

# HMG-CoA Reductase Inhibitors (“Statins”) Clinical Pearls for Washington Rx Therapeutic Interchange Program (TIP)

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## Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared lovastatin and atorvastatin to be the “preferred” statins for patients covered by their prescription insurance. Patients currently using “non-preferred” agents” must be evaluated for conversion to lovastatin or atorvastatin. Furthermore, once the TIP program is operational, MAA-DSHS patients presenting with prescriptions for non-preferred agents from “endorsing practitioners” (i.e., providers that have signed the TIP agreement) may be automatically converted to preferred agents by pharmacists.

## Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agents.

### Currently Available Statin Agents in the US

<b>Atorvastatin (Lipitor®)*</b>	<b>Lovastatin (generic)*</b>	<b>Simvastatin (Zocor®)</b>
<b>Fluvastatin (Lescol®)</b>	<b>Pravastatin (Pravachol®)^</b>	<b>Rosuvastatin (Crestor®)</b>

\* Washington State Evidence Based Preferred Drug List Agents

^Pravastatin is available via an EPA for patients with drug interaction concerns with the preferred agents.

## Clinical Efficacy

### *Reduction of Cardiovascular Events*

No head-to-head trials exist that compare the ability of statins to reduce coronary events. Atorvastatin, lovastatin, pravastatin and simvastatin have been shown to reduce clinical events in a number of well-designed, large-scale, long-term trials. These four statins have demonstrated improvements in CHD outcomes across a broad spectrum of patients, including those with normal cholesterol levels. Rosuvastatin has outcome trials in planning, but none are complete at this time. It is remarkable that all statin outcome studies to date have shown relative mortality reductions within a very narrow range (22 to 30%), especially considering that the studies were conducted in diverse populations with a wide range of absolute risk. While there is not conclusive evidence, this notable similarity suggests that a class effect is likely, whereby all statins are presumed to have a similar effect on clinical outcomes.

### *Effects on LDL-c*

A large body of evidence from ecologic studies, cohort studies and randomized clinical trials associate lowering of LDL-C with reduced risk of cardiovascular outcomes of interest. Statins given in equivalent doses achieve a similar reduction in LDL-c as well as percent of patients who meet NCEP ATPIII LDL-c goals. Any of the statins are effective at an LDL-c reduction of up to 40%. In patients requiring an LDL-c reduction of 40% or greater, only daily doses of atorvastatin  $\geq$  20mg, lovastatin 80mg, rosuvastatin  $\geq$  5mg and simvastatin  $\geq$  20mg are likely to allow patients to reach their NCEP goal. Daily doses of atorvastatin 80mg and rosuvastatin  $\geq$  20mg are the only statin regimens demonstrating the ability to achieve a 50% or greater reduction in LDL-c.

### *Effects on Other Lipids*

Accumulating evidence suggests that other lipid markers besides LDL-c are also important in monitoring treatment of dyslipidemias. While ATPIII raised the threshold definition of low HDL, the panel stopped short of establishing a target HDL level for treatment, as there was felt to be insufficient evidence on which to base such a recommendation. Simvastatin and rosuvastatin have demonstrated greater ability to increase HDL, however, the effects of statins on HDL are variable and modest compared to those of niacin and the fibrates. If a large HDL increase is desired in a particular patient, combination therapy will likely still be required. Likewise, triglycerides are a significant risk factor for cardiovascular disease. All statins lower triglycerides, however, patients with severe or persistent elevations will generally require therapy with fibrates or niacin if other drug and non-drug interventions are not effective.

## Safety Overview

### Overall

Statins share the less worrisome side effects of GI upset, headache, dizziness and mild skin rashes. Statin toxicity is dose-related, with most serious adverse effects occurring at higher doses. This may rightfully discourage use of the maximum doses of these agents, especially since marginal lipoprotein gains are seen compared to the increased risks.

### Myopathy and Rhabdomyolysis

The overall risk of statin associated myopathy is low and the incidence of rhabdomyolysis is rare. Rates of myotoxicity and resultant rhabdomyolysis are no different between statins. Factors that increase the overall risk of developing myopathy include using statins at higher doses, drug interactions, concomitant use of other myotoxic drugs (such as fibrates or niacin), increased age, hypothyroidism, surgery or trauma, heavy exercise, excessive alcohol intake, and renal/hepatic impairment.

### Hepatotoxicity

All statins are rarely associated with elevated liver transaminase (>3x ULN) (approx 1% of pts). Risk increases at higher doses.

### Drug Interactions with Statins<sup>^</sup>

Drug	CYP450 Metabolic Route	Drugs that may increase plasma levels of this statin
Atorvastatin, Lovastatin, Simvastatin	3A4	Amiodarone, clarithromycin, cyclosporine, delavirdine, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, nefazodone, protease inhibitors, ketoconazole, verapamil, voriconazole *Note: the degree of interaction with the above agents may be greater with lovastatin and simvastatin as compared to atorvastatin.
Pravastatin		Overall rate of significant drug interactions is low. Caution is still recommended with some agents (i.e., amprenavir, cyclosporine, erythromycin, gemfibrozil).
Rosuvastatin	2C9 (minor pathway)	Overall rate of significant drug interactions is low, however, this agent is new to the market and there are no long-term clinical trial data. Interactions with gemfibrozil and cyclosporine have been reported.

