



Ask the Expert: Exploring Clinical Controversies in Dyslipidemia—Combination Therapy, Chronic Kidney Disease, and New Evidence

A continuing education (CE) activity entitled *Current Controversies in the Management of Dyslipidemia: Separating Fact from Fiction* was presented as one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at www.ashpadvantage.com/cemornings). The program was presented by Joseph Saseen, Pharm.D., FCCP, FNLA, BCPS, CLS. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Saseen in a live webinar conducted on February 2, 2011. The highlights of this webinar are described in this and another e-Newsletter to be released in May 2011.

Combination Lipid-Lowering Therapy

Statins are the lipid-lowering drugs of first choice for patients with or at risk for coronary heart disease (CHD).¹ The benefits of statin monotherapy for lowering low-density lipoprotein (LDL) cholesterol and the risk for cardiovascular events in these patients are well documented.¹

However, combination lipid-lowering therapy using a statin plus ezetimibe, a fibrate, or niacin is needed to achieve lipid goals in some patients. Whether the use of combination lipid-lowering therapy produces greater reductions in cardiovascular events than statin monotherapy has been controversial, and clinicians have been uncertain about which drug combination is most effective for reducing CHD risk.

In the 2-year, randomized, double-blind ENHANCE study of 720 patients with heterozygous familial hypercholesterolemia, adding ezetimibe to statin therapy led to a significant reduction in LDL cholesterol, but not in carotid intima media thickness (a surrogate measure of the progression of atherosclerosis that has been shown to correlate with risk of cardiovascular events).² In the 14-month, open-label ARBITER-6 study, 208 patients with CHD or a CHD risk equivalent (e.g., diabetes) who were receiving long-term statin therapy were randomly assigned to the addition of extended-release niacin or ezetimibe.³ Adding niacin led to a greater reduction in mean carotid intima media thickness than adding ezetimibe. There was a greater increase from baseline in high-density lipoprotein (HDL) cholesterol (despite a smaller reduction from baseline in LDL cholesterol) and a lower incidence of major cardiovascular events in the niacin group than in the ezetimibe group.

In the randomized, double-blind, placebo-controlled Oxford Niaspan Study, adding extended-release niacin to statin therapy in 71 patients with a low HDL cholesterol concentration and either: 1) type 2 diabetes with CHD or 2) carotid

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or peripheral atherosclerosis led to a significant increase in HDL cholesterol concentrations and a significant decrease in LDL cholesterol concentrations compared with placebo over a 12-month period.⁴ The carotid artery wall area (the primary end point) decreased from baseline in patients treated with extended-release niacin and increased from baseline in the placebo group. As with carotid intima media thickness, the carotid artery wall area is a surrogate measure of the progression of atherosclerosis that has been shown to correlate with risk for cardiovascular events, but carotid artery wall area is measured using magnetic resonance imaging and carotid intima media thickness usually is measured using ultrasonography. The difference between treatment groups was significant. These findings support the addition of niacin to statin therapy in patients with a low HDL cholesterol concentration and type 2 diabetes with CHD or carotid or peripheral atherosclerosis.

In the randomized, open-label, placebo-controlled ACCORD study of 5518 patients with type 2 diabetes treated with statin therapy, the impact of adding fenofibrate on the annual rate of nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death was not significantly different from placebo after a mean follow-up time of 4.7 years.⁵ A subgroup analysis suggested that the treatment effect differed by sex, with a possible benefit for men and possible harm to women. A possible benefit for patients with both a high baseline triglyceride concentration and a low baseline HDL cholesterol concentration also was identified in a subgroup analysis.

Thus, the impact of various combination lipid-lowering therapies on cardiovascular events in patients with or at risk for CHD is complex and may hinge on sex, lipid profile, and other factors. Additional research is needed to identify which drug combinations to use to reduce the risk of cardiovascular events in specific patient populations.

“Combination lipid-lowering therapies have been shown to improve lipid profiles to a greater extent than monotherapy in patients with dyslipidemia, but reductions in cardiovascular events have not been demonstrated with all commonly-used combinations.”

