Oregon Health Resources Commission

HMG-CoA Reductase Inhibitors (Statins)

Subcommittee Report

Update #4, October 2006

This report is the 4th update of the initial Statin Subcommittee Report of June 2002. All revisions are highlighted.

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Overview for Update #4

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Department of Human Services on this Plan.

In January of 2002 the HRC appointed a subcommittee to perform an evidence-based review of the use of 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors for the management of hypercholesterolemia. Members of the subcommittee consisted of physicians, pharmacists, nurse practitioners, other health care professionals, consumers and advocates. The subcommittee held eight meetings, two of which were general sessions of orientation and evidence-based analysis education. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with Oregon Health and Science University's Evidence-based Practice Center (OHSU-EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

Using standardized methods, the OHSU-EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion/exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU-EPC's report titled "*Drug Class Review on HMG-CoA Reductase Inhibitors (Statins)*" was completed the week of May 13, 2002, circulated to subcommittee members and posted on the web. The subcommittee met on May 21, 2002, to review the document. By consensus, the subcommittee members agreed to adopt the report. Time was allotted for public comment, questions and testimony. At the subcommittee's meeting on May 28, 2002, members of the HRC were invited to attend the meeting to clarify policy issues that were complicating decision-making for the subcommittee. Policy was discussed, then Commissioners were excused. Subcommittee deliberations continued but no final conclusions were drawn. The subcommittee next met on June 4, 2002. The final meeting was held on June 12, 2002, and final conclusions were drawn. Again, time was allowed for public testimony. All available sources of information; the OHSU-EPC report, which includes information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the Statins Subcommittee comprise the body of this report.

The OHSU EPC's Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) updated final report 4 August 2006 was circulated to the Standing Update Subcommittee members and posted on the OHPR website at http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml. On October 17, 2006 the subcommittee members worked with the OHSU-EPC reviewing the evidence for both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities. By consensus, the subcommittee members agreed to adopt the OHSU-EPC report. Time was allotted for public comment, questions, and oral testimony. All available sources of information from the OHSU-EPC report that included information submitted by pharmaceutical manufacturers and public testimony, were considered.

This report is prepared to facilitate the HRC in providing recommendations to the Oregon Medical Assistance Program (OMAP) for the Plan Drug List (PDL). This report was presented to the HRC on October 20, 2006 at which time public testimony was heard and due consideration given. This report was approved by the HRC and commended to OMAP. This update report does not recite or characterize all the evidence that was discussed by the OHSU-EPC, the Standing Update Subcommittee or the HRC. For further information provided during the committee process, readers are encouraged to review the source materials on the website.

The HRC working together with the OHSU-EPC, OMAP, and the OSU College of Pharmacy, will continue to monitor medical evidence for new developments in this drug class. Within a year emerging pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PDL will be made. Significant new evidence for pharmaceuticals already on the PDL will be assessed and FDA changes in indications and safety recommendations will be evaluated. The Statin Subcommittee Report will be amended if indicated.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report Update 4* is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:
http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and it's subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/PMPDP.shtml

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from OHSU Center for Evidence-based Policy (Center) by contacting:

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There will be a charge for copying and handling in providing documents from OHPR and from the Center.

Critical Policy:

- *Senate Bill 819*
  "The Department of Human Services shall adopt a Practitioner-Managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission:*
  - "Clinical outcomes the most important indicator of comparative effectiveness;
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Inclusion Criteria:

- *Scope*
  Adult patients targeted for primary or secondary prevention of coronary heart disease (CHD) or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia. Children and rare, severe forms of Hypercholesterolemia (LDL-c greater than 250mg/dl) were excluded.

