respiratory: Cough, Pharyngitis, Rhinitis<br>• Other: Infectious disease | • Cardiovascular: Atrial fibrillation, Congestive heart failure, Myocardial infarction, Ventricular tachycardia<br>• Gastrointestinal: Gastrointestinal ulcer, Hematemesis, Melena<br>• Hematologic: Anemia, Hemorrhage<br>• Ophthalmic: Bleeding eye<br>• Respiratory: Asthma, Epistaxis, Hemoptysis |

| Drug | Common ADEs (frequency %) | Serious ADRs (frequency %) |
|---|---|---|
| **Clopidogrel** | • Cardiovascular: Bleeding (Mild), Chest pain, Edema, Hypertension<br>• Dermatologic: Purpuric disorder, Rash<br>• Endocrine metabolic: Hypercholesterolemia<br>• Gastrointestinal: Abdominal pain, Constipation, Diarrhea, Dyspepsia, Gastritis<br>• Musculoskeletal: Arthralgia, Back pain<br>• Neurologic: Dizziness, Headache | • Cardiovascular: Atrial fibrillation (<2.5%), Congestive heart failure (<2.5%)<br>• Dermatologic: Erythema multiforme (rare)<br>• Gastrointestinal: Gastrointestinal hemorrhage (2%, 2.7% with aspirin), Gastrointestinal ulcer<br>• Hematologic: Agranulocytosis (<1%), Anemia (<2.5%), Neutropenia (rare), Thrombotic thrombocytopenic purpura (rare)<br>• Hepatic: Hepatitis (rare), Liver function tests abnormal (rare)<br>• Immunologic: Anaphylaxis (rare)<br>• Neurologic: Intracranial hemorrhage (0.4%)<br>• Ophthalmic: Intraocular hemorrhage (rare)<br>• Renal: Abnormal renal function (<1%), Acute renal failure (<1%) |
| **Dipyridamole** | • Cardiovascular: ECG abnormal (15.9%), Hypotension, IV (4.6%)<br>• Gastrointestinal: Abdominal discomfort, Oral (6.1%), Nausea, IV (4.6%)<br>• Neurologic: Dizziness (12%), Headache, IV (12.2%), Headache, Oral (2.3%) | • Cardiovascular: Angina pectoris, Exacerbation with IV (19.7%), Myocardial infarction (rare), Ventricular arrhythmia (rare)<br>• Respiratory: Bronchospasm (rare) |
| **Ticlopidine** | • Dermatologic: Pruritus, Rash<br>• Gastrointestinal: Abdominal pain, Diarrhea, Dyspepsia, Loss of appetite, Nausea<br>• Hematologic: Purpuric disorder<br>• Hepatic: Liver function tests abnormal<br>• Neurologic: Dizziness | • Hematologic: Aplastic anemia (rare), Neutropenia (2.4%), Thrombotic thrombocytopenic purpura (rare) |

## VII. Dosing and Administration

**Table 8. Usual Dosing for the Platelet-Aggregation Inhibitors[12]**

| Drug | Usual Adult Dosage | Usual Pediatric Dosage | Availability |
|---|---|---|---|
| Aspirin | • Arthritis: initial oral 3 g a day (divide every 4-6 hr), increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL<br>• Cerebrovascular accident - Transient ischemia: 50-325 mg orally once a day<br>• Coronary artery bypass graft: 325 mg orally once a day start 6 hr post-procedure, continue for 1 yr<br>• Disorder of joint of spine: up to | • Juvenile rheumatoid arthritis: initial 90-130 mg/kg/day (divide every 4-6 hr) orally, increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL<br>• Kawasaki disease: high-dose (acute phase), 80-100 mg/kg/day (divided every 6 hr) ORALLY; continue therapy until afebrile for 48 to 72 hours, OR until day 14 of illness and afebrile for at least 48 hours; then low-dose, 3 to 5 mg/kg/day until no evidence of | Oral Capsule, Delayed-release: 81 mg<br>Oral Gum: 227 mg<br>Oral Tablet: 81 mg, 325 mg, 486 mg, 500 mg, 650 mg, 800 mg<br>Oral Tablet, Chewable: 81 mg<br>Oral Tablet, Enteric Coated: 81 mg, 162 mg, 325 mg, 487.5 mg, 500 mg, 650 |

