

Disease State Management: Hyperlipidemia Treatment Updates

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Educational Goal: To provide up-to-date information on medications used for the treatment of hyperlipidemia, including new FDA recommendations, clinical trial results, and potential emerging therapies.

Objectives:

After completing this knowledge-based program, the participant will be able to:

- Specify the recent FDA recommendations regarding the prescribing of simvastatin 80 mg
- Recall the new contraindications and dose limitations of simvastatin 80 mg
- State the risks involved with the use of high dose HMG-CoA Reductase Inhibitors
- Evaluate the implications of the AIM-HIGH trial on the use of niacin in combination with a HMG-CoA Reductase Inhibitor for the treatment of hyperlipidemia
- Discuss anacetrapib and darapladib as investigational therapies in the management of hyperlipidemia and atherosclerosis, respectively.

The National Cholesterol Education Program's (NCEP) Adult Treatment Panel (ATP) III guidelines were initially released in 2002 and have since been the primary resource used by clinicians in diagnosing and treating hyperlipidemia. The guidelines were last updated in 2004, but several new recommendations and announcements have been released since that time concerning common drugs used for hyperlipidemia management. This article addresses some of the new safety announcements regarding the use of HMG-CoA Reductase Inhibitors and discusses the results and implications of several clinical trials that have recently been

completed on common medications used for hyperlipidemia management. Additionally, darapladib and anacetrapib will be discussed as investigational therapies for the prevention and treatment of hyperlipidemia and its complications.

HIGH DOSE STATINS

HMG-CoA Reductase Inhibitors, more commonly referred to as "statins," were introduced in the early 1970's and have since then been established as first line LDL lowering therapy for patients diagnosed with hyperlipidemia. Although statins have proven their ability to lower cholesterol and aid in the prevention of major vascular events including

heart attack, stroke, and need for revascularization, the increased risk of myopathy that occurs with the use of statins has brought them under much scrutiny over the years. In 2010, following publication of the SEARCH (Clinical Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial, the U.S. Food and Drug Administration (FDA) released a public warning stating that simvastatin 80 mg is associated with an increased risk for myopathy, including rhabdomyolysis.¹ Since then, the FDA has continued to review the safety of high-dose statins, leading to an updated safety announcement on June 8, 2011. This announcement recommended limiting the use of simvastatin 80 mg to only those patients who have been taking this dose for at least 12 months or more without evidence of muscle injury.² This means that simvastatin 80 mg should not be started in new patients, including those who were already taking a lower dose of simvastatin without muscle injury. In their recommendation, the FDA cited evidence showing that the risk of developing myopathy appears to be the greatest within the first year of statin therapy and specific patient populations at increased risk include females and the elderly.² Additionally, a genetic variant of a liver

transporter was found in over 60% of patients who developed myopathy with simvastatin treatment, suggesting that this may also play a role.² Simvastatin and Vytorin® (simvastatin/ezetimibe) labels have both been revised to include the new 80 mg dose restriction. Furthermore, the labels of simvastatin, Vytorin®, and Simcor® (Niacin extended-release/ezetimibe) have all been revised to include -new dose limitations of simvastatin when used in combination with certain drugs that increase the risk of developing myopathy. The dose limitations and contraindications on the new simvastatin label are presented in Table 1. Despite the recent publicity regarding the negative side effect profile associated with simvastatin, it continues to be highly effective for the treatment of primary hypercholesterolemia and is shown to reduce mean LDL concentrations by approximately 26-47%.³ Additionally, it has been shown to significantly decrease the risk of coronary events in high risk individuals including patients with existing coronary disease, diabetes, peripheral vascular disease, or patients with a history of stroke.³ The new FDA recommendation is a means of getting the most benefit out of statin therapy while subjecting the patient to the least risk of injury due to side effects of this drug class.