- *Definition of HMG-CoA Reductase Inhibitors:*

Atorvastatin (Lipitor)
Fluvastatin (Lescol, Lescol XL)
Lovastatin, (Mevacor)
Extended Release Lovastatin (Altoprev)
Pravastatin (Pravachol)
Rosuvastatin (Crestor)
Simvastatin (Zocor)

Key Questions:

1. **How do Statins compare in their ability to reduce LDL-c?**
   - **a. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?**
   - **b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Program (NCEP) goals?**

2. ~~**What is the correlation between the magnitude of LDL-c lowering and adverse events?**~~

2. **How do Statins compare in their ability to raise HDL-c?**

3. **How do Statins compare in their ability to reduce the risk of non-fatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?**

4. **Are there differences in the efficacy or safety of statins in different demographic groups (age, sex, race)?**

5. **Are there differences in the safety of statins when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we focused on the following populations and adverse effects:**
   - **a. Patients with diabetes**
   - **b. Patients with HIV**
   - **c. Organ transplant recipients**
   - **d. Patients at high risk for myotoxicity**
   - **e. Patients at high risk for hepatotoxicity**
   - **f. Patients using fibrates (gemfibrozil, fenofibrate) or niacin**

New Findings: September 2006

- The EPC received no new dossiers from pharmaceutical manufacturers.
- Using the same search strategy from the original Statin report, the EPC found 113 new randomized controlled trials that provided useable data.

- There are 19 new randomized controlled trials that meet criteria
  - 12 head-to-head trials
  - 2 active controlled trials
  - 6 observational studies for adverse effects
- There is one new systematic review but the conclusions don't change the report

Amended Summary of Results

1. ***How do Statins compare in their ability to reduce LDL-c?***

   A. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?

The ideal study would be a double-blind, intention-to-treat randomized trial in which equivalent doses of different statins were compared with regard to LDL-lowering, withdrawals, and adverse effects. No studies met these stringent criteria.

When statins are provided in doses that are approximately equivalent, a similar percent reduction in LDL-c can be achieved The Statin subcommittee will henceforth define "equipotent" doses of statins as the equivalent daily doses for statins with respect to their LDL-c lowering abilities.

Table 1. Equipotent doses of statins

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 mg or 10 mg	40 mg
40 mg					80 mg
80 mg				20 mg	
				40 mg	

Sixty eight randomized clinical trials compared the LDL-c lowering ability of two or more Statins in patients with baseline LDL-c greater than 250 mg/dl. In 39 of the trials, the NCEP goal was also evaluated. In almost all, the mean percent LDL-c reduction for a particular Statin dose showed little variation across studies. From these data, approximate equivalent daily doses for Statins with respect to their LDL-c lowering abilities were determined. (See Table 1) The EPC estimates based on head-to-head trials were consistent with the actual values from a more recent meta-analysis of placebo-controlled trials.

Three studies directly compared atorvastatin 80 mg and simvastatin 80 mg daily. The first showed atorvastatin with a reduction of LDL-C by 53.6% compared to

simvastatin 48.1% ($p<0.001$)[1]and the second revealed a 53% to 47% comparison ($p<0.0001$).[2] The **STELLAR** trial[3], with the mean percent change in LDL level after 6 weeks of 51% in the atorvastatin group and 46% in the simvastatin group, a difference (5.3 percentage points) was similar to those found in the two other studies comparing atorvastatin 80 mg to simvastatin 80 mg. While these results have a high degree of statistical significance their clinical significance is yet to be established. A post hoc sub-analysis of 811 patients in the **STELLAR** trial with metabolic syndrome had results similar to the overall sample.[4]

Atorvastatin, simvastatin and rosuvastatin are considered high potency statin because they can lower LDL-c more than 40%. Three studies directly compared rosuvastatin 5mg and 10 mg with atorvastatin 10mg with rosuvastatin 5mg reduced LDL-c by 41.9% and 46.7% versus 46.7% and 50% for rosuvastatin 10mg and 36.4% and 39.8% for atorvastatin 10 mg at 12 weeks showing a significantly greater treatment difference of (-12.11%, $p<0.0001$) with rosuvastatin.

There were six new head-to-head trials of LDL-c lowering: atorvastatin vs rosuvastatin (4 trials), atorvastatin vs. pravastatin (1 trial), and atorvasttin vs simvastatin (1 trial). The percent LDL-c lowering was consistent with existing evidence. There was no difference when equipotent doses were compared.

Comparative data on safety and efficacy for higher doses of rosuvastatin (20mg-40mg) are sparse. Rosuvastatin 40mg, atorvastatin 80mg, and simvastatin 80mg had similar 6% withdrawal rates due to adverse events.

