This double-blind, double-dummy drug, international trial included patients aged 19 to 80 years who presented with an accelerating pattern of prolonged (>20 minutes) or recurrent angina, either at rest or during minimal exertion within the preceding 48 hours, in association with positive cardiac biomarkers (troponin or creatinine kinase MB isoenzyme), with at least one coronary stenosis that required PCI. Although not mandated, a strategy of early invasive management (within 24 hours of hospital admission) was the standard of care at all participating centers for patients who presented with an acute coronary syndrome (ACS) and elevated cardiac biomarkers. All patients were treated with 325 to 500 mg of aspirin and 600 mg of clopidogrel before study drug administration.

A total of 1721 NSTEMI patients were randomized to abciximab plus UFH (n=861) or bivalirudin (n=860) immediately before PCI. Baseline characteristics were well balanced between groups. The mean age of patients was 67.5 years, over 20% were female, almost one-third had diabetes mellitus, and there was a nearly 50-50 split between patients with 1- to 2-vessel coronary artery disease compared with 3-vessel disease. One in 5 patients had a prior MI, one-third had a prior PCI, 10% had prior coronary artery bypass, and the mean left ventricular ejection fraction (LVEF) was 51%, suggesting that these patients were representative of moderate- to high-risk ACS patients who are seen in routine clinical practice.

The primary endpoint occurred in 10.9% of the patients in the abciximab group and in 11.0% in the bivalirudin group (relative risk [RR] with abciximab/UFH, 0.99; 95% CI, 0.74 to 1.32; p=0.94). The secondary endpoint occurred in 12.8% of the patients in the abciximab group and in 13.4% in the bivalirudin group (RR, 0.96; 95% CI, 0.74 to 1.25; p=0.76). Major bleeding occurred in 4.6% of the patients in the abciximab group (n=40) versus 2.6% in the bivalirudin group (n=22; RR, 1.84; 95% CI, 1.10 to 3.07; p=0.02) [Kastrati et al. *N Engl J Med* 2011].

In patients with NSTEMI who are treated with an early invasive strategy, many studies have been performed to define the optimal antithrombotic therapy to be used as adjunct to PCI. Prior to the ISAR-REACT 4 trial, the ACUITY trial also studied patients with NSTEMI [Stone GW. *NEJM* 2006] and demonstrated similar 30-day rates of net clinical benefit (ischemic plus bleeding outcomes) in patients who were treated with either bivalirudin alone (10.1%), GPIIb/IIIa inhibitor/bivalirudin (11.8%), or a GPIIb/IIIa inhibitor/UFH strategy (11.7%), with significantly lower rates of major bleeding (3.0%, 5.3%, and 5.7% respectively). Despite these impressive results, the ACUITY trial failed to sway many interventional cardiologists, particularly in the United States, to implement these results and start using bivalirudin more frequently in NSTEMI because of concerns of potential bias that could have been introduced in the open-label design of ACUITY. Now, ISAR-REACT 4 has reported virtually the same results as ACUITY in patients with NSTEMI who have been treated with an early invasive approach in a rigorously conducted double-blind trial, which is reassuring and strengthens the evidence of efficacy and safety for treating patients with ACS who undergo PCI with bivalirudin instead of the previous standard of a GPIIb/IIIa inhibitor and UFH.

According to Prof. Kastrati, it appears that bivalirudin merits use in MI patients (including either patients with STEMI, based on the HORIZONS AMI trial [Stone *NEJM* 2008;358:2218-30], or NSTEMI) but not in stable patients or in those with unstable angina without troponin elevations. He estimated that STEMI and NSTEMI patients together make up about one-third of all those who undergo PCI. "The other two-thirds may just as well receive heparin, as there is no benefit of using bivalirudin, and it is much more expensive," he said.

CETP Inhibitor Evacetrapib Reduces LDL-C and Raises HDL-C Levels

Written by Rita Buckley

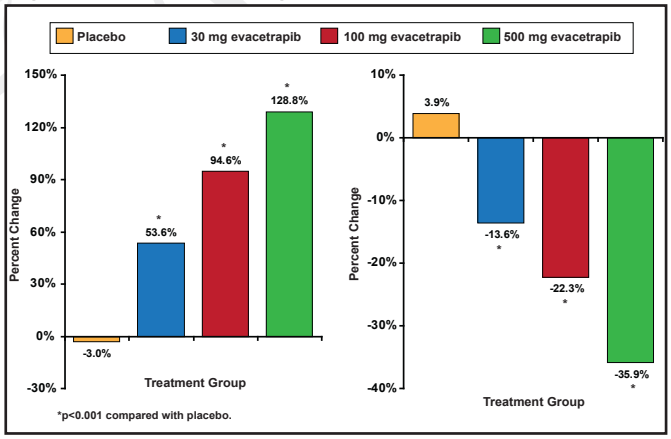
Stephen J. Nicholls, MBBS, PhD, Cleveland Clinic Heart & Vascular Institute, Cleveland, Ohio, USA, presented results from a Phase 2 randomized controlled trial of the novel cholesteryl ester transfer protein (CETP) inhibitor evacetrapib. Compared with placebo or statin monotherapy, evacetrapib with or without a statin increased high-density lipoprotein cholesterol (HDL-C) and decreased low-density lipoprotein cholesterol (LDL-C) levels in patients with dyslipidemia [Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or with Statins on HDL and LDL Cholesterol Trial; NCT01105975].

Several CETP inhibitors are currently undergoing clinical evaluation. However, their effects in combination with the most commonly used statins have not been fully characterized. The purpose of this randomized, double-blind, multicenter, dose-ranging study was to examine the biochemical effects, safety, and tolerability of evacetrapib as monotherapy and in combination with statins in patients with hypercholesterolemia or low HDL-C levels. The co-primary endpoints were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

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