Table 1: Contraindications and dose limitations of simvastatin

Contraindicated with simvastatin	Do not exceed 10 mg simvastatin (Avoid Simcor ®)	Do not exceed 20 mg simvastatin
Itraconazole	Amiodarone (previously 20 mg simvastatin limit)	Amlodopine (New)
Ketoconazole	Verapamil (previously 20	Ranolazine (New)

	mg simvastatin limit)	
Posaconazole (New)	Diltiazem (previously 40 mg simvastatin limit)	
Erythromycin		
Clarithromycin		
Telithromycin		
HIV protease inhibitors		
Nefazodone		
Gemfibrozil (previously 10 mg simvastatin limit)		
Cyclosporine (previously 10 mg simvastatin limit)		
Danazol (previously 10 mg simvastatin limit)		

Aside from the increased risk of myopathy associated with the use of high-dose statins, recent studies have shown that statins may also increase the risk of diabetes in a dose-dependent manner.⁴ A meta-analysis published in the Journal of the American Medical Association (JAMA) in 2011 analyzed 5 statin trials and concluded that use of either atorvastatin 80 mg or simvastatin 80 mg is associated with a higher risk of new-onset diabetes compared with moderate-dose statins.⁴ Of the 37,742 study participants included in the meta-analysis, 2749 developed diabetes; 1449 of these participants were on intensive-dose statin therapy and 1300 were taking a moderate-dose statin.^{4,5} This translated to a number needed to harm equal to 498, meaning that for every 498 patients treated with 80 mg atorvastatin or simvastatin that one would develop diabetes.⁴ On the other hand, the meta-analysis revealed that the high-dose statin therapy caused a significant decrease in cardiovascular events compared to moderate-dose statins and for every 155 patients treated with an intense dose statin that one major cardiovascular event would be prevented.⁴ The results of this study suggest that although major benefits are seen from the use of high-dose atorvastatin and simvastatin, clinicians should be cautious of the increased risk of

diabetes in those receiving intensive statin therapy and initiate appropriate monitoring.

HDL-RAISING MEDICATIONS

HDL is commonly referred to as “good cholesterol” due to its ability to remove excess cholesterol from the blood and carry it to the liver where it can be broken down. Optimal HDL control is believed to offer protection against developing coronary heart disease (CHD), and thus low HDL is believed to be a strong independent predictor of CHD risk.⁶ If a patient’s HDL is low, defined by ATPIII guidelines as HDL<40 mg/dl, then a potential pharmacologic therapy that may be initiated is niacin (nicotinic acid) due to its favorable effects on elevating HDL. Because of the inverse relationship that has been suspected between HDL and CHD incidence, it has been assumed that the use of niacin could lower the rate of major adverse cardiovascular events in high risk individuals who have suboptimal HDL cholesterol; however, the results of the 2011 AIM-HIGH trial suggests otherwise.⁷ The National Heart, Lung, and Blood Institute (NHLBI) recently stopped the AIM-HIGH trial 18 months in advance due to a lack of benefit seen from adding extended-release niacin to statin treatment in people with history of cardiovascular disease.⁸ The AIM-HIGH trial recruited 3,414 patients who were optimally treated

on a statin (LDL 40-80 mg/dL) but still had low HDL cholesterol.⁷ These patients were given either placebo or extended-release niacin 1500-2000 mg/day in addition to their statin and observed for the primary endpoint which was a major accidental coronary event.⁷ The trial was stopped on April 25, 2011 by the data and safety monitoring board after determining that there was no difference in the rate of clinical events between the treatment and placebo groups.⁷ Those who were assigned to the niacin treatment group did see positive effects on their HDL and triglycerides as expected, and yet this did not significantly reduce their risk of major coronary events. Furthermore, there was a slight unexplained increase in the rate of ischemic strokes observed in patients who received treatment with extended-release niacin during the trial in comparison to the placebo group (28 strokes vs. 12 strokes).^{7,8,9} Currently, the FDA has made no recommendations regarding the use of extended-release niacin for the treatment of hyperlipidemia.⁹

Fibric acid derivatives, although not as effective at raising HDL as nicotinic acid, is another class of drugs that may be considered if an increase in HDL is warranted. Though fibric acid derivatives have favorable effects on HDL and triglycerides, similarly to the AIM-HIGH trial, the recent ACCORD trial did not demonstrate a reduced risk of cardiovascular events in patients who were given fenofibrate in combination with a statin.¹⁰ Overall, patients on fenofibrate (Tricor®) plus statin therapy did not experience any statistically significant difference in the number of major adverse events compared with those receiving statin therapy and placebo. The research did however note that those patients who exhibited the lowest HDL cholesterol plus the highest triglycerides had lower rates of cardiovascular events with combination statin and fibrate therapy versus those patients on statin therapy alone.¹⁰ On May 19 of this year, the FDA announced that they still support the indication of fenofibric acid for co-administration with a statin; however, they voted that Abbott be required to conduct a new study to further support the efficacy of a statin and fibrate combination.¹¹