Results of a large number of trials are generally consistent with information from the manufacturer.

B. Is there a difference in the ability of a statin to achieve National Cholesterol Education Panel (NCEP) goals?

Problems in equivalent dosing limit the validity of many of the thirty trials that met inclusion criteria and reported the percentage of patients achieving NCEP goals. In some head-to-head comparisons, the maximal recommended dosage was not reached by the "inferior" drug.

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[1] Illingworth RD, Crouse IJ, Hunninghake DB, et al A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. Current Medical Research & Opinion 2001;17(1):43-50

[2] Shepard J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. American Journal of Cardiology 2003;91(5A):11C-17C,; discussion 17C-19C

[3] Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doess (STELLAR*Trial) American Journal of Cardiology 2003;92(2):152-60.

[4] Deedwania PC, Hunninghake DB, Bays, HE et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia I patients with characteristics of the metabolic syndrome. American J. of Cardiology. 2005;95(3):360-366.

In a meta-analysis of three 12-week randomized trials of rosuvastatin versus atorvastatin, pravastatin, or simvastatin; 76% of patients taking rosuvastatin 10 mg reached their ATP III goal, versus 53% of those taking atorvastatin 10 mg, 64% for simvastatin and 49% for pravastatin.[5]

The only long (1 year) head-to-head study of rosuvastatin vs atorvastatin revealed that results are similar for those starting at rosuvastatin 5 mg (89%)and 10 mg (98%).[6] In short-term studies, rosuvastating 40 mg had greater reductions in LDL-c than atorvastatin, with similar rates of adverse events.

In other studies of atorvastatin lasting one year or longer, percentages of patients meeting their NCEP goal ranged from 46% to 61% for those titrated from 10-40 mg and 51%-95% for 10-80mg.

There is fair-to-good evidence that for patients who require LDL-c reductions of up to 40% to meet their goal, all Statins are effective.

There is fair to good quality evidence that for patients requiring an LDL-c reduction of 40% to 49%, atorvastatin 20 mg or greater, lovastatin 80 mg, rosuvastatin 10 mg, or simvastatin 40 mg or greater are likely to meet this goal.

The subcommittee concludes by consensus that:

- ***All statins in equipotent doses are effective to reduce LDL-c up to 40%.***
- ***That atorvastatin, lovastatin, rosuvastatin and simvastatin are effective in achieving a goal of LDL-c reduction of 40-49%***
- ***Atorvastatin at doses of 40 mg or higher, or rosuvastatin at 20 mg or higher, can achieve on average a LDL-c reduction of 50% or greater.***

2. *How do statins compare in their ability to increase HDL-c?*

When statins are provided in doses that are approximately equivalent, a similar percent increase in HDL-c can be achieved. Fifty-seven head-to-head

[5] . Shepard J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk : a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. American Journal of Cardiology 2003 ;91(5A) :11C-17C ; discussion 17C-19C.

[6] Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 53 weeks of treatment in patients with hypercholesterolemia. American Heart Journal. 2002;144(6):1044-51.

trials designed to compare LDL-c lowering of two or more statins also reported changes in HDL-c. The amount of increase in HDL in these studies ranges from no increase to 19% with the great majority between 5%-9%.

There is conflicting evidence about simvastatin vs atorvastatin in head-to-head trials (6 studies reporting greater increases with simvastatin, but 12 others reporting no difference.) Some studies found greater increases in HDL-c with rosuvastatin, compared to atorvastatin, while other studies found no difference. There is no data available to conclude that differences among the statins in their ability to raise HDL levels effects clinical cardiovascular outcomes.

The subcommittee concludes by consensus that all statins when compared at equivalent doses achieve a similar increase in HDL-c.

3. How do Statins compare in their ability to reduce the risk of non-fatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?

There are three head-to-head trials: **PROVE-IT, IDEAL** and Stone, 2005. **PROVE IT** compares the ability of different statins to reduce the risk of coronary events, stroke, or death. In this fair quality trial 4,162 patients who had been hospitalized in the previous 10 days for an acute coronary syndrome (MI or unstable angina) were randomized to treatment with atorvastatin 80 mg daily (intensive therapy) or pravastatin 40 mg daily (routine therapy.) The atorvastatin group had a 22.4% vs 26.3% (p=0.005) for major cardiovascular events representing a 16% reduction in coronary events in this secondary prevention trial.