—Joseph Saseen, Pharm.D., FCCP, FNLA, BCPS, CLS

Managing Dyslipidemia in Patients with Chronic Kidney Disease

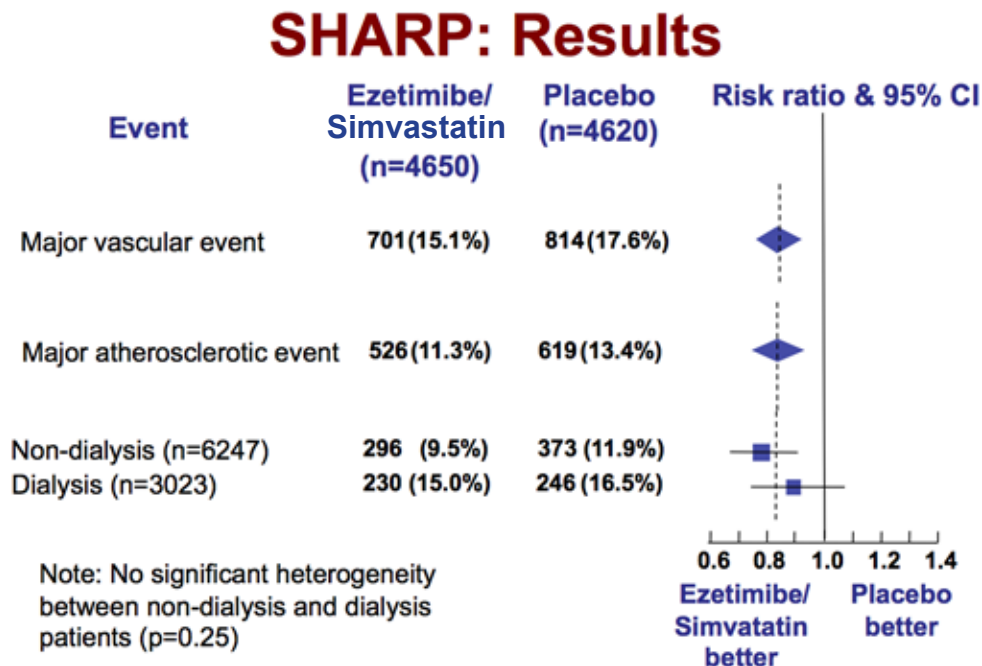
Cardiovascular disease is a common comorbidity and the mortality rate is high in patients with end-stage renal disease (ESRD) who require hemodialysis.⁶ The primary target of lipid-lowering therapy in most of these patients is LDL cholesterol.¹ Statin therapy significantly reduces LDL cholesterol concentrations in patients with ESRD requiring hemodialysis, but whether such lipid reductions translate into reductions in cardiovascular events in this patient population is unclear.⁶ In a 3.8-year, randomized, double-blind, placebo-controlled study of 2776 patients requiring long-term hemodialysis (the AURORA study) and a 4-year, randomized, double-blind, placebo-controlled study of 1255 patients with diabetes who required long-term hemodialysis (the 4D study), a reduction in cardiovascular events was not demonstrated from the use of statin therapy.^{7,8}

The impact of the statin simvastatin with or without ezetimibe on cardiovascular events in more than 9000 adults at least 40 years of age with chronic kidney disease but no history of MI was evaluated in the Study of Heart and Renal Protection, a randomized, double-blind, placebo-controlled study referred to as SHARP.⁹ The results were presented in



a late-breaking session at the American Society of Nephrology Renal Week on November 20, 2010.¹⁰ Roughly one third of the study participants were receiving hemodialysis or peritoneal dialysis. Study participants were randomly assigned to receive placebo, simvastatin alone, or simvastatin plus ezetimibe. Most of the patients in the simvastatin monotherapy group were randomized again after 1 year to receive simvastatin plus ezetimibe or placebo alone because of the availability of 1-year data demonstrating the safety of ezetimibe in combination with simvastatin. The median follow-up time was 4.9 years. Major vascular events (cardiac death, MI, any stroke, or any revascularization) was the pre-specified primary end point, although the primary end point was changed after 1 year to major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization). The average reduction from baseline in LDL cholesterol concentration with simvastatin plus ezetimibe treatment was 43 mg/dL and 33 mg/dL greater than that achieved with placebo after 1 year and 2.5 years, respectively. The use of simvastatin plus ezetimibe instead of placebo significantly reduced the risk of major atherosclerotic events by 17% and the risk of major vascular events by 15%. The reduction in major atherosclerotic events from use of simvastatin plus ezetimibe was smaller in dialysis patients than in non-dialysis patients, although the difference between dialysis patients and non-dialysis patients was not significant (Figure 1). There were no significant differences between the two treatment groups in major adverse events (e.g., muscle pain, hepatic transaminase elevations). Thus, statin-based therapy in patients with chronic kidney disease requiring long-term hemodialysis has not consistently produced reductions in cardiovascular events.

Figure 1. SHARP Study Results: Risk of Major Vascular Events and Major Atherosclerotic Events



Baigent C, Landry M. Presented at the American Society of Nephrology Renal Week, November 20, 2010. <http://www.ctsu.ox.ac.uk/~sharp/slides.htm>.



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