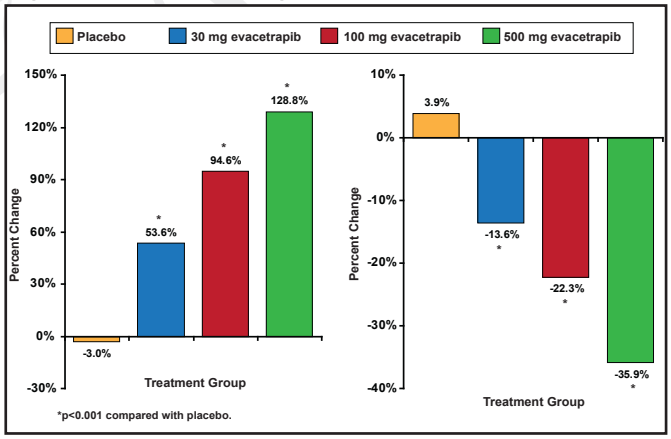
Following a dietary lead-in, 398 patients were randomly assigned to one of 10 treatment groups for 12 weeks: placebo; evacetrapib monotherapy (30, 100, or 500 mg/day); or statin therapy (simvastatin, 40 mg/day; atorvastatin, 20 mg/day; or rosuvastatin, 10 mg/day) with or without evacetrapib 100 mg/day. A total of 393 patients received the study drug and were included in the final analysis.

The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL [1.42 mmol/L] and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL [3.73 mmol/L]. As monotherapy, evacetrapib produced dose-dependent increases of HDL-C of 30.0 to 66.0 mg/dL [0.78 to 1.71 mmol/L] (53.6% to 128.8%) compared to a decrease with placebo of -0.7 mg/dL [-0.02 mmol/L] (-3.0%; p<0.001 for all compared with placebo). Decreases in LDL-C were -20.5 to -51.4 mg/dL [-0.53 to 1.33 mmol/L] (-13.6% to -35.9%) compared to an increase with placebo of 7.2 mg/dL [0.19 mmol/L] (3.9%; p<0.001 for all compared with placebo; Figure 1).

Figure 1. Percent Changes in HDL-C and LDL-C.



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In combination with statin therapy, evacetrapib, 100 mg/day, produced absolute increases in HDL-C of 42.1 to 50.5 mg/dL [1.09 to 1.31 mmol/L] (78.5% to 88.5%; p<0.001 for all compared with statin monotherapy) and absolute decreases in LDL-C of -67.1 to -75.8 mg/dL [1.74 to 1.96 mmol/L] (-11.2% to -13.9%; p<0.001 for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reduction in LDL-C (p<0.001), but no greater increase in HDL-C (p=0.39). Evacetrapib was well tolerated, with a low rate of treatment-related adverse events or discontinuation of therapy. No evidence of adverse blood pressure or mineralocorticoid effects was observed as was seen previously with torcetrapib.

The development of CETP inhibitor drugs to increase HDL-C levels has been challenging and marked by failure with the first agent developed. In the ILLUMINATE trial, torcetrapib increased cardiovascular death and had off-target effects (increase in aldosterone) that led to increases in blood pressure [Barter PJ et al. *N Engl J Med* 2007]. However, the outcomes from this and other Phase 2 trials with anacetrapib and dalcetrapib suggest promise for second generation CETP inhibitors as cardioprotective agents.

Two large cardiovascular outcome studies (dal-OUTCOMES [Schwartz GG et al. *Am Heart J* 2009] and REVEAL HPS-3 TIMI-55 [Melloni C et al. *Am Heart J* 2010]) are ongoing to determine whether CETP inhibitors can further reduce the substantial residual risk of cardiovascular disease still observed in patients with established coronary artery disease despite the use of existing lipid therapies.

Further reading: Nicholls SJ et al. *JAMA* 2011.

AIM-HIGH: Niacin Provides No Added Benefit for Statin Users With Well-Controlled LDL

Written by Anne Jacobson

Add-on therapy with high-dose extended-release (ER) niacin provides no additional reduction in cardiovascular (CV) events in patients with dyslipidemia and a history of cardiovascular disease (CVD) who are treated to target low-density lipoprotein (LDL) levels with a statin, according to findings from a randomized trial.

William E. Boden, MD, University of Buffalo, Buffalo, New York, USA, presented the final analysis of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes trial [AIM-HIGH; NCT00120289]. The AIM-HIGH trial was stopped prematurely in May 2011 after an interim analysis revealed futility (lack of efficacy with niacin) for the primary endpoint and an unexpected higher rate of ischemic stroke in the niacin group.

Despite the beneficial effects of statins on LDL levels, patients with dyslipidemia face residual CV risk that is associated with low high-density lipoprotein (HDL) levels. AIM-HIGH was designed to evaluate whether raising HDL levels with ER niacin would reduce CV events in patients who are treated aggressively to low LDL levels with a statin (target 40 to 80 mg/dL [1.03 to 2.07 mmol/L]).