| Drug | Usual Adult Dosage | Usual Pediatric Dosage | Availability |
|---|---|---|---|
| | 4 g orally per day (divide every 4-6 hr)<br>• Fever: 325-650 mg orally every 4 hr as needed; maximum 4 g in 24 hr<br>• Myocardial infarction-acute: 160 to 325 mg orally, followed by indefinite therapy, 75 to 162 mg/d.<br>• Myocardial infarction; Prophylaxis: 75-325 mg orally every day<br>• Osteoarthritis: initial oral 3 g a day (divide every 4-6 hr), increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL<br>• Pain: 325-650 mg orally every 4 hr as needed; maximum 4 g in 24 hr<br>• Percutaneous coronary intervention: initial 325 mg orally 2 hr pre-procedure; maintenance 160-325 mg daily<br>• Pleurisy - Systemic lupus erythematosus: initial oral 3 g a day (divide every 4-6 hr), increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL<br>• Rheumatoid arthritis: initial oral 3 g a day (divide every 4-6 hr), increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL<br>• Stable angina, chronic: 75-325 mg orally once a day<br>• Unstable angina: 75-325 mg orally once a day | coronary changes, usually 6 to 8 weeks after onset of illness; continue low-dose aspirin indefinitely for patients with underlying coronary abnormalities (per AHA and AAP recommendations)<br>• Pain: 40-60 mg/kg/day (divide every 4-6 hr) orally, MAX 4 g in 24 hr | mg, 975 mg<br>Oral Tablet, Extended-release: 650 mg, 800 mg, 975 mg<br>Rectal Suppository: 1.2 g, 60 mg, 125 mg, 200 mg, 325 mg, 650 mg<br>Tablet: 325 mg |
| Cilostazol | • Intermittent claudication: 100 mg orally twice a day | Safety and efficacy in pediatric population have not been established | Tablet:<br>50 mg, 100 mg |

| Drug | Usual Adult Dosage | Usual Pediatric Dosage | Availability |
|---|---|---|---|
| Clopidogrel | • Coronary syndrome, acute - Thrombotic disorder; Prophylaxis: initial, 300 mg orally once; maintenance, 75 mg orally once daily<br>• Myocardial infarction - Thrombotic disorder; Prophylaxis: 75 mg orally once daily<br>• Peripheral arterial occlusive disease - Thrombotic disorder; Prophylaxis: 75 mg orally once daily<br>• Thromboembolic stroke - Thrombotic disorder; Prophylaxis: 75 mg orally once daily | Safety and efficacy in pediatric population have not established | Tablet:<br>75 mg |
| Dipyridamole | • Myocardial imaging, With thallium: 0.142 mg/kg/min (0.57 mg/kg total) IV over 4 min prior to thallium; maximum 60 mg<br>• Prosthetic cardiac valve thrombosis; Prophylaxis: 75-100 mg orally 4 times daily as an adjunct to warfarin therapy | Safety and efficacy in the pediatric population have not been established | Injection, solution:<br>5 mg/mL (2 mL, 10 mL)<br><br>Tablet:<br>25 mg, 50 mg, 75 mg |
| Ticlopidine | • Placement of stents in coronary artery, in combination with aspirin: 250 mg orally twice a day for 30 days<br>• Thromboembolic stroke prophylaxis: 250 mg orally twice a day | Safety and efficacy in pediatric population have not been established | Tablet:<br>250 mg |

