was given as a loading dose (40 mg) at least 1 hour prior to revascularization, followed by a maintenance dose (2.5 mg daily). The primary efficacy endpoint was the composite of cardiovascular (CV) death, MI, stroke, hospitalization for ischemia, or urgent revascularization. The secondary efficacy endpoint was the composite of CV death, MI, or stroke. Safety-related endpoints included the composite of moderate and severe GUSTO bleeding and clinically significant TIMI bleeding.

The mean age of participants was 64 years, 28% was female, 31.4% had DM, 29% prior had MI, and 94% had elevated cardiac biomarkers at baseline. The majority of participants were from western Europe. Concomitant antiplatelet therapy consisted of aspirin (~97% of patients) and thienopyridine (~87%). The majority of patients (88%) underwent angiography, with 58% having subsequent PCI and 10% CABG.

Follow-up in the trial was terminated early (median follow-up of 502 days) after a review by the data safety monitoring board. Treatment with vorapaxar did not significantly reduce the primary endpoint compared with placebo (18.5% vs 19.9%; HR, 0.92; 95% CI, 0.85 to 1.01; p=0.07). Although the primary endpoint was neutral, there was a reduction in the secondary endpoint, a composite of death from CV causes, MI, or stroke with vorapaxar compared with placebo (14.7% vs 16.4%; HR, 0.89; 95% CI, 0.81 to 0.98; p=0.02), which was primarily driven by a reduction in spontaneous MI (11.1% vorapaxar vs 12.5% placebo; HR, 0.88; 95% CI, 0.79 to 0.98; p=0.02). The individual rates of CV death, stroke, and hospitalization for ischemia, urgent revascularization, stent thrombosis, and all-cause mortality were not significantly different between the two groups.

Treatment with vorapaxar was associated with increased bleeding compared with placebo, including the primary safety endpoint of GUSTO moderate/severe bleeding (7.2% vs 5.2%; HR, 1.35; 95% CI, 1.16 to 1.58; p<0.001) as well as ICH (1.1% vs 0.2%; HR, 3.39; 95% CI, 1.78 to 6.45; p<0.001). The excess bleeding with vorapaxar occurred early and continued to accrue over time. Clinically significant TIMI, severe GUSTO, and major TIMI bleeding were also significantly (p<0.001) higher for the patients who were randomized to vorapaxar. Fatal bleeds were low and not different between the two groups. Rates of nonhemorrhagic adverse events were similar in the two groups. There was an interaction between GUSTO moderate or severe bleeding with vorapaxar and thienopyridine therapy at randomization (p=0.04), with no significant hazard with vorapaxar for patients who were not taking thienopyridines (HR, 0.95; 95% CI, 0.65 to 1.40) but a significant hazard for those who were taking thienopyridines (HR, 1.45; 95% CI, 1.23 to 1.71). In addition, patients with lower body weight had higher rates of bleeding (p-interaction=0.03),

Overall, these results show that vorapaxar, as administered in this trial (40-mg loading dose and 2.5 mg daily), was not associated with a reduction in ischemic events and was associated with increased bleeding, with significant interactions for concomitant thienopyridine therapy and low body weight. Whether PAR-1 blockade improves outcomes with different medication strategies or in other patient populations with coronary artery disease requires further study.

Further reading: Tricoci P et al. *N Engl J Med* 2011.

ISAR-REACT 4 – Bivalirudin Similar to Abciximab/Heparin in Reducing Ischemic Outcomes in NSTEMI and Has Significantly Less Bleeding

Written by Rita Buckley

A strategy of intravenous (IV) abciximab (a glycoprotein [GP] IIb/IIIa inhibitor) plus unfractionated heparin (UFH), compared with bivalirudin, an IV direct thrombin inhibitor, failed to improve clinical outcomes and increased the risk of bleeding in patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) who were undergoing percutaneous coronary intervention (PCI), according to Adnan Kastrati, MD, Deutsches Herzzentrum, Technische Universitat, Munich, Germany, who presented the results of the ISAR-REACT 4 trial [NCT00373451].

The ISAR-REACT 4 Trial was designed to assess whether abciximab, added to UFH, was superior to bivalirudin in patients with NSTEMI. The primary outcome measure was a composite of death, large recurrent myocardial infarction, urgent target vessel revascularization (UTVR), or major bleeding in 30 days. Secondary efficacy endpoints were a composite of death, any MI (new Q waves or CK-MB elevation >3 times above the upper limit of normal), or UTVR within 30 days. The primary safety endpoint was major bleeding within 30 days. The study was designed with a sample size of 1700 patients to achieve 80% power (two-sided alpha of 0.05) to detect a 30% reduction in the primary endpoint, assuming a 10.7% event rate in those who were assigned to abciximab/UFH compared with a 15.3% event rate in the bivalirudin group, based on prior trials.

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.