Table 1. Adverse Outcomes in Dabigatran Versus Warfarin Treated Patients

	Population A		Population B		All patients	
	Dabigatran (n=133)	Warfarin (n=66)	Dabigatran (n=66)	Warfarin (n=18)	Dabigatran (n=168)	Warfarin (n=84)
Death, n (%)	1(1)	2(3)	0	0	1(1)	2(2)
Stroke, n(%)	9(7)	0	0	0	9(5)	0
Death/stroke/SE/MI, (n%)	11(8)	2(3)	2(6)	0	13(8)	2(2)
Death/stroke/TIA/SE/MI, n(%)	12(9)	4(6)	3(9)	0	15(9)	4(5)
Major bleeding, n(%)	7(5)	2(3)	0	0	7(4)	2(2)
Major bleeding with pericardial location, n(%)	7(5)	2(3)	0	0	7(4)	2(2)
Any bleeding, n(%)	35(26)	8(12)	10(29)	2(11)	45(27)	10(12)

MI=myocardial infarction; SE=systemic embolism; TIA=transcient ischemic attack.

RE-ALIGN showed that dabigatran was associated with significantly more bleeding and was less effective for preventing thromboembolic complications compared with warfarin in patients with mechanical heart valves. Prof. Van der Werf concluded that patients with mechanical heart valves should not be treated with dabigatran. The United States Food and Drug Administration and the European Medicines Agency have both already issued black box warnings for all novel oral anticoagulants that they should not be used off-label in patients with mechanical heart valves.

Thrombus Aspiration Fails to Improve Mortality Following STEMI

Written by Emma Hitt, PhD

Thrombus aspiration with percutaneous coronary intervention (PCI) did not improve mortality compared with PCI alone in patients with ST-elevation myocardial infarction (STEMI) in a large, randomized trial. Ole Fröbert, MD, PhD, Örebro University Hospital, Örebro, Sweden, presented data from the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia trial [TASTE; Fröbert O et al. *N Engl J Med* 2013].

Coronary artery thrombus aspiration performed in conjunction with PCI has been inconsistently demonstrated to improve blood flow and ST-segment elevation in patients with STEMI. The purpose of the TASTE trial was to evaluate the impact of thrombus aspiration in conjunction with PCI in patients with STEMI.

In the multicenter, prospective, registry-based TASTE trial, 7244 patients with STEMI were randomized to receive manual thrombus aspiration followed by PCI or PCI only. Patients with STEMI were eligible if they experienced symptoms for >30 minutes and <24 hours and STEMI or left bundle-branch block was confirmed on the electrocardiogram. Exclusion criteria were limited to age <18 years, previous randomization in the TASTE trial, and requirement for emergency coronary artery bypass grafting. The primary endpoint was time to all-cause mortality at Day 30. Secondary endpoints included time to rehospitalization with reinfarction at 30 days and time to stent thrombosis at 30 days. Prespecified analyses were performed in the intention-to-treat (ITT) population as well as a per-protocol population among those who received the actual treatment.

The time from symptom onset to PCI was similar among both treatment arms with a mean of ~180 minutes. In the PCI plus thrombus aspiration arm, the cumulative risk of all-cause mortality was 2.8% compared with 3.0% in the PCI-only arm (HR, 0.94; 95% CI, 0.72 to 1.22; p=0.63) in the ITT analysis and (HR, 0.88; 95% CI, 0.66 to 1.17; p=0.38) in the per-protocol analysis [Fröbert O et al. *N Engl J Med* 2013].

The cumulative risk of rehospitalization due to reinfarction was 0.5% in the PCI plus thrombus aspiration arm compared with 0.9% in the PCI-only arm (HR, 0.61; 95% CI, 0.34 to 1.07; p=0.09) [Fröbert O et al. *N Engl J Med* 2013]. In addition, 0.2% of patients that received thrombus aspiration experienced stent thrombosis, compared with 0.5% of patients that received PCI only (HR, 0.47; 95% CI, 0.20 to 1.02; p=0.06). The rates of stroke, neurologic complications, perforation, tamponade, heart failure, or left ventricular dysfunction at hospital discharge were similar among both treatment arms [Fröbert O et al. *N Engl J Med* 2013].

Prof. Fröbert stated that, in his opinion, the data from the TASTE trial indicate that thrombus aspiration plus PCI does not reduce number of deaths or rehospitalization in patients with STEMI compared with PCI only. Therefore, Prof. Fröbert suggested that there is likely no place for routine thrombus aspiration in conjunction with PCI in clinical practice.

Edoxaban Noninferior to Warfarin in Recurrent VTE and PE

Written by Emma Hitt, PhD

Edoxaban was noninferior to warfarin for prevention of recurrent venous thromboembolism (VTE) in patients with acute VTE who were initially treated with heparin. Harry R. Büller, MD, University of Amsterdam, Amsterdam, The Netherlands, presented data from the Comparative Investigation of Edoxaban Tosylate (DU176b) Versus Warfarin in the Treatment of Symptomatic Deep-Vein Clots and/or Lung Blood Clots trial [Edoxaban Hokusai-VTE Study; Büller HR et al. *N Engl J Med* 2013].