## VIII. Effectiveness

**Table 9. Outcomes Evidence of Platelet-Aggregation Inhibitors**

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| International Stroke Trial (IST)[14]<br><br>Patients with acute ischemic stroke were randomized to either aspirin 300 mg daily or heparin 5000 or 12,500 IU twice daily, or a combination of aspirin and heparin within 48 h of stroke onset | Randomized, open trial<br><br>n=19,435<br><br>up to 14 days | Death within 14 days and death or dependency at 6 months | Aspirin-allocated patients:<br>• Slightly fewer deaths within 14 days (9.0% vs 9.4%)<br>• Significantly fewer recurrent ischemic strokes (2.8% vs 3.9%) with no significant excess of hemorrhagic strokes (0.9% vs 0.8%)<br>• Trend toward a reduction in death or dependence at 6 month (61.2% vs 63.5%)<br>(Only the results for the aspirin groups are presented.) |
| Chinese Acute Stroke Trial (CAST)[15]<br><br>Hospitalized patients with acute ischemic stroke were randomized to aspirin 160 mg/d or placebo within 48 h of stroke onset | Randomized, placebo-controlled trial<br><br>n=21,106<br><br>up to 4 weeks | Death from any cause during the 4-week treatment period, and death or dependence at discharge | • Aspirin group demonstrated small but significant reductions in both early mortality (3.3% vs 3.9% p=0.04) and recurrent ischemic strokes (1.6% vs 2.1% p=0.01)<br>• Aspirin-treated group reported a smaller proportion of patients who were dead or dependent (30.5% vs 31.6% p=0.08) |
| Antithrombotic Trialists' Collaboration[16]<br><br>Antiplatelet agents vs control or one antiplatelet regimen versus another among patients at high risk of occlusive vascular events | Meta-analysis<br><br>n=144,051 | "Serious vascular event": nonfatal MI, nonfatal stroke or vascular death | Overall, antiplatelet therapy:<br>• Reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15%<br>• 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.<br>• Clopidogrel reduced serious vascular event by 10% (4%) compared with aspirin, which was similar to the 12% (7%) reduction observed with ticlopidine<br>• The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| The Canadian American Ticlopidine Study (CATS)[17]<br><br>Patients with strokes occurring from 1 week to 4 months earlier were randomized to 250 mg of ticlopidine twice a day or placebo | Randomized, double-blind, placebo-controlled<br><br>n = 1072<br><br>up to 3 years | Event rate per year for stroke, myocardial infarction, or vascular death | Compared to placebo:<br>• Ticlopidine reduced the relative risk of stroke, MI or vascular death by 30%, to 10.8% (p=0.006) in the on-treatment analysis and 23% (p=0.020) using the intent-to-treat approach<br>• Ticlopidine reduced the relative risk of ischemic stroke by 33.5% (p=0.008) in the on-treatment analysis |
| Ticlopidine-Aspirin Stroke Study (TASS)[18]<br><br>250 mg ticlopidine twice a day vs 650 mg aspirin twice a day in patients with ischemic symptoms that occurred within 3 months of randomization | Randomized, blinded, randomized, multicenter trial<br><br>n = 3069<br><br>2-6 years | Primary endpoint defined as nonfatal stroke or death | Compared to aspirin:<br>• Ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate 17% ticlopidine vs 19% aspirin; p = 0.048)<br>• Ticlopidine reduced the risk of stroke after 3 years by 21% (10% ticlopidine vs 13% aspirin; p=0.024)<br>• Ticlopidine significantly increased total cholesterol compared to aspirin (9% vs 2%; p<0.01)<br>• Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites were infrequent and about equal in the two treatment groups<br>• Severe neutropenia occurred in 0.9% of patients |
| African American Antiplatelet Stroke Prevention Study [19]<br><br>Black men and women who recently had a noncardioembolic ischemic stroke were randomized to ticlopidine 250 mg twice daily vs aspirin 325 mg once daily | Randomized, double-blind, multicenter<br><br>n=1809<br><br>up to 2 years | Primary outcomes: recurrent stroke, MI, or vascular death<br><br>Secondary outcomes: fatal or nonfatal stroke | • No statistically significant difference between ticlopidine and aspirin in the prevention of recurrent stroke, MI or vascular death<br>• Nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group<br>• The frequency of laboratory-determined serious neutropenia was 3.4% ticlopidine vs 2.2% aspirin |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| CAPRIE[20]<br><br>Clopidogrel 75 mg/day vs aspirin 325 mg/day in patients with recent ischemic stroke, recent MI and symptomatic peripheral arterial disease | Randomized, blinded, multicenter trial<br><br>N = 19,185<br><br>1-3 years | Risk of composite outcome of ischemic stroke, MI or vascular death; and safety | • 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 relative risk reduction of 8.7% in favor of clopidogrel (p=0.043), and an absolute risk reduction of 0.5%.<br>• Corresponding on-treatment analysis yielded a relative-risk reduction of 9.4% in favor of clopidogrel<br>• For the 6,431 patients admitted to the study with stroke, the relative risk reduction for ischemic stroke, MI, or vascular death was 7.3% (p=0.26), and the relative risk reduction for the endpoint of stroke was 8% (p=.28)<br>• No significant differences between aspirin and clopidogrel in terms of safety |
