

**Indian Health Service National Pharmacy and Therapeutics Committee
Review of Statins, Fibrates, and Niacin
February 12-13, 2009, San Diego**

Introduction

Heart disease is the leading cause of death in the Native American population. High levels of cholesterol are an important contributor to cardiovascular disease and death. Drugs aimed at lipid reduction that will be reviewed in this report include HMG CoA Reductase Inhibitors (statins), fibrates, and niacin.

In FY 2008, the Indian Health Service spent 8 million dollars on statins, fibrates, and niacin. Current agents on the IHS National Core Formulary aimed at lipid lowering include lovastatin, fluvastatin, simvastatin, atorvastatin 80 mg, niacin, and gemfibrozil.

Of note, the statin class is currently closed to include the statins listed above. Despite the statin's closed class designation, and despite atorvastatin 80 mg being the only Core Formulary dose of atorvastatin, \$5.1 million of the \$8 million total spent on lipid lowering agents in FY 2008 was spent on atorvastatin 10 mg, 20 mg, and 40 mg.

Hyperlipidemia

The Adult Treatment Panel (ATP) III of the National Cholesterol Education Program has established guidelines for the treatment of hyperlipidemia. All ATP reports have identified low density lipoprotein cholesterol (LDL-C) as the primary target of therapy. Many trials have documented the effectiveness of LDL lowering on the reduction of cardiovascular mortality. ATP III has established guidelines for LDL lowering in 2001, and these were updated in 2004.

ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy¹

Risk Category	LDL-C Goal	Initiate Lifestyle Δ	Consider drug RX
High risk (CHD or CHD risk equiv*) 10 year risk >20%	<100 mg/dL (optional goal <70 mg/dl)	≥ 100 mg/dL	≥ 100 mg/dL Consider drug options < 100
Moderately high risk (2+ risk factors**) 10 year risk 10 to 20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL Consider drug options 100-129 mg/dL
Moderate risk (2+ risk factors) 10 year risk <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk (0-1 risk factor)	<160 mg/dL	≥160 mg/dL	≥190 mg/dL

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*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia; CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease, diabetes)

**Risk factors include cigarette smoking, hypertension, low HDL cholesterol (<40 mg/dL), family history of premature CHD (in males <55 and females <65) and age (men >45 and women >55)

Some studies have also demonstrated that markers other than LDL cholesterol are predictors of cardiovascular disease and death. These markers include non-HDL cholesterol, ApoB, and C Reactive Protein. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol.² ApoB is a molecule found in chylomicrons, VLDL, IDL, LDL, and Lp(a) particles that can be measured without a fasting blood sample.³ For patients already treated with statins, it has been suggested that non-HDL cholesterol and ApoB levels may be indicators of residual risk for cardiovascular disease. For highest risk patients, the non-HDL cholesterol level recommendation is <100 mg/dL.⁴

Some evidence also suggests that there may be a role for highly sensitive C Reactive Protein in predicting future cardiovascular events. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) demonstrated that patients with high levels of C Reactive Protein – regardless of low LDL levels – benefited from statin treatment.⁵

HMG CO-A REDUCTASE INHIBITORS (STATINS)

There are currently 6 statins on the market – atorvastatin, fluvastatin, lovastatin, pravastatin, and rosuvastatin, and simvastatin. Each of these agents has been associated with a reduction in cardiovascular events. Rosuvastatin, the newest statin available on the market, was only recently able to make this claim. The JUPITER trial (Justification for Use of Statins in Prevention: and Intervention Trial Evaluating Rosuvastatin) -- published in 11/2008 -- found that rosuvastatin was associated with nearly a 50% reduction in myocardial infarction, stroke, or death from cardiovascular causes.

Mechanism of action

Statins work by blocking the HMG-CoA reductase enzyme that is the rate-limiting step in cholesterol production. Statins also lower triglycerides, improve endothelial function, decrease platelet aggregation, and reduce inflammation.⁶

Side effects

Side effects of statins include myopathy (with or without elevated CK levels), increased aminotransferases, polyneuropathy, memory loss, sleep disturbances, impotence, gynecomastia, lupus-like syndrome, and pancreatitis.⁷ In their report, the Oregon Evidence-based Practice Center concluded that there is insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity. The clinical

significance of asymptomatic liver enzyme elevations resulting from statins has been questioned.⁸

There have also been reports in head to head trials of proteinuria developing in patients on rosuvastatin 40mg (1.2%) versus atorvastatin 80 mg (0.3%); simvastatin 80 mg and pravastatin 40 mg were not associated with this effect.⁹ Adverse event rates in patients taking atorvastatin 80 mg vs. rosuvastatin 40 mg were similar.¹⁰

Questions have also been raised regarding associations of cancer incidence and death with statin use. According to The Medical Letter, a meta-analysis of 26 large randomized trials using low to intermediate dose statins did not show any effect on cancer incidence or death.¹¹

Drug interactions

Simvastatin and lovastatin are metabolized by the CYP3A4 system in the liver, and as such, their plasma concentrations can be increased by concurrent use of CYP3A4 inhibitors such as itraconazole, ketoconazole, clarithromycin, erythromycin, cyclosporine, fluconazole, verapamil, amiodarone, nefazodone, and many protease inhibitors.