In the **IDEAL** fair-quality trial, post MI patients were randomized to high-dose atorvastatin (80 mg) vs usual-dose simvastatin.[7] The starting dose of simvastatin was 20 mg, but 23% of these patients were titrated up to 40 mg by the end of the study. The LDL-c reduction was greater in the atorvastatin group at 12 weeks (49% vs 33%). High dose atorvastatin (80mg) and simvastatin (20mg) did not differ in the primary endpoing (coronary death, hospitalization for nonfatal acute MI, or cardiac arres with resuscitation.

[7] Pedersen

In the Stone trial intensive atorvastatin up to 80 mg was used to target an LDLc < 80 mg as compared to low-dose lovastatin if needed (91% of patients) to target an LDL < 130 mg. Three hundred patients with stable coronary artery disease were followed for 1 year for a primary outcome of change in number and duration of ischemic episodes. There was no difference between groups for fequency and duration of ischemia at 6 and 12 months.

A placebo-controlled trial of 20 mg atorvatstatin by Wanner targeted 1,255 patients with type 2 diabetes who were undergoing dialysis and followed them for 4years showing a 42% reudction in LDLc to 72 mg. The primary endpoint (composite of cardiac death, non-fatal MI, and stroke) showed no difference (HR 0.92, 95% CI 0.77, 1.10)

Subgroup analysis of previously reported studies revealed that in **ASCOT-LLA** (patients with type 3 diabetes) comparing 10 mg atorvastatin to placebo, there was a similar risk reduction of CV events and procedures (HR 0.77, 95% CI 0.61, 0.98) to patients without diabetes.[8] In **LIPS** subgroup analysis of patients with Type 2 diabetes[9]or patients with renal dysfunction[10], fluvastatin reduced CV events in these subgroups similar to the whole population studied.

L-CAD comparing pravastatin 20 or 40 mg vs usual care showed 22.9% vs. 52% major coronary events after two years (p=0.005). **MIRACL**, a short (16 weeks) study of atorvastatin showed a significant reduction (17.4% vs. 14.8%) in major coronary events, but no difference between groups for MI or all-cause mortality. **FLORIDA** was a study of fluvastatin 80 mg vs. placebo over 1 year that showed no difference in major coronary events.

Many trials compared a Statin to placebo. Thirty-one trials meeting criteria for inclusion reported cardiovascular outcomes in patients randomized to receiving a Statin compared to placebo control.

Twenty large multi-center studies designed to assess cardiovascular health outcomes in patients without known CHD, compared a Statin with placebo. Thirteen studies rated good quality were entirely in outpatients, and 7 studies rated fair were started as inpatients with acute MI or unstable angina. All studies showed relative reduction in coronary events, and three studies reported absolute reductions in coronary events.

Twelve studies had a primary endpoint of progression of atherosclerosis and also reported rates of coronary or cardiovascular events. All patients had known CHD. The studies were fair-to-poor quality. Evidence about fluvastatin showing significant reduction in CHD events was inconclusive. Evidence for

[8] Sever
[9] Arampatzis
[10] Lemos

lovastatin, pravastatin and simvastatin was already known from the primary prevention studies.

Six secondary prevention studies of reduction of CHD in re-vascularized patients were of fair or fair-to-poor quality. These studies were small and the endpoint was generally the rate of re-stenosis. Five other studies that reported health outcomes that did not fit into the first categories of primary or secondary prevention were included as "miscellaneous" trials.

In a post-hoc analysis of 2,073 patients in the LIPID trial with both low LDL-c and low HDL-c, pravastatin was associated with a relative risk reduction of 27% (95% CI, 8%-42%) a 4% ARR and an NNT of 22.[11]

Primary prevention studies provide consistent good-quality evidence that atorvastatin, lovastatin, pravastatin and simvastatin reduce cardiovascular events. Atorvastatin has good quality evidence that it reduces coronary events in primary and secondary prevention trials. Pravastatin, simvastatin and lovastatin have good-quality evidence for both primary and secondary prevention. Pravastatin and simvastatin have good quality evidence for secondary prevention and also reduced deaths from cardiac disease. Three separate studies showed that the risk of stroke was significantly reduced in the secondary prevention trials for atorvastatin, pravastatin, and simvastatin. Only one post-revascularization study and another miscellaneous study provided fair evidence about the efficacy of fluvastatin.