| MATCH[21]<br><br>Aspirin vs placebo in high-risk patients with recent ischemic stroke or transient ischemic attack on clopidogrel | Randomized, double-blind, placebo-controlled<br><br>N=7599<br><br>18 months | Primary endpoint composite of ischemic stroke, MI, vascular death or rehospitalization for acute ischemia | • 15.7% patients reached primary endpoint in aspirin + clopidogrel group compared with 16.7% clopidogrel alone (p=0.244)<br>• Life-threatening, major and minor bleeding were significantly higher in the aspirin + clopidogrel group versus clopidogrel alone (P < 0.0001) |
| Leonardi-Bee et al[22]<br><br>Dipyridamole with or without aspirin vs aspirin alone vs control in patients with previous ischemic stroke or TIA | Meta-analysis of 5 randomized, controlled trials<br><br>n = 11,459 | Number of stroke/TIA recurrences | Dipyridamole, +/- aspirin:<br>• Reduced stroke recurrence in patients with previous ischemic cerebrovascular disease<br>Dipyridamole + aspirin:<br>• Reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with ASA alone |
| Sacco et al[23]<br><br>Aspirin + ER dipyridamole (Aggrenox®) vs aspirin only | Post-hoc analysis using data from the European Stroke Prevention Study 2<br><br>n = 1650 (Aggrenox®)<br>n = 1649 (ASA only) | Number of strokes | Compared to aspirin alone:<br>• Aspirin plus extended-release dipyridamole was more effective in reducing the risk of stroke (relative risk reduction 23%, p=.006) and stroke or vascular risk (relative risk reduction 22%, p=.003)<br>• The difference in efficacy increased in higher-risk patients |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| CURE[24]<br><br>Clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo in patients with non-ST-segment elevation, presenting within 24 hours of symptom onset, in addition to aspirin for 3 to 12 months | Randomized trial, double-blind, placebo-controlled<br><br>n = 12,562<br><br>3-12 months | First primary outcome-a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke<br><br>Second primary outcome-death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia | • 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 (p<0.001)<br>• 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 and aspirin versus aspirin alone<br>• The rate of the second primary outcome was 16.5% in the clopidogrel and aspirin group compared to 18.8% for the aspirin (p <0.001)<br>• There were significantly more patients with major bleeding in the clopidogrel and aspirin group than in the aspirin group (3.7% vs 2.7% p=0.001) but there were not significantly more patients with episodes of life-threatening bleeding or hemorrhagic strokes |
| PCI-CURE[25]<br><br>Patients from the CURE study undergoing percutaneous coronary intervention (PCI)<br><br>Prior to PCI, patients received aspirin with clopidogrel or placebo; after PCI, stented patients received an open-label thienopyridine in combination with aspirin for 2-4 weeks, then the randomly assigned study medication was resumed (for 3-12 months after initial randomization) | n=2658<br><br>(see CURE study) | Primary endpoint defined as composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI | • 4.5% patients in the clopidogrel and aspirin group had the primary endpoint compared with 6.4% in the aspirin group (p=0.03)<br>• Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, myocardial infarction, or any revascularization (p=0.03) and of cardiovascular death or myocardial infarction (p=0.047)<br>• Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or myocardial infarction (p=0.002) |
| CREDO[26]<br><br>Clopidogrel and aspirin vs aspirin alone in patients likely to undergoing (PCI) | Randomized, double-blind, placebo-controlled, multi-center<br><br>n = 2116<br><br>12 months | One-year incidence of the composite of death, MI, or stroke<br><br>28-day incidence of the composite of death, MI or urgent target vessel revascularization | • Long-term clopidogrel and aspirin therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke versus aspirin alone (p=0.02)<br>• Clopidogrel at least 6 hours before PCI, reduced the relative combined risk of death, MI, or stroke by 38.6% compared with no reduction with treatment less than 6 hours before PCI (p=.051) |