Atorvastatin undergoes less metabolism by the CYP3A4 system, and most 3A4 inhibitors have only mild effects on atorvastatin's plasma concentration. Fluvastatin is metabolized by CYP2C9, and is not often associated with drug interactions.

Pravastatin is not significantly metabolized by the cytochrome system; rosuvastatin is only 10% metabolized by the CYP2C9 system. Nonetheless, the manufacturer does recommend dose limits for rosuvastatin in patients on cyclosporine, gemfibrozil, antacids, and patients with severe renal disease/ESRD, and in Asian Americans.¹²

There have also been reports of excessive anticoagulation occurring in patients taking warfarin with lovastatin, simvastatin, fluvastatin, or rosuvastatin. It is therefore recommended that the international normalized ratio be monitored in warfarin patients who are initiated on statins or who change to a different statin.¹³

Monitoring

Recommendations on the frequency of monitoring liver enzymes of patients on statin therapy are variable. The Medical Letter consultants suggest that a reasonable approach would include checking baseline transaminases and liver function tests, followed by measurements after 3 months of treatment and annually thereafter. More frequent testing, if clinically indicated, should be considered.¹⁴

Comparison of statins

LDL lowering

According to a recent drug class review completed by the Oregon Evidence-based Practice Center, patients requiring LDL-c reductions of up to 35% will achieve results with any of the statins. Patients requiring 35 to 50% reductions will meet these goals with atorvastatin 20 mg or more, lovastatin 80 mg, rosuvastatin 10 mg or more, and simvastatin 20 mg or more.

Doses of statins that result in similar percent reductions in LDL-c¹⁵

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	--

HDL increases

The Oregon Evidence-based Practice Center's review of statins concluded that when statins are provided in doses that reduced LDL by equivalent amounts, similar percent increases in HDL can be achieved. Regarding comparisons between the abilities of simvastatin and atorvastatin to increase HDL, some studies find no difference in HDL increases between the two drugs, while others find simvastatin to be superior. Some studies have also shown rosuvastatin to produce greater increases in HDL than atorvastatin, while others have found no difference.¹⁶

Cardiovascular mortality

Controlled trials in patients with coronary disease reveal that atorvastatin, lovastatin, pravastatin, and simvastatin can lower cardiac events, stroke, and mortality from all causes – even among patients with normal LDL levels.¹⁷ Similar results were noted for rosuvastatin in the JUPITER trial published in November, 2008.¹⁸ Fluvastatin has also been shown to reduce coronary events when started after percutaneous coronary intervention.¹⁹

Cost comparison

Among the statins, lovastatin, pravastatin, and simvastatin are all available generically. As would be expected, there are tremendous differences in price among these drugs that are highlighted in the table below:

Current Statin Pricing*

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
10 mg \$1.78	20 mg \$1.43	10 mg \$0.08	10 mg \$0.06	10 mg \$1.78	10 mg \$0.02
20 mg \$2.52	40 mg \$1.44	20 mg \$0.08	20 mg \$0.06	20 mg \$1.76	20 mg \$0.03
40 mg \$2.52	80 mg \$1.83	40 mg \$0.14	40 mg \$0.09	40 mg \$2.00	40 mg \$0.04
80 mg \$2.54			80 mg \$0.14		80 mg \$0.07

*Pricing data were supplied by the National Supply Service Center.

Recommendations and conclusions regarding statins

HMG CoA reductase inhibitors are clearly an important and vital component of the IHS National Core Formulary. The Committee should re-evaluate, however, the current drugs included in the closed class category. Fluvastatin should be removed from the National Core Formulary given the availability of cheaper and more potent statins. Rosuvastatin should be considered as an alternative to atorvastatin 80 mg given its cost advantage and the existence of newly favorable mortality data. Finally, if the Committee decides to maintain the closed class designation of the statin class, it needs to consider new methods of formulary implementation and enforcement since spending data reveal that the IHS is not adhering to existing formulary constraints for low dose atorvastatin.