The subcommittee concludes by consensus that:

- ***There are no head-to-head trials of equivalent doses of different statins for reducing coronary events.***
- ***There is good quality evidence for improved cardiac outcomes with atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin when compared with placebo***
- ***There is good quality evidence for reduction of risk of stroke with atorvastatin, pravastatin and simvastatin when compared with placebo***
- ***In diabetics with previous successful PCI there are reduced coronary events with fluvastatin as compared to control.***
- ***To date, there is no evidence for improved cardiac outcomes with rosuvastatin.***

[11] Colquhoun D, Keech A, Hunt D, et al. Effects of pravastatin on coronary events in 2073 patients with low levels of both low-density lipoprotein cholesterol and high-density lipoprotein cholesterol:Results from the LIPID study. European Heart J. 2004;25(9):771-777.

4. Are there differences in the efficacy or safety of Statins in different demographic groups (age, sex, race)?

A. Efficacy in Demographic Subgroups

Women and the Elderly: A meta-analysis of five large, long-term, primary and secondary prevention trials provides good evidence that Statins are efficacious in men, women and persons over age 65.[12] An observational study in the elderly showed risk reduction in all ten-year age groups from age 60 to age 100. While it is clear from the Heart Protection Study (**HPS)** that women can benefit from simvastatin compared to placebo**,** in most of the other trials, risk reduction was smaller or non-existent in women, possibly because there were fewer women and they have an inherently lower risk than men.

African-Americans: African-Americans have the greatest overall CHD mortality and the highest out-of-hospital coronary death rates of any other ethnic group in the US. Of the 27 trials reporting clinical events, only one provided numbers of participating African-American, and events were not analyzed by racial group. There is no evidence whether Statins differ in their ability to reduce CHD events in this population.

The subcommittee concludes by consensus that:

- ***All statins are effective in men, women and the elderly***
- ***There is no evidence supporting differences in efficacy between racial groups.***

B. Safety in Demographic Subgroups

All of the statins used in the major long-term trials were tolerated equally well among men, women, and healthy elderly subjects. In a large observational study of lovastatin; men, women and the elderly experienced similar rates of adverse effects. The rates of myopathy and liver enzyme elevations increased with increasing doses of lovastatin, but did not differ among men, women, and healthy elderly subjects. A meta-analysis of randomized trials of simvastatin 80 mg had similar results.

A subgroup analysis examined the safety of lovastatin vs. placebo in African Americans. There was a significantly higher incidence of creatine kinase (CK) elevation in African-Americans compared to white Americans, but this was true in

[12] LaRosa JC, He J, Vupputuri S, Effects of statins on risk of coronary artery disease:A metanalysis of randomized controlled trials. JAMA 1999;282(24):23-46

both the placebo and lovastatin treatment groups. No cases of myopathy, defined as CK elevations of >10 X the upper limit of normal occurred in African Americans.

In pre-marketing studies, Japanese and Chinese patients living in Singapore had higher levels of rosuvastatin in blood than Caucasians living in Europe.[13] The FDA has asked for an appropriately conducted pharmacokinetic study of Asians residing in the US that will be reported upon in future updates.

Asians: A pharmacokinetic study conducted in the US demonstrated a 2X elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a White control group. The rosuvastatin label has been revised to note that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

The subcommittee concludes by consensus that:

- ***Based on available evidence there is no reason to believe that safety differences exist in women or the elderly.***
- ***Initial dosing should be started lower in Asian patients, because of differences in pharmacokinetic studies between Asian and White patients.***

5. *Are there differences in the safety of Statins when used in special populations?*

Populations considered: Diabetics; patients with HIV; organ transplant patients; patients at high risk for myotoxicity; patients at high risk for hepatotoxicity.