| Study | Study Design | Efficacy Variables | Results |
|---|---|---|---|
| CLASSICS[27]<br><br>Clopidogrel with a loading dose + aspirin, clopidogrel without a loading dose + aspirin or ticlopidine + aspirin after stent placement | Randomized<br><br>n=1020<br><br>28 days | Primary endpoint defined as major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation due to noncardiac adverse event<br><br>Secondary objective to evaluate the incidence occurrence of cardiac events | • Primary endpoint occurred in 9.1% of patients in the ticlopidine group and 4.6% of patients in the combined clopidogrel group (relative risk 0.50; p=0.005)<br>• Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups |
| Takeyasu et al[28]<br><br>Cilostazol + ASA (C group) or Ticlopidine + ASA (T group) in patients stent patients | Randomized trial<br><br>n = 321 (C)<br>n = 321 (T)<br><br>6 months | Rate of stenosis according to Qualitative Coronary Angiography (QCA) analysis of minimal lumen diameter (MLD) of artery | Compared with ticlopidine:<br>• Rate of stenosis with cilostazol was similar (no P-value reported)<br>• Rate of subacute thrombosis was significantly greater with cilostazol (P=0.02) |
| Leon et al[29]<br><br>3 Regimens:<br>ASA alone (557 patients), ASA and warfarin (550 patients), or ASA and ticlopidine (546 patients) | Randomized, multicenter study<br><br>n = 1653 | Rate of stent thromboses | • Compared to ASA alone, and ASA + warfarin, treatment with ASA and ticlopidine resulted in a lower rate of stent thrombosis (P=0.001) following coronary stenting<br>• There were more hemorrhagic complications with ASA alone (P<0.001) |

**Additional Evidence**

Dose Simplification: Aspirin and clopidogrel can be dosed once a day. Ticlopidine and dipyridamole require more frequent daily dosing. A search of Medline and Ovid did not reveal any information regarding improved clinical outcomes due the dosing administration schedule.

Stable therapy: A frequent clinical problem is patients who are already on aspirin because of coronary heart disease or a prior cerebral ischemic event, and then suffer a first or recurrent TIA or stroke. No single clinical trial has investigated this problem, particularly switching from aspirin to another platelet-aggregation inhibitor. A search of Medline and Ovid did not reveal any further information pertinent to this topic.

Impact on Physician Visits: A search of Medline and Ovid did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" has been created to provide a comparison of the average cost per prescription for medications within this 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. The relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

For new drug products, and/or those agents for which sufficient drug history does not exist upon which to base a relative cost value, the relative cost assigned to that product is determined based upon the discounted average wholesale price (AWP) of that product at its expected most common daily dosing.

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

| | |
|---|---|
| $ | $0 - $25 per Rx |
| $$ | $26 - $50 per Rx |
| $$$ | $51 - $75 per Rx |
| $$$$ | $76 - $100 per Rx |
| $$$$$ | Over $101 per Rx |