FIBRIC ACID DERIVATIVES

Fibrates work at the nuclear transcription factor peroxisome proliferator activated receptor-alpha (PPAR alpha) that regulates genes controlling lipid and glucose metabolism, endothelial function, and inflammation.²⁰ In the United States, this class of drugs currently includes gemfibrozil and fenofibrate. Fibrates generally lower triglycerides by 25-50 percent, and they increase HDL by 10-35%. They have the potential to increase LDL, but may also lower it.²¹ Of note, there are no data from clinical trials that establish that triglyceride lowering independently leads to lower cardiovascular disease event rates.²² In general, triglyceride serum concentrations of up to 500 mg/dL seem to respond to statin therapy, whereas greater elevations typically require medications such as fibrates or niacin.²³

Mortality reduction and cardiac outcomes

According to the VA's "Statin-Fibrate Report: Focus on Safety," there is a lack of evidence to support a reduction in cardiovascular mortality with the statin-fibrate combination. Looking at fibrates individually, however, gemfibrozil does have some mortality data to support its use; the Helsinki Heart Study was a randomized, double blind five year trial in which 4081 asymptomatic middle aged men with dyslipidemia were randomized to receive gemfibrozil or placebo for 5 years. Gemfibrozil increased HDL and decreased LDL in the treatment group. There was a reduction of 34 percent in

the incidence of coronary artery disease at the end of 5 years. A follow-up to the Helsinki Heart Study demonstrated that patients treated with gemfibrozil had a 32% reduction in coronary mortality.²⁴

The major study involving fenofibrate did not have such impressive results. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a randomized controlled trial with 9795 participants with type 2 diabetes who were randomized to receive fenofibrate or placebo. Overall, fenofibrate did not reduce the primary outcome of coronary events by a significant amount, but a significant reduction in non-fatal myocardial infarctions was noted. The benefit of fenofibrate may have been masked by a large number of patients in the placebo group who had started statin therapy.²⁵

Adverse events

There is no difference in the risk of adverse events between gemfibrozil and fenofibrate when they are used as monotherapy according to the VA's Statin-Fibrate Safety Report. According to the same safety report's review of the literature, the question of whether one fibrate is safer than another in combination with a statin is unknown.

Within the VA, reviews of statin-fibrate combinations were also done. These revealed 149 cases of rhabdomyolysis or ATN over a 2 year period in 93,677 patients on a combination of any statin with gemfibrozil. The overall rate of rhabdo or ATN in this population was 0.16%. In the 1830 patients on combination therapy with fenofibrate and a statin, no cases of rhabdomyolysis were noted. The huge difference in the number of patients on gemfibrozil compared with fenofibrate makes it difficult to draw many firm conclusions. The VA concluded that most cases of rhabdomyolysis were, in fact, exceedingly small and appeared to be dose related.²⁶

Of note, the VA review also notes all of the manufacturer recommendations regarding statin-fibrate combinations. It notes that atorvastatin and lovastatin product information warns against using these drugs in combination with any fibrate, whereas fluvastatin, pravastatin, rosuvastatin, and simvastatin specifically recommend against use in combination with gemfibrozil specifically. Rosuvastatin and simvastatin are specifically recommended not to be used at doses exceeding 10 mg daily in combination with a fibrate, and the lovastatin dose is recommended to be limited to 20 mg daily.²⁷

Regarding the pharmacokinetics of the statin-fibrate combination, the VA does note that the gemfibrozil/fluvastatin combination does not significantly alter fluvastatin serum concentrations, and that the fenofibrate/pravastatin and fenofibrate/rosuvastatin combination does not significantly affect statin pharmacokinetics.²⁸

Pricing

According to data supplied by the National Supply Service Center, the current price of gemfibrozil 600 mg is \$0.06/tablet. There are multiple forms of fenofibrate currently

available. Some of these brands include Triglide, Tricor, Lofibra, and Fenoglide; Triglide appears to have the current lowest price per tablet of \$0.17 to \$1.18 per tablet, depending on the dose.

National Core Formulary

Gemfibrozil is currently on the Indian Health Service's National Core Formulary. The fibrate class is not a closed class.

NIACIN

Niacin modifies all elements of the lipid profile favorably; it lowers triglycerides by 20-35 percent, LDL by 5-25%, and increases HDL by 15-35%. It comes in three preparations: immediate release, sustained release, and extended release. Some adverse effects – particularly flushing – are more common with immediate release niacin. Sustained release niacin preparations have been known to be hepatotoxic in doses greater than or equal to 2 grams daily.²⁹ The National Lipid Association, in a 2006 letter to the Center for Medicare and Medicaid Services, points out that the safety of the prescription strength extended release niacin is well-established. The letter points out that no case of severe hepatic toxicity is reported in the medical literature with this formulation.³⁰

According to a consensus report published by the American Diabetes Association and the American College of Cardiology Foundation, the “preferred agent to use in combination with a statin is nicotinic acid because there is somewhat better evidence for reduction in cardiovascular disease events with niacin, as monotherapy or in combination, than there is for fibrates.”³¹

Dosing

Niacin IR (Niacor) should be started initially at 250 mg once daily (with the evening meal) and can be increased every 4-7 days up to 2 grams daily in 2-3 divided doses. After 2 months, and at 2 to 4 week intervals, the drug can be titrated up to 6 grams daily in 3 divided doses.

