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.

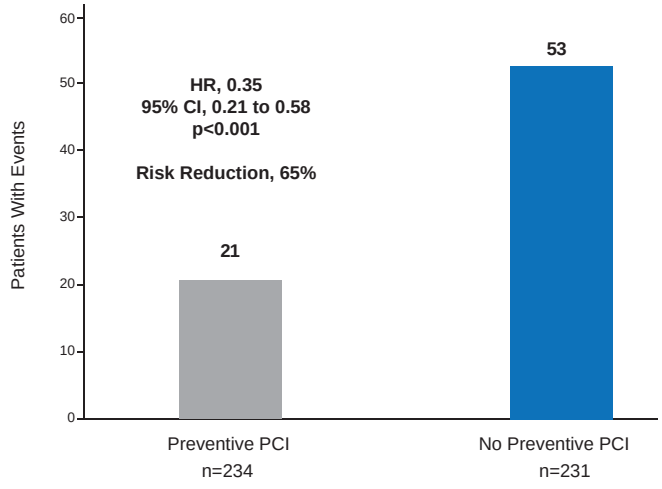
A total of 465 consecutive patients with acute STEMI and multivessel coronary disease detected at the time of emergency PCI of the infarct artery were enrolled in this randomized, multicenter, single-blind study between 2008 and 2013. Multivessel disease was defined as >50% stenosis in one or more noninfarct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

prior coronary artery bypass graft surgery, >50% stenosis in either the left main or ostia of both the left anterior descending and circumflex arteries or if the only noninfarct stenosis was a chronic total occlusion. The patients were randomized after successful emergency PCI to preventive PCI (n=234) or no preventive PCI (n=231) in the noninfarct artery while they were still in the catheterization laboratory. The patients were examined and evaluated with electrocardiography at 6 weeks and annually thereafter.

Baseline characteristics were similar between the two groups. The mean age in both groups was 62 years, 76% were male, and the majority of infarcts involved the inferior wall, with approximately one-third anterior infarcts. The trial was stopped on January 24, 2013, due to a highly significant difference in the primary outcome in favor of preventive PCI (p<0.001).

The mean follow-up was 23 months. Ten patients in the preventive PCI group and 8 in the no preventive PCI group were lost to follow-up. The primary composite outcome occurred in 21 patients in the preventive PCI group (9.0%) and 53 patients in the no preventive PCI group (22.9%), with a risk reduction of 65% in the preventive PCI group (HR, 0.35; 95% CI, 0.21 to 0.58; p<0.001; Figure 1). This translates into an absolute risk reduction of ~14% or a number needed to treat of 7 patients to prevent one primary endpoint event at 1 year.

Figure 1. Cardiac Death, Nonfatal MI or Refractory Angina



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Cardiac death or nonfatal MI occurred in 11 (4.7%) patients in the preventive PCI group and 27 (11.7%) patients in the no preventive PCI group, with a risk reduction of 64% for patients treated with preventive PCI (HR, 0.36; 95% CI, 0.18 to 0.73; p=0.004). This translates into an absolute risk reduction of ~7% or a number needed to treat of 15 patients to prevent one cardiac death or nonfatal MI at 1 year.

Procedure-related complications occurred in 10 patients in the preventive PCI group and 9 patients in the no preventive PCI group, and were composed of contrast nephropathy, bleeding requiring transfusion or surgery, and stroke. However, the trial was not powered to adequately compare the safety of these two strategies.

The results of the PRAMI trial demonstrate that preventive PCI performed in noninfarct arteries immediately after emergency PCI for STEMI provides a substantial cardiac benefit at 1 year. The robust results of this preventive PCI trial in the context of primary STEMI care are counter to current standards of care. Previously, due to uncertainty of the value of preventive PCI, its practice varied among cardiologists. It will be interesting to see whether the next iterations of major cardiovascular guidelines adopt the results of this trial.

Pretreatment Before PCI With Prasugrel Does Not Reduce Ischemic Events in Patients With NSTE-ACS

Written by **Rita Buckley**

Pretreatment with prasugrel at the time of diagnosis of non-ST-segment elevation (NSTE) acute coronary syndromes (ACS), rather than at the time of percutaneous intervention (PCI), did not reduce ischemic events and increased bleeding, according to results from A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non-ST Elevation Myocardial Infarction (NSTEMI) [ACCOAST; NCT01015287; Montalescot G et al. *N Engl J Med* 2013]. Gilles Montalescot, MD, PhD, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France, presented results from the study.

Treatment with prasugrel has been shown to be superior to clopidogrel for reducing ischemic events in patients presenting across the spectrum of ACS intended for interventional treatment; however, treatment was only administered at the time of PCI after angiography was completed [Wiviott SD et al. *N Engl J Med* 2007]. ACCOAST was a randomized, double-blind, event-driven study to evaluate the administration of prasugrel, a P2Y12 antagonist, at the time of diagnosis (pretreatment) compared with after coronary angiography if PCI was indicated as previously studied. A total of 4033 patients with NSTEMI scheduled for catheterization within 2 to 48 hours were randomized.

The primary composite endpoint was the first occurrence of death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIB/IIIa inhibitor rescue therapy (glycoprotein IIB/IIIa bailout) through Day 7 [Montalescot G et al. *Am Heart J* 2011]. Safety endpoints were major and minor bleeding risks according to TIMI criteria.