Rx=prescription

**Table 10. Relative Cost of Single Entity Platelet-Aggregation Inhibitors**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Aspirin | chewable tablet, delayed-release capsule, delayed-release tablet, enteric-coated tablet, packet, rectal suppository, sustained-release tablet, tablet | Arthritis Foundation®^, Aspir 81®^, Aspir-Low®^, Children's Aspirin®^, Children's Chewable Aspirin®^, Easprin®^, EC Aspirin®^, Eco-5®^, Ecotrin®^, Ecpirin®^ Empirin®^, Genacote®^, Genprin®^, St. Joseph Aspirin®^, Stanback Analgesic®^, Sureprin 81®^, ZORprin®^ | $ | $ |
| Cilostazol | tablet | Pletal®* | $$$$ | $$$$ |
| Clopidogrel | tablet | Plavix® | $$$$$ | N/A |
| Dipyridamole | injection, tablet | Persantine®* | $$$$ | $$ |
| 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 have been shown to significantly reduce the combined odds of stroke, MI or vascular death. Aspirin, cilostazol, dipyridamole and ticlopidine are available generically, and aspirin is available over-the-counter. Aspirin has been the most frequently studied antiplatelet inhibitor and is recommended first-line in most treatment guidelines for general use. Long-term aspirin administration, at doses of 75-150 mg/day, is at least as effective as higher daily doses in reducing serious vascular events among high risk patients, according to one meta-analysis. In some high risk patients, clopidogrel and ticlopidine further reduced the number of serious vascular events.

With or without aspirin, dipyridamole was shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease, and with aspirin, dipyridamole reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone.

Clinical trials have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. The two randomized studies that compared ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin. 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. More significant hemorrhagic complications were observed with aspirin alone. One disadvantage to this regimen, however, is that ticlopidine was shown to appreciably increase total cholesterol levels in patients.

When ticlopidine was compared to cilostazol in stent patients, the rate of stenosis was similar between agents. 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.

ADP-receptor antagonist therapy, including both clopidogrel and ticlopidine, significantly reduced the odds of a serious vascular event (stroke, MI, or vascular death). Aspirin is recommended first-line in most treatment guidelines for general use, with other platelet-aggregation inhibitors reserved for patients with contraindications or severe intolerance to aspirin. The CAPRIE study reported that clopidogrel was more effective than aspirin in reducing the combined risk of ischemic stroke, MI or vascular death in patients with atherosclerotic vascular disease; however, no statistically significant benefit over aspirin was seen for the stroke patients entered in this study.[20] On the basis of the CURE study, the use of clopidogrel has been incorporated into several guidelines for the management of acute coronary syndrome. [24]

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

## XI. Recommendations

No brand single entity 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 agents.

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**Alabama Medicaid Agency**
**Pharmacy and Therapeutics Committee Meeting**
**Pharmacotherapy Class Review**
**Platelet-Aggregation Inhibitors Combination Products**
**Aggrenox® (Aspirin/Dipyridamole) AHFS 241292**
**February 22, 2006**

## I. Overview

Aspirin, cilostazol, clopidogrel, dipyridamole and ticlopidine are all classified as platelet-aggregation inhibitors and were previously reviewed as single entity products. Aspirin and dipyridamole are the only platelet-aggregation inhibitors commercially available as a combination product. This review encompasses all dosage forms and strengths. (See Table 1.)

**Table 1. Combination Platelet-Aggregation Inhibitors Included in this Review**

| Generic Name | Formulation | Example Brand Name (s) | Current PDL Agent(s) |
|---|---|---|---|
| Aspirin and dipyridamole | oral capsule extended-release | Aggrenox® | none |

*There are no generics or over-the-counter products in this class.

## II. Evidence Based Medicine and Current Treatment Guidelines

Please refer to this section under the Single Entity Platelet-Aggregation Inhibitors.

## III. Indications

The fixed-dose combination product of aspirin and extended-release (ER) dipyridamole is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or complete ischemic stroke due to thrombosis. [1]

## IV. Pharmacokinetics

**Table 2. Pharmacokinetics of the Combination Platelet-Aggregation Inhibitors[2]**

| **Drug** | Aspirin | Dipyridamole |
|---|---|---|
| **Bioavailability** | 50% to 75% | 37% to 66% |
| **Protein binding** | 50% to 80% | 91% to 99% |
| **Metabolism** | Hepatic | Hepatic |
| **Active metabolites** | Yes; salicylate | None |
| **Elimination** | Renal (5.6% to 35.6%) | Fecal |
| **Half-life** | 15-20 minutes (parent compound) 3-10 hours (metabolite) | 10-12 hours |

## V. Drug Interactions

No drug-drug interaction studies have been conducted with fixed dose combination product of aspirin and ER dipyridamole. Please refer to the drug interaction section (Table 6) in the Single Entity Platelet-Aggregation Inhibitor Pharmacotherapy Class Review.