Niacin ER (Niaspan) should be started at 500 mg at bedtime for 4 weeks, then increased to 1 gram at bedtime for 4 weeks and then adjusted according to response and tolerance up to a maximum of 2 grams daily. It should not be increased by more than 500 mg/day over 4 week intervals.

Niacin SR (e.g., Slo-Niacin) is available over-the-counter. Its dosing guidelines are similar to those of niacin ER. There have been case reports of abnormal liver function tests, hepatic failure or death resulting from certain formulations of niacin SR.³²

Side effects

According to a recent overview of the various niacin formulations, the variable adverse event profile of niacin formulations can be explained by “differences in their dissolution and absorption rates and metabolic disposition.”³³ Specifically, the ER formulation has a dissolution rate in between that of the IR and SR formulations, resulting in decreased flushing and hepatic effects compared with the IR and SR formulations of the drug.

Flushing can be diminished by having the patient take aspirin or a low dose NSAID 30 to 60 minutes before the dose. Cardiac arrhythmias, dry skin, rashes, glucose intolerance, dyspepsia, thrombocytopenia, hepatic necrosis, and leg cramps have all been reported side effects. Since cases of hepatotoxicity have occurred when sustained release products replaced immediate release products at the same doses, it is recommended that patients be initiated with low doses of niacin and titrated up to achieve the desired response.³⁴

Regarding monitoring, it is recommended that LFTs be checked at baseline, and then every 6-12 weeks for 6 months, and then q6 months. Uric acid levels should be monitored if patients have a history of gout, and blood glucose should be monitored in patients with diabetes. Phosphorus levels should be monitored in patients at risk for hypophosphatemia.

Pricing

Niacin ER (Niaspan) ranges in price from \$0.36 to \$0.48/tablet depending on pill strength. There are also combinations of Niacin ER and simvastatin (Simcor) and Niacin ER and lovastatin (Advicor). Simcor pricing ranges from \$0.36 to \$0.48/tablet, and Advicor ranges from \$1.63 to \$2.11 per tablet.

National Core Formulary

Currently, niacin is listed on the Core Formulary without an IR or ER extension. The Committee should consider adding one or both of these extensions given the superior safety of these formulations over the SR formulations.

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² Brunzell, et al. “Lipoprotein Management in Patients with Cardiometabolic Risk: Consensus Conference Report from the American Diabetes Association and the American College of Cardiology Foundation.” *Journal of the American College of Cardiology*. January 6, 2009, p. 1516.

³ Brunzell, et al. “Lipoprotein Management in Patients with Cardiometabolic Risk: Consensus Conference Report from the American Diabetes Association and the American College of Cardiology Foundation.” *Journal of the American College of Cardiology*. January 6, 2009, p. 1516.

⁴ Brunzell, et al. “Lipoprotein Management in Patients with Cardiometabolic Risk: Consensus Conference Report from the American Diabetes Association and the American College of Cardiology Foundation.” *Journal of the American College of Cardiology*. January 6, 2009, p. 1519.

⁵ Ridker, et al. “Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein.” *New England Journal of Medicine*. Vol. 359, no. 21, pp. 2195-2207.

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- ⁶ “Drugs for Lipids.” Treatment Guidelines from The Medical Letter. Vol 6, Issue 66, February, 2008, p. 9.
- ⁷ “Drugs for Lipids.” Treatment Guidelines from The Medical Letter. Vol 6, Issue 66, February, 2008, p. 12.
- ⁸ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.37.
- ⁹ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.18.
- ¹⁰ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.9.
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- ¹⁵ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.12.
- ¹⁶ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.18.
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- ¹⁸ Ridker, et al. “Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein.” New England Journal of Medicine. Vol. 359, no. 21, pp. 2195-2207
- ¹⁹ Helfand, Carson, and Kelley. “Drug Class Review on HMG-CoA Reductase Inhibitors (Statins) Final Report.” August 2006, p.20.
- ²⁰ “Drugs for Lipids.” Treatment Guidelines from The Medical Letter. Vol 6, Issue 66, February, 2008, p. 12.
- ²¹ “Drugs for Lipids.” Treatment Guidelines from The Medical Letter. Vol 6, Issue 66, February, 2008, p. 12.
- ²² Brunzell, et al. “Lipoprotein Management in Patients with Cardiometabolic Risk: Consensus Conference Report from the American Diabetes Association and the American College of Cardiology Foundation.” Journal of the American College of Cardiology. January 6, 2009, p. 1516.
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