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DRUG EFFECTIVENESS REVIEW PROJECT

P&T Committee Brief
Drug Class Review on HMG-CoA Reductase Inhibitors (Statins)

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P&T Committee Brief Disclaimer

This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on HMG-CoA Reductase Inhibitors, Update 4" dated August 2006, which is a product of the OR Evidence-based Practice Center at Oregon Health & Sciences University. You can find the original report online at the following web address: http://www.ohsu.edu/drugeffectiveness/reports/final.cfm. Although at least one of the authors of this report reviewed and commented on the brief, its content and conclusions are those of the CEBP and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

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P & T COMMITTEE BRIEF
HMG-CoA Reductase Inhibitors (Statins): Comparative Drug Class Review

In the United States, coronary heart disease (CHD) is the leading cause of mortality and a significant cause of morbidity. High levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-c), are an important risk factor for CHD. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum LDL-c concentrations. The statins work by blocking an enzyme, HMG-CoA reductase, which is the rate-limiting step in the production of cholesterol. Statins reduce LDL-cholesterol, total cholesterol, and triglycerides and slightly increase high-density lipoprotein (HDL-c, also known as the good cholesterol).

The third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III {ATP-III}), updated in August 2004, stresses that the intensity of treatment should be directed by the degree of cardiovascular (CV) risk. For most patients who are prescribed a statin, the target LDL-c level will be <130mg/dL (3.4 mmol/L) or <100mg/dL (2.6 mmol/L), depending on the number of existing risk factors such as smoking, hypertension, etc. An LDL-C goal of <70mg/dL (1.8 mmol/L) for high-risk patients is a therapeutic option. The 2006 update of the American Heart Association /American College of Cardiology consensus statement on secondary prevention states, "…low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL (2.6 mmol/L) for all patients with CHD and other clinical forms of atherosclerotic disease, but in addition, it is reasonable to treat to LDL-C <70 mg/dL (1.8 mmol/L)in such patients." They assigned this recommendation a grade of II-1 meaning "…there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment [but the]…weight of evidence/opinion is in favor of usefulness/efficacy."

Six statins are available in the US and Canada:

- Atorvastatin (Lipitor)
- Fluvastatin (Lescol), fluvastatin extended release (Lescol XL)
- Lovastatin (Mevacor), lovastatin extended release (Altoprev, available in USA only)
- Pravastatin (Pravachol)
- Rosuvastatin (Crestor)
- Simvastatin (Zocor)

Usual starting daily doses are rosuvastatin 10mg, atorvastatin 10mg, pravastatin 40mg, and 20mg of the other statins. The maximum daily dose for rosuvastatin is 40mg. For all other statins, the maximum FDA-approved daily dose is 80mg.

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Methodology

The Drug Effectiveness Review Project (DERP) reviews all pertinent studies, solicits and accepts public input and updates reviews frequently. The original Statin review has been updated four times. Study eligibility was determined by pre-set criteria based on study design, patient population, interventions, and outcomes. Outcome measures included both intermediate measures (LDL-c reduction, HDL-c elevation, percent of patients meeting National Cholesterol Education Panel (NCEP) goal) and health outcomes (nonfatal myocardial infarction (MI), angina, cardiovascular (CV) death, all-cause mortality, stroke, need for revascularization). Studies published as abstracts only or not in English were excluded. The quality of all included studies was appraised.

Evidence Available

Literature searches identified 8,667 citations. Relevant information consisted of 113 randomized controlled trials (RCTs), including 68 head to head comparisons, and 77 additional publications (used for either indirect comparison between statins or for background information).

Key Questions and Findings:

Question # 1: How do statins compare in their ability to reduce LDL-c?

- For patients who require no more than a 35% reduction in LDL-c from their baseline measurements to meet their goal, any of the statins are effective.
- In patients requiring an LDL-c reduction of 35% to 50% to meet their goal, atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more, and simvastatin 20mg or more daily are likely to meet the goal.
- In general, mean percent LDL-c reduction for a particular statin dose varied little across studies and was consistent with package insert estimates. Equivalent dosages are listed in the table below:

Doses of statins that result in similar percent reductions in LDL-c*

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
–	40 mg	20 mg	20 mg	–	10 mg
10 mg	80 mg	40 or 80 mg	40 mg	–	20 mg
20 mg	–	80 mg	80 mg	5 or 10 mg	40 mg
40 mg	–	–	–	–	80 mg
80 mg	–	–	–	20 mg	–
–	–	–	–	40 mg	–

*estimates based on results of head-to-head trials

- Atorvastatin, simvastatin, and rosuvastatin are considered high potency statins because they can lower LDL-c more than 40%. When compared for efficacy and adverse events, 23 studies of atorvastatin and simvastatin provide evidence that adverse events are similar for doses below 80mg. Two trials suggest that 80mg of

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atorvastatin is more effective at lowering LDL-c than the same dose of simvastatin, but also leads to more adverse events. Fifteen studies compared atorvastatin with rosuvastatin, though nearly all studies compared doses that result in different degrees of LDL-c lowering.