## VI. Adverse Drug Events

Adverse events that were reported in more than 2% of patients are listed in Table 3. Discontinuation due to adverse effects was 25% for aspirin and dipyridamole combination, 25% for dipyridamole, 19% for aspirin and 21% for placebo.

**Table 3. Adverse Drug Events (%) Associated with Combination Platelet-Aggregation Inhibitors[1]**

| Adverse reaction | Aspirin/Dipyridamole Extended-Release Combination (n=1650) | Dipyridamole Extended-Release (n=1654) | Aspirin (n=1649) | Placebo (n=1649) |
|---|---|---|---|---|
| % patients with one or more treatment events | 79.9 | 78.9 | 80.2 | 70.1 |
| Headache | 39.2 | 38.3 | 33.8 | 32.9 |
| Amnesia | 2.4 | 2.4 | 3.5 | 2.1 |
| Abdominal pain | 17.5 | 15.4 | 15.9 | 14.5 |
| Dyspepsia | 18.4 | 17.4 | 18.1 | 16.7 |
| Nausea | 16 | 15.4 | 12.7 | 14.1 |
| Vomiting | 8.4 | 7.8 | 6.1 | 7.2 |
| Diarrhea | 12.7 | 15.5 | 6.8 | 9.8 |
| Hemorrhage NOS | 3.2 | 1.5 | 2.8 | 1.5 |
| Epistaxis | 2.4 | 1 | 2.7 | 1.5 |
| Arthralgia | 5.5 | 4.5 | 5.5 | 4.6 |
| Arthritis | 2.1 | 1.5 | 1 | 1.2 |
| Pain | 6.4 | 5.3 | 6.2 | 6 |
| Fatigue | 5.8 | 5.6 | 5.9 | 5.5 |
| Back pain | 4.6 | 4.7 | 4.5 | 3.9 |
| Accidental injury | 2.5 | 1.5 | 3.1 | 2.2 |

NOS= not otherwise specified

## VII. Dosing and Administration

**Table 4. Usual Dosing for the Combination Platelet-Aggregation Inhibitors[1]**

| Drug | Usual Adult Dosage | Usual Pediatric Dosage | Availability |
|---|---|---|---|
| Aspirin and dipyridamole extended-release | 1 capsule orally twice a day, one in the morning and one in the evening | Safety and effectiveness in pediatric patients have not been studied; due to the aspirin component, this product is not recommended in the pediatric population | Aspirin 25 mg and dipyridamole 200mg extended-release capsule |

## VIII. Effectiveness

**Table 5. Clinical Efficacy Trials of Combination Platelet-Aggregation Inhibitors**

| Study | Methods | Efficacy Variables | Results |
|---|---|---|---|
| Sacco et al[23]<br><br>Aspirin + ER dipyridamole (Aggrenox®) vs aspirin only | Post-hoc analysis using data from the European Stroke Prevention Study 2<br><br>n = 1650 (Aggrenox®)<br>n = 1649 (ASA only) | Number of strokes | Compared to aspirin alone:<br>• Aspirin plus extended-release dipyridamole was more effective in reducing the risk of stroke (relative risk reduction 23%, p=.006) and stroke or vascular risk (relative risk reduction 22%, p=.003)<br>• The difference in efficacy increased in higher-risk patients |
| Leonardi-Bee et al[4]<br><br>Dipyridamole with or without aspirin versus control for secondary prevention after ischemic stroke or TIA | Meta-analysis of 5 randomized, controlled trials<br><br>n = 11,459 | Number of stroke/TIA recurrences | Dipyridamole +/- aspirin:<br>Reduced stroke recurrence in patients with previous ischemic cerebrovascular disease<br><br>Dipyridamole + aspirin:<br>Reduced the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death as compared with aspirin alone |
| Caplain et al[5]<br><br>Clopidogrel 75 mg + ASA 75 mg/day, ASA 75 mg/day, or ER-dipyridamole 200mg/ASA 25 mg twice a day for ex-vivo platelet effects | Crossover<br><br>10 days | Ex vivo platelet aggregometry | Clopidogrel + ASA:<br>• Significantly more effective than ER-dipyridamole + ASA in inhibiting collagen-induced platelet aggregation in whole blood (P=0.0009<br>• Significantly more effective than ASA or dipyridamole + ASA in inhibiting ADP-induced platelet aggregation in whole blood and platelet-rich plasma (p< or =0.0001) and in inhibiting collagen-induced aggregation in PRP (p, or =0.0001)<br>ASA alone and clopidogrel + ASA:<br>• Significantly more effective than dipyridamole + ASA in inhibiting arachidonic acid-induced platelet aggregation in whole blood (p<=0.0001)<br>The clinical significance of this finding remains to be confirmed. |
| Cadroy et al[6]<br><br>Once daily clopidogrel 75 mg/day + ASA 75 mg, or twice daily ER-dipyridamole 200 mg + ASA 25 mg | Randomized, double-blind, placebo-controlled, crossover study in healthy volunteers<br><br>n = 23<br><br>Two 10-day treatment periods, separated by a 14-day washout period | Assess antithrombotic effect using a human ex vivo model of arterial thrombosis | Clopidogrel + ASA showed significantly greater antithrombic efficacy compared with ER dipyridamole + ASA (p<0.0001) |