The third most frequent cardiovascular disease, VTE is estimated to affect about 700,000 North Americans annually [White RH. *Circulation* 2003]. The traditional therapy for VTE, initial treatment with heparin followed by vitamin K antagonists [Kearon C et al. *Chest* 2012], has been challenged by several novel oral anticoagulants which have been studied either as monotherapy or after initial treatment with heparin in the treatment of VTE [Schulman S et al. *N Engl J Med* 2009; EINSTEIN Investigators. *N Engl J Med* 2010, 2012; Agnelli G et al. *N Engl J Med* 2013]. The Edoxaban Hokusai-VTE Study tested the hypothesis that treatment with edoxaban would be noninferior to warfarin after acute therapy with heparin in patients presenting with acute VTE.

The international Phase 3 Edoxaban Hokusai-VTE trial randomized 8240 patients with acute symptomatic deep-vein thrombosis (DVT) or pulmonary embolism (PE) to receive 60 mg daily edoxaban or warfarin with a target INR of 2-3. Those patients with a creatinine clearance of 30 to 50 mL/min, body weight of <60 kg, or those patients treated with potent P-glycoprotein inhibitors randomized to edoxaban received a reduced dose of 30 mg daily. The duration of therapy was left to the treating physician and ranged from 3 to 12 months [Büller HR et al. *N Engl J Med* 2013]. Patients were eligible if they were aged ≥18 years, and were diagnosed with either an acute and symptomatic DVT in the popliteal, femoral, or iliac veins, or an acute and symptomatic PE. All patients were initially treated with low molecular weight or unfractionated heparin for at least 5 days. Blinded treatment allocation was maintained through the use of a point-of-care device for INR measurement in all patients that provided sham values for patients who were randomized to edoxaban.

The mean age of trial participants was 56 years and 57% were male. Overall, 4921 patients had DVT and 3391 patients had PE. The 30-mg dose of edoxaban was administered to 18% and 17% of patients in the edoxaban and warfarin arms, respectively. Patients in the warfarin arm had a mean time in the therapeutic window of 63.5%. Approximately 40% of patients were treated for 12 months.

The primary efficacy endpoint was recurrent symptomatic VTE (either DVT or PE). The efficacy analyses were performed in a modified intention-to-treat population consisting of all patients randomized who received at least one dose of the study drug. The upper confidence interval for noninferiority was 1.5. The primary safety endpoint was a composite of clinically relevant major and non-major bleeding.

Rates of recurrent VTE were similar with edoxaban compared with warfarin (3.2% vs 3.5%; HR, 0.89; 95% CI, 0.70 to 1.13; p<0.001 for noninferiority) [Büller HR et al. *N Engl J Med* 2013]. Similar results were found when limiting the analysis to events which occurred while on treatment (HR, 0.82; 95% CI, 0.60 to 1.14; p<0.001 for noninferiority). In a subgroup of patients with evidence of severe PE (evidence of right ventricular dysfunction or elevated natriuretic peptides), edoxaban reduced recurrent VTE (HR, 0.52; 95% CI, 0.28 to 0.98).

Rates of clinically relevant bleeding (major or nonmajor) were lower with edoxaban compared with warfarin (8.5% vs 10.3%; HR, 0.81; 95% CI, 0.71 to 0.94; p=0.004) [Büller HR et al. *N Engl J Med* 2013]. Major bleeding was similar with edoxaban compared with warfarin (1.4% vs 1.6%; HR, 0.84, 95% CI, 0.59 to 1.21; p=0.35).

Prof. Büller concluded by noting that the Edoxaban Hokusai-VTE Study confirmed the hypothesis that in patients with acute VTE treated initially with heparin, treatment with edoxaban is noninferior to warfarin for the prevention of recurrent VTE. In addition, he highlighted that edoxaban had similar efficacy as warfarin but did have a lower rate of clinically relevant bleeding and a similar rate of major bleeding when compared with warfarin.

Preventive PCI Reduces Cardiac Events by 65% in Patients With Acute STEMI

Written by Toni Rizzo

Emergency percutaneous coronary intervention (PCI) of an infarcted coronary artery is an efficacious treatment for patients with acute ST-segment elevation myocardial infarction (STEMI). Patients presenting with STEMI commonly also have other, noninfarct-artery major stenoses. However, the value of performing PCI on these arteries (preventive PCI) during primary PCI for STEMI is unknown. Based on a lack of evidence for preventive PCI in patients with stable coronary artery disease, cardiovascular guidelines recommend against such practice. The objective of the Preventive Angioplasty in Myocardial Infarction trial [PRAMI; Wald DS et al. *N Engl J Med* 2013], presented by David S. Wald, MD, Barts and the London Medical School, London, United Kingdom, was to determine whether preventive PCI performed during the same procedure as the infarct-artery PCI would reduce the incidence of cardiac-related death, nonfatal MI, or refractory angina with evidence of ischemia.

A total of 465 consecutive patients with acute STEMI and multivessel coronary disease detected at the time of emergency PCI of the infarct artery were enrolled in this randomized, multicenter, single-blind study between 2008 and 2013. Multivessel disease was defined as >50% stenosis in one or more noninfarct arteries suitable for PCI. Ineligible patients included those with cardiogenic shock,