- 39 reports measured the percentage of patients meeting their NCEP goals; however problems with dosing limit the validity of many of the studies, since often non-equivalent doses were used. In addition, for those studies that titrated the dose to the NCEP goal, the maximum dose for one drug was often lower than the maximum approved dose available today. The only one-year head-to-head trial found rosuvastatin and atorvastatin similar in the percentage of patients reaching their goal.

Question # 2: How do statins compare in their ability to increase HDL-c?

- When statins are provided in doses that reduce LDL-c by equivalent amounts, a similar percent increase in HDL-c can be achieved.
- There is conflicting evidence about simvastatin and atorvastatin, with 12 studies finding no difference and 6 finding simvastatin superior in its ability to raise HDL-c.
- Five studies found greater increases in HDL-c with rosuvastatin compared with atorvastatin, but only when comparing doses that result in greater LDL-c lowering. Three other studies found no difference.

Question # 3: How do statins compare in their ability to reduce the risk of CV disease and mortality?

- Information from head-to-head trials is limited. There is no information from head-to-head trials in patients who have never had CHD or CHD equivalents (primary prevention).
- In patients who had a recent MI, high dose **atorvastatin 80mg** daily reduced all-cause mortality and CV events compared with **pravastatin 40 mg** daily (PROVE-IT). For every 25 patients treated with **atorvastatin 80mg** instead of **pravastatin 40mg**, one coronary event was prevented.
- In patients who had a history of MI (IDEAL), high-dose **atorvastatin (80 mg)** and **simvastatin (20 mg)** did not differ in the primary endpoint (coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation). More high-dose atorvastatin patients discontinued due to adverse events (9.6% vs. 4.2%, $p<0.001$), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin.
- The amount of information on CV outcomes available from placebo-controlled trials for each statin differs substantially. In patients with known CDH, simvastatin and pravastatin reduced mortality and CV events, while fluvastatin reduced coronary events when started after percutaneous coronary intervention (PCI). There is also fair quality but indirect evidence that **lovastatin** is effective in preventing CV events in patients with CHD.

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- There are good efficacy data for people with diabetes. Atorvastatin 10 mg reduced CV events in a primary prevention trial of patients with diabetes (CARDS), and simvastatin 40 mg reduced CV events in patients with diabetes in the Heart Protection Study. In a subgroup analysis of the LIPS trial, there was a reduction in coronary events with fluvastatatin 80 mg in patients with diabetes who had undergone successful PCI.

Question # 4: Are there differences in the efficacy or safety of statins in different demographic groups?

- There is good evidence from RCTs that women and the elderly benefit from statin therapy. All of the statins used in the major long-term RCTs were tolerated equally well among men, women, and healthy elderly subjects.
- Data about efficacy and safety in African-Americans, Hispanics, and other ethnic groups are weaker. There is no evidence that one statin is safer than another in these groups, although one study found that Asian patients have higher blood levels of rosuvastatin than Caucasians.

Question #5: Are there differences in the safety of statins?

General population:

- Evidence is insufficient to determine which statin or statins are safer with regard to muscle and liver toxicity. All of the available statins have been associated with infrequent myotoxic adverse events ranging from myalgia and myopathy to rhabdomyolysis. Although elevations of laboratory markers of muscle damage (creatinine phosphokinase or CPK) are common, the risk of symptomatic myopathy is low.

Special populations and drug interactions:

- Studies that included people with diabetes did not have higher rates of adverse events than other studies.
- In theory, **pravastatin, fluvastatin, and rosuvastatin** have the lowest potential for interactions with drugs that are potent inhibitors of CYP 3A4, while **atorvastatin, lovastatin and simvastatin** have the greatest potential for clinically important interactions. For drugs that inhibit CYP 2C9, **pravastatin** has the lowest potential for drug interactions.
- The combination of any statin with fibrates and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.

Conclusion:

All statins are effective in reducing LDL-c up to 35% from their baseline measurements. Varying doses of atorvastatin, simvastatin, lovastatin and rosuvastatin are likely effective in reducing LDL-c between 35% and 50, while only atorvastatin and rosuvastatin reduce LDL-c more than 50%. In general, statins raise HDL-c in proportion to their ability to lower LDL-c, although there is conflicting evidence about simvastatin, atorvastatin and

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rosuvastatin. There is evidence that atorvastatin, simvastatin, fluvastatin and pravastatin all improve CV outcomes, and that 80mg of atorvastatin reduces mortality more than 40mg of pravastatin in patients who have had a recent MI, but there is no difference between atorvastatin and simvastatin in patients who have a more remote history of MI. In general, the evidence is insufficient to determine which statins are safer with regard to muscle or liver toxicity, although high dose atorvastatin appears to have a higher incidence of significant liver enzyme elevations.

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