PE is one of the most preventable causes of death among hospitalized patients [Goldhaber SZ et al. *Lancet* 1999]. Recent improvements in inpatient thromboprophylaxis have reduced in-hospital mortality rates. Although average hospital stays are shortening, patients remain vulnerable to VTE-related complications after discharge [Ridker PM et al. *N Engl J Med* 2003]. The ADOPT trial evaluated whether extended thromboprophylaxis with a novel oral factor Xa anticoagulant, apixaban, compared with standard short-term treatment, would reduce the risk of VTE and VTE-related death in hospitalized medically ill patients.

The ADOPT trial enrolled 6528 patients who were hospitalized with congestive heart failure, acute respiratory failure, or other risk factors for VTE. Patients were randomly assigned to treatment with oral apixaban 2.5 mg twice daily for 30 days (n=3255) or subcutaneous enoxaparin 40 mg daily for 6 to 14 days (n=3273). Patients were evaluated with systemic compression ultrasonography at hospital discharge and on Day 30. The primary efficacy endpoint was the 30-day composite of death that was related to VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT.

Samuel Z. Goldhaber, MD, Senior Cardiologist, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School, Boston, Massachusetts, USA, presented findings from the ADOPT trial.

Overall, 2.71% of patients in the apixaban group and 3.06% of those in the enoxaparin group reached the primary endpoint by Day 30 (RR, 0.87; 95% CI, 0.62 to 1.23; p=0.44). This 13% reduction in events favored apixaban but did not achieve statistical significance. Apixaban did increase the risk of major bleeding compared with enoxaparin (0.47% vs 0.19%; RR, 2.53; p=0.04), but there were no deaths from bleeding and no intracranial hemorrhages.

"The ADOPT trial does not provide evidence to justify a policy of extended prophylaxis in a broad population of medically ill patients after hospital discharge," Dr. Goldhaber said. However, findings from ADOPT illustrate the importance of effective thromboprophylaxis beyond hospital discharge. The cumulative risk of VTE and VTE-related death continued to increase during follow-up, particularly after thromboprophylaxis was discontinued.

In a secondary endpoint analysis, investigators examined outcomes during the postparenteral period, when blinded parenteral therapy was discontinued in the enoxaparin group and oral prophylaxis continued in the apixaban group. During this period, patients in the apixaban group had a 56% reduction in the risk of VTE-related death and symptomatic VTE compared with those in the enoxaparin group (95% CI, 0.19 to 1.00).

Several limitations of the study are worthy of consideration when interpreting the results. Because one-third of all protocol-mandated ultrasonography examinations were not obtained or nonevaluable, resulting in a high rate of patient exclusion from the efficacy analysis, the ADOPT trial had substantially less statistical power than initially planned. In addition, the study protocol mandated treatment with enoxaparin for at least 6 days and up to 14 days, even if patients were discharged earlier. This resulted in better efficacy with enoxaparin than would be expected in routine practice, in which VTE prophylaxis is discontinued at the time of hospital discharge. The Day 10 ultrasonography examination also distorted the natural history of DVT because of early identification and treatment of asymptomatic DVT. Despite these measures that went beyond standard practice, the number of primary endpoints in the control group increased steadily throughout the trial after enoxaparin was discontinued. These findings support further VTE prevention studies in high-risk populations.

Results from the TRA•CER Trial

Written by Maria Vinall

The results of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA•CER trial), reported by Kenneth W. Mahaffey, MD, Duke Clinical Research Institute, Durham, North Carolina, USA, showed that vorapaxar does not significantly improve outcomes in high-risk patients with non-ST-segment elevation (NSTE) acute coronary syndrome (ACS) and significantly increases the risk of major bleeding, including intracranial hemorrhage (ICH).

The TRA•CER trial [NCT00527943] evaluated the efficacy and safety of vorapaxar, a first-in-class, orally active, potent, and selective platelet protease-activated receptor-1 (PAR-1) antagonist, compared with placebo in high-risk patients with NSTE-ACS who were treated with the current standard of care. TRA•CER was a prospective, randomized, double-blind, placebo-controlled trial that enrolled 12,944 ACS patients from 37 countries. Eligible patients had ischemic symptoms within 24 hours of hospital presentation, either elevated troponin or CK-MB or ST-segment changes on ECG, and at least 1 additional high-risk criterion: age ≥55 years, prior myocardial infarction (MI) or revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]), diabetes mellitus (DM), or peripheral arterial disease. Vorapaxar or placebo

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.