Special Populations and Safety:

Diabetics: Post-hoc subgroup analyses evaluated the benefits of Statins in reducing the risk of major coronary events in patients with diabetes and/or with impaired fasting glucose. In sixty-seven trials reviewed there was no data to support any additional safety concerns in diabetics compared to non-diabetics, though no evidence specifically addressed this question. Although the outcome

[13] FDA CfDEaR Medical Review of Rosuvastatin. http://www/fda.gov/cder/foi/nda/2003/21-366_Crestor.htm

measures were not uniform across studies, there were trends of statistically significant reduced overall mortality and/or major CHD events and revascularizations in patients treated with simvastatin and pravastatin.

A recent study reviewed the FDA's adverse event reporting database between 1990-2002 in which simvastatin or atorvastatin was listed as the suspect in causing adverse events in which thiazolidinediones (TZDs) were listed as concomitant medications. Atorvastatin-associated muscle or liver toxicity were more likely to list concomitant TZDs compared with simvastatin-associated adverse events.

The Collaborative Atorvastatin Diabetes Study (**CARDS)** is a new good-quality , multicenter trial of atorvastatin 10 mg for primary prevention of cardiovascular disease in 2838 patients with type 2 diabetes without elevated cholesterol levels (mean LDL 107) revealed that even patients without a history of cardiovascular disease, but at least one of the following risk factors retinopathy, albuminuria, current smoking or hypertension showed significant reduction in cardiovascular events compared to placebo after 3.9 years. (RR – 0.37 95% CI –0.52, -0.17). The average reduction in LDL-c was 40%.[14]

Organ Transplant Recipients:

The Holdass study[15] presents good evidence that fluvastatin has long term (over 5 years) safety in renal transplant patients. Based on pharmacologic information, case reports and small series of patients, Statins, when used in the lowest doses, have safety profiles for transplant patients similar to the general population. In a pre-marketing study, cyclosporine had a clinically significant effect on the pharmacokinetics of rosuvastatin in heart transplant patients. The product label recommends limiting the dose of rosuvastatin to 5 mg in patients taking cyclosporine.

HIV Patients:

A significant portion of HIV patients have medication-induced hyperlipidemia. There are no prospective randomized clinical trials evaluating the benefits of Statins in HIV patients; however, the Adult Aids Clinical Trials Research Group (AACTG) Cardiovascular Disease Focus Group and the Centers for Disease Control and Prevention (CDC)/Henry J Kaiser Foundation have made recommendations regarding the use of Statins in HIV infected individuals receiving protease inhibitors. Recommendations are based primarily on

[14] Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study **(CARDS)**:Multicenter randomized placebo-controlled trial; Lancet 2004;364(9435):685-696.

[15] Holdass H, Fellstr AmB, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients:A multicentre, randomized placebo-controlled trial. Lancet 2003;361(934):2024-31.

pharmacologic similarities in how proteases and most HMG-CoA reductase inhibitors are metabolized and are not evidence-based. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.

A trial in HIV seronegative volunteers evaluated the potential interaction between the combination of protease inhibitors ritonavir plus saquinavir and statins.[16] The authors concluded that simvastatin and atorvastatin should be avoided in patients receiving the protease inhibitors ritonavir plus saquinavir or used in lower doses in order to avoid potential toxicity from these agents. Reduced doses of pravastatin are not necessary.

One small (N=20) placebo-controlled trial of pravastatin in patients receiving protease inhibitors showed an 18.3% reduction in total cholesterol, but mean LDL-c and HDL levels did not change. During this 8 week trial one patient developed an asymptomatic increase in CK > 2X ULN and another had > 3X ULN. Two subjects developed severe myalgias, but neither discontinued therapy.[17]

***Myotoxicity*:**

There is a significant increase in relative risk for myopathy when Statins are used, but the absolute risk remains very small for all Statins. Conclusions cannot be made regarding difference in risk of severe muscle toxicity between the Statins. All have rarely caused rhabdomyolysis, and in the majority of cases an additional drug with a potential for increasing the serum Statin level was identified.