<sup>^</sup>**Fibric Acid Derivatives (gemfibrozil, fenofibrate) in combination therapy with statins:** The concurrent use of fibrates and statins is generally not recommended. If concurrent therapy is required, monitor the patient for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness, or weakness). Monitor creatine kinase (CK) levels and discontinue use if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

## Special Populations

### Overview

Statins have been shown to be effective in women and the elderly despite poor representation of these groups in the earlier trials. There is little to no data to suggest that one statin is more effective in any ethnic subgroups.

### HIV

HIV infected patients are often placed on statin therapy due to protease inhibitor induced hyperlipidemia. Protease inhibitors (PIs) are potent CYP 3A4 inhibitors. Simvastatin, lovastatin, and atorvastatin are metabolized by 3A4. Fluvastatin is metabolized by CYP 2C9. Rosuvastatin is partially metabolized by CYP 2C9 and 2C19. Pravastatin is not metabolized by CYP isoenzymes. The use of PI's or other 3A4 inhibitors with simvastatin, lovastatin and atorvastatin increases the risk of elevated statin levels and subsequent toxicity. It is recommended that simvastatin and lovastatin are avoided in patients on PI's or other 3A4 inhibitors, while pravastatin, fluvastatin and atorvastatin be used with caution. There insufficient evidence at this time for a conclusive statement regarding use of PI's with rosuvastatin.

### Organ Transplant

There is a dose-related risk of statin toxicity when statins are used in conjunction with cyclosporine, a potent 3A4 inhibitor. At low doses, statins appear to have a similar safety profile in transplant patients as the general population. Pravastatin and fluvastatin have the least potential for interactions with cyclosporine. Impaired renal function could potentially increase the risk of toxicity with atorvastatin, lovastatin, rosuvastatin and simvastatin.

### Diabetics

There is no evidence that there is any difference between statins in terms of safety or efficacy in diabetic patients.

## Cost of Statins

### Cost comparisons based on degree of LDL-lowering\*#^

% LDL Reduction	Atorvastatin Dose (\$)	Lovastatin Dose (\$)	Simvastatin Dose (\$)	Pravastatin Dose (\$)	Rosuvastatin Dose (\$)
20-30%		20mg (\$35)	10mg (\$68)	20mg (\$78)	
30-40%	10mg (\$62)	40mg (\$64)	20mg (\$118)	40mg (\$115) 80mg (\$115)	
40-45%	20mg (\$94)	80mg (\$128)	40mg (\$118)		5 mg (\$65)
46-50%	40mg (\$94)		80mg (\$118)		10 mg (\$65)
50-55%	80mg (\$94)				20mg (\$66)
56-60%					40mg (\$66)

\*Costs per 30-days supply

#LDL-c lowering effects based on package insert data

^ This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials. Practitioners should exercise common sense in the practical application of this guide, including consideration for a patient's current lipoprotein goal status and other clinical variables.

## Steps in Converting Patients to Preferred Statin Agents

### #1. Determine if there is any rationale or justification for use of the current agent.

- Does the patient have any history of intolerance or adverse reactions to atorvastatin or lovastatin (ie, myalgias or myositis)?
  - If yes, then DSHS prior authorization to continue the current non-preferred statin is advised.
- Does the patient have any drug interaction concerns that would limit use of the preferred agents?
  - If yes, pravastatin would be the recommended agent and this can be utilized via the EPA process.

### #2. Determine the appropriate, comparable conversion doses for the preferred agents based on the current statin dose (using the chart above or other tools). Then decide which preferred agent is most appropriate.

- Lovastatin, at doses of 10 – 40 mg, is the most cost-effective agent for patients with LDL-lowering goals of < 40%. Since statin toxicity is dose-related, it is not generally recommended to use the 80mg dose of lovastatin.
- Atorvastatin is the most potent preferred agents and is suitable for patients with greater LDL-lowering needs (ie, > 40%).
- Consideration should be given to the patients overall cardiovascular risk and whether they have reached their LDL-c goal. For instance, a patient presenting on simvastatin 20mg could convert to atorvastatin 10mg or lovastatin 40mg. If the patient has known CHD or its equivalent (ie, diabetes) and/or has not reached their LDL-c goal of < 100mg/dl, then atorvastatin 10mg may be considered a better option as it allows for dosage titration and maximal LDL lowering.

### #3. Patient Education and Consultation

- The patient should be counseled on the rationale behind this conversion.
- The patient should be specifically instructed to stop the previous statin agent and begin taking the new agent with emphasis on the risk of using both medications.
- Counseling should include advising the patient on adverse reactions that may occur with all statin medications and what to do should they experience any significant reactions (ie. myalgia).
- The patient should be advised to contact the pharmacy for any questions related to the medication or to contact their physician/prescriber for any health-related concerns.

### #4. Notification of Prescriber Regarding Conversion

- The pharmacist/pharmacy is legally obligated to communicate information regarding medication changes that occur via the TIP for all patients to ensure continuity of care.

## References and Resources

Oregon Health Policy and Research (OHPR) Evidence-based Drug Reviews (<http://www.ohprr.state.or.us/index.html>)

Lipids Online: <http://www.lipidonline.org/>

National Cholesterol Education Program (NCEP) at NHLBI/NIH:

Professional Information: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>

Patient Information: <http://www.nhlbi.nih.gov/chd/>