INVESTIGATIONAL THERAPIES

Despite the profound effect that statins have on improving cholesterol, complications related to atherosclerotic cardiovascular disease are still prevalent. There is much need for novel therapies that will further reduce the risk of cardiovascular complications linked to hyperlipidemia. Of recent interest as a potential therapy for the treatment of hyperlipidemia is a drug known as anacetrapib which fits into a class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors. Anacetrapib works by mediating the transfer of cholesterol and triglycerides between lipoprotein particles and results in a significant increase in HDL cholesterol and decrease in LDL cholesterol. A recent phase III clinical trial known as DEFINE showed that those taking anacetrapib had an average 40% decrease in their LDL cholesterol and a 138% increase in their HDL cholesterol.^{12,13} More specifically, the HDL increased from the low 40s to 101 mg/dL on average and the LDL decreased from 81 mg/dL to 45 mg/dL on average.¹² Additionally, Apolipoprotein A1 levels were shown to increase and Apolipoprotein B levels decrease, which are responsible for carrying HDL and LDL cholesterol, respectively.¹² The study was designed to assess the lipid-modifying efficacy as well as the safety and tolerability of anacetrapib 100 mg when used in combination with a statin in those with coronary artery disease. Of particular interest in the DEFINE trial was the side effect profile of anacetrapib considering that another CETP inhibitor, torcetrapib, was found to cause an excess of deaths and cardiovascular events related to an increase in blood pressure when studied in the ILLUMINATE trial of 2007. The mechanism behind the adverse effects noted with torcetrapib therapy included increases in serum sodium and aldosterone levels in addition to altered serum electrolyte levels. Unlike torcetrapib, there was not a statistically significant difference between blood pressure, electrolytes, or aldosterone in the anacetrapib treatment group versus the placebo group.¹² Additionally, there were no cases of rhabdomyolysis in either the treatment or placebo groups.¹² Though the results of the DEFINE trial show great potential for the CEPT inhibitor anacetrapib as a novel hyperlipidemia therapy, a larger phase III trial known as REVEAL is currently

underway to further test the safety and efficacy of this drug.

Aside from CETP, another enzyme that is a target for emerging hyperlipidemia medications is lipoprotein-associated phospholipase-A2 (Lp-PLA₂). Studies have shown that Lp-PLA₂ is associated with an increased risk of heart attack and stroke and is present in many atherosclerotic plaques that are prone to rupture.¹⁴ An investigational drug known as darapladib is an anti-atherosclerosis agent that inhibits Lp-PLA₂ and improves the stability of arterial plaques preventing them from rupture. In phase II trials, darapladib was shown to stop the extension of necrotic core of plaques and demonstrated favorable effects on markers of inflammation and plaque stability.^{15,16} It was proven to produce sustained inhibition of Lp-PLA₂ activity in a dose dependent fashion and also decreased interleukin-6 and C Reactive protein which are both biomarkers of CV risk.¹⁵ The STABILITY study is a phase III clinical trial currently underway to test the safety and efficacy of darapladib in people with coronary artery disease. Another phase III trial known as SOLID-TIMI 52 has also been planned to study the effects of darapladib and will include 11,500 patients.

The NCEP ATP IV guidelines are currently in development and should become available for public review and comment in fall of this year with an expected release date in spring of 2012. The updated guidelines will likely address many of the issues concerning statins, fibric acid derivatives, and nicotinic acid. Until then, it is important to remain up to date on the new evidence and recommendations involving these medications and their role in the treatment of hyperlipidemia and related complications. Despite the use of current cholesterol medications, there continues to be a high number of cardiovascular accidents related to hyperlipidemia. Hopefully some of the emerging medications, including anacetrapib and darapladib, will demonstrate effectiveness at improving patient lipid panels and decreasing risk of cardiovascular complications while avoiding major adverse events.

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