Myopathy in Statin-Fibrates Combination:

Because of the nature of adverse effect reporting and the available evidence, the answer to the question of whether one statin is safer than another with regard to combination with a fibrate is unknown. The FDA has approved the following recommendations for combining a Statin with a fibrate or niacin:

- Atorvastatin: Closely monitor patients on combined therapy with gemfibrozil or niacin
- Fluvastatin or pravstatin: Avoid the combination with gemfibrozil unless the benefit outweighs the risk of such therapy
- Simvastatin or lovastatin: Limit doses of simvastatin to 10 mg and lovastatin to 20 mg if combined with gemfibrozil or niacin.

[16] Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 2002;16(4):569-77.

[17] Stein JH, Merwood MA, Bellehumeur JI, et al. Effects of pravastatin on lipoproteins and endothelia function in patients receiving HIV protease inhibitors. American Heart Journal. 2004;147(4):E-18.

- Rosuvastatin: Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. If used in combination with gemfibrozil, the dose should be limited to 10 mg once daily.

Hepatotoxicity:

All of the Statins are rarely associated with clinically important elevations of liver transaminases. No evidence supports a significant difference in the rates of clinically relevant elevations in liver enzymes between equipotent doses of Statins.

In the **PROVE IT** trial more patients in the atorvastatin 80 mg group had elevations in alanine aminotransferase levels than those in the pravastatin group. (3.3% vs 1.1%, $p<0.001$)

The subcommittee concludes by consensus that:

- ***In shorter-term studies there is no evidence to suggest that Statins differ in their safety in diabetic patients. Furthermore, long-term studies have shown that atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin can be used safely in patients with diabetes and impaired fasting glucose.***
- ***In organ transplant patients or patients with HIV, consideration of drug interactions between statins and immunosuppressants or protease inhibitors is important.***
- ***In a single good quality long-term study, fluvastatin demonstrated tolerability in renal transplant patients.***
- ***While there are no prospective randomized clinical trials evaluating the benefits of Statins in HIV patients, two groups of experts recommend using pravastatin with second drug of choice either atorvastatin or fluvastatin, but avoid simvastatin or lovastatin in HIV infected individuals receiving protease inhibitors. These recommendations are based on potential drug interactions between protease inhibitors and those Statins that are metabolized through the cytochrome P-450 3A4 enzyme system, and supported by one pharmacokinetic trial in normal subjects. Fluvastatin, pravastatin and rosuvastatin are not metabolized through this system.***
- ***The current evidence reviewed for this report does not demonstrate a difference in liver toxicity and myotoxicity at equipotent doses.***

Conclusion

In a series of public meetings with the opportunity for public questions, comment and testimony, the Statin Subcommittee of the HRC, reviewed the medical evidence comparing HMG-CoA reductase inhibitors for lipid lowering. All available sources of information including OHSU-EPC's update report, *"Drug Class Review on HMG-CoA Reductase Inhibitors Updated Final Report #4,"* and additional information presented in public testimony were considered. Using all available sources of information, the Subcommittee came to conclusions about the comparative effectiveness and safety of HMG-CoA Reductase Inhibitors in their ability to reduce the risk of nonfatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke or the need for revascularization (coronary artery bypass graft, angioplasty, or stenting) as supported by analysis of the medical

It is the decision of the Statin Subcommittee that:

1. ***Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin to improve coronary heart disease clinical outcomes.***
2. ***Atorvastatin, pravastatin and simvastatin have been shown to reduce strokes.***
3. ***No evidence supports differences between Statins in adverse effects in sub-populations by race and ethnicity, age, or gender.***
4. ***There is good efficacy and safety data with atorvastatin for diabetics for primary prevention of cardiovascular disease and for fluvastatin for secondary prevention of coronary events in diabetics***
5. ***Although experts recommend atorvastatin, pravastatin and fluvastatin for hyperlipidemia in HIV infected individuals receiving protease inhibitors, there is one small fair study with pravastatin that has looked at the safety of this statin for this population.***
6. ***Consideration of drug interactions with immunosuppressants in organ transplant patients is important. In a single good quality long-term study, fluvastatin demonstrated tolerability in renal transplant patients.***

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The Commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the Commission subject to approval by a majority of the Commission. The appointees have appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee and public testimony in development of final reports.