The AIM-HIGH trial included 3414 patients aged ≥45 years with a history of coronary heart disease (CHD), cerebrovascular disease, or peripheral artery disease. Patients also had low HDL cholesterol (<40 mg/dL

[1.03 mmol/L] for men; <50 mg/dL [1.29 mmol/L] for women), high triglyceride (TG) levels (150 to 400 mg/dL [1.69 to 4.52 mmol/L]), and LDL levels <180 mg/dL [4.65 mmol/L] if they were not taking a statin at baseline.

All patients were treated with simvastatin 40 to 80 mg/day and randomly assigned to additional therapy with high-dose ER niacin in gradually increasing doses up to 1500 to 2000 mg per day (n=1718) or placebo (n=1696). To achieve LDL levels within the target range of 40 to 80 mg/dL [1.03 to 2.07 mmol/L], the dose of simvastatin was adjusted, and in 515 patients a second LDL-lowering drug, ezetimibe, was also added. Because LDL levels were unblinded and reported to clinical sites, more patients in the statin monotherapy group than the statin/niacin group received high-dose 80-mg/day simvastatin (25% vs 18%; p=0.02) and more received additional treatment with ezetimibe (22% vs 10%; p<0.001). The cumulative rate of study drug discontinuation was 20% in the statin monotherapy group and 25% in the statin/niacin group (p<0.001).

Patients who were taking simvastatin/niacin had more favorable changes in lipid parameters than those in the simvastatin group. After 2 years, HDL levels increased from baseline by 25% (42 mg/dL [1.09 mmol/L]) in the simvastatin/niacin group and by 9.8% in the simvastatin group (38 mg/dL [0.98 mmol/L]; p<0.001). TG levels also decreased by 29% and 8% in the simvastatin/niacin and simvastatin groups, respectively (p<0.001). LDL levels had more modest decreases of 12% and 5%, respectively (p<0.001). The beneficial changes in lipid levels persisted through 3 years of follow-up.

Despite these achieved differences in lipid profiles, no difference in the primary composite endpoint of CHD death, nonfatal myocardial infarction (MI), ischemic stroke, hospitalizations for acute coronary syndrome, or revascularization procedures were present when the Data Safety Monitoring Board (DSMB) decided in April 2011 to recommend that the blinded study be stopped because of futility (ie, very low likelihood the trial would demonstrate efficacy of simvastatin/niacin over simvastatin).

After a mean follow-up of 36 months, 16.4% of patients in the statin/niacin group and 16.2% of patients in the statin monotherapy group reached the primary endpoint (HR, 1.02; 95% CI, 0.87 to 1.21; p=0.79). There were no differences between treatments in the prespecified subgroups, defined by age, gender, diabetes, metabolic syndrome, history of MI, or statin use at study entry.

Although the DSMB observed that more patients in the statin/niacin group had an ischemic stroke compared with the statin monotherapy group in the interim analysis, this difference was not statistically significant in the final analysis (29 vs 18 patients; HR, 1.61; 95% CI, 0.89 to 2.90; p=0.11). No other differences in individual endpoints were observed.

Previous lipid-modifying therapy may have limited the ability to show a favorable treatment effect with ER niacin, Dr. Boden said. At study entry, 94% of all patients were on a statin, and 20% had a history of niacin use. Moreover, 75% of all patients had been on statins for at least 1 year, during which vulnerable plaques may have converted to stable plaques, limiting the ability to demonstrate a difference in cardiovascular events between AIM-HIGH treatment groups.

The current role of niacin in managing dyslipidemia is unclear, Dr. Boden said. Investigators at the Late-Breaking Clinical Trials session said that they eagerly await findings from the Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE; NCT00461630], which will evaluate whether the combination of ER niacin and laropiprant prevents CV events in approximately 25,000 patients with existing vascular disease.

Further reading: AIM-HIGH Investigators. *N Engl J Med* 2011.

Free Post-MI Medications Improve Adherence Without Added Costs

Written by Maria Vinall

Researchers recommended widespread adoption of a program that eliminates copayments for preventive medications after the Post-Myocardial Infarction Free Rx Event and Economic Evaluation trial [MI FREEE; NCT00566774] showed that the policy improved treatment adherence without increasing overall health costs. The outcomes from the trial were presented by Niteesh K. Choudhry, MD, PhD, Harvard Medical School, Boston, Massachusetts, USA.

The investigator-initiated, cluster-randomized, controlled policy study enrolled patients who were discharged after myocardial infarction (MI) and randomly assigned by their insurance plan sponsors to full or usual prescription coverage for all statins, β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers. Antiplatelet therapy was not included. The randomization was by plan sponsor (ie, employer, union, government, association) and not by patient. The primary outcome was the first major vascular event or revascularization. Secondary outcomes were rates of medication adherence, total major vascular events