| Study | Methods | Efficacy Variables | Results |
|---|---|---|---|
| AGATE[7]<br><br>ER-dipyridamole 200 mg + ASA 25 mg versus aspirin 81 mg + placebo | Randomized<br><br>n=40<br><br>30 days | Platelet function | • In 61 of 90 direct comparisons, aspirin was equivalent to ER-dipyridamole + ASA.<br>• In 25 of 90 direct comparisons, the combination product demonstrated better platelet properties, whereas in 4 of 90 comparisons aspirin was better than the combination.<br>• The clinical significance of these results is no known. |

ER = extended-release
ASA=acetylsalicylic acid

**Additional Evidence**

Dose Simplification:
The combination product aspirin and ER dipyridamole is dosed two times a day. There are no studies that have shown that administration of the combination products resulted in better clinical outcomes when compared to administering the individual components.

Stable Therapy:
A literature search of Medline and Ovid did not reveal clinical studies that have investigated the effect of changing from combination products to individual components or vice versa. The fixed-dose combination product of aspirin and ER dipyridamole is not interchangeable with the individual components of aspirin and dipyridamole tables as the strengths of the ingredients are different in the fixed dose combination product and the individual ingredients.

Impact on Physician Visits:
A search of Medline and Ovid did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" has been created to provide a comparison of the average cost per prescription for medications within this 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. The relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

For new drug products, and/or those agents for which sufficient drug history does not exist upon which to base a relative cost value, the relative cost assigned to that product is determined based upon the discounted average wholesale price (AWP) of that product at its expected most common daily dosing.

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

| | |
|---|---|
| $ | $0 - $25 per Rx |
| $$ | $26 - $50 per Rx |
| $$$ | $51 - $75 per Rx |
| $$$$ | $76 - $100 per Rx |
| $$$$$ | $101 - $150 per Rx |

Rx=prescription

**Table 6. Relative Cost of Combination Platelet-Aggregation Inhibitors**

| Generic Name | Formulations | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Aspirin + dipyridamole | extended-release capsule | Aggrenox® | $$$$$ | N/A |

There are no generic or over-the-counter products in this class.
N/A = not available

## X. Conclusions

Dipyridamole and/or aspirin have been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease. Dipyridamole with aspirin reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone. Aspirin and dipyridamole are available generically; however, the fixed dose combination product contains strengths of aspirin and dipyridamole that are not commercially available. There are no studies that have shown that the combination product produces better clinical outcomes than administration of the individual ingredients. In comparison to other combinations of antiplatelet agents, in vivo data reports greater platelet inhibition and antithrombotic efficacy with the combination clopidogrel and aspirin; but, the clinical significance of these findings is not known.

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

## XI. Recommendations

No brand platelet-aggregation inhibitor 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 agents.

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