Dabigatran Inferior to Warfarin in Patients With Mechanical Heart Valves

Written by Toni Rizzo

Dabigatran 150 mg BID had superior efficacy compared with warfarin in patients with nonvalvular atrial fibrillation in the Randomized Evaluation of Long-Term Anticoagulation Therapy trial [RE-LY; Connolly SJ et al. *N Engl J Med* 2009]. Patients with mechanical heart valves typically require lifelong anticoagulant therapy. Although valve thrombosis can be effectively prevented with vitamin K antagonists in this population, the therapeutic window for such agents is narrow, with the potential for diet, alcohol, and pharmacologic interactions, and the need for frequent coagulation monitoring.

Preclinical studies in porcine mechanical heart valve models suggested that dabigatran may effectively prevent valve thrombosis [Schomburg JL et al. *J Invest Surg* 2012]. These results led to A Randomized, Phase 2 Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement [RE-ALIGN; Eikelboom JW et al. *N Engl J Med* 2013], presented by Frans Van de Werf, MD, PhD, KU Leuven, Leuven, Belgium. The aim of the RE-ALIGN trial was to evaluate a dosing algorithm of dabigatran based on the RE-LY study to prevent thromboembolic complications in patients with mechanical heart valve replacement.

Patients who had aortic or mitral valve replacement in the past 7 days (Population A; n=199) or who had received a mechanical mitral valve >3 months before randomization (Population B; n=53) were randomized in a 2:1 ratio to treatment with dabigatran (n=168) or warfarin (n=84). Dabigatran was started at 150 mg BID in patients with creatinine clearance (CrCl) <70 mL/minute (15%), 220 mg BID in patients with CrCl of 70 to 109 mL/minute (54%), and 300 mg BID in patients with CrCl ≥110 mL/minute (31%). The dose was increased at prespecified intervals to achieve a plasma dabigatran level of 50 ng/mL or higher. Dabigatran was discontinued and patients switched to a nonstudy vitamin K antagonist if the trough level remained at <50 ng/mL at the highest dose. Warfarin dose was based on the international normalized ratio (INR) target range specified in the valvular heart disease guidelines [Vahanian A et al. *Eur Heart J* 2012].

The primary endpoint was the trough plasma level of dabigatran. Other efficacy and safety outcomes were stroke, systemic embolism (SE), transient ischemic attack (TIA), valve thrombosis, venous thromboembolism, myocardial infarction (MI), bleeding, and death. RE-ALIGN was a 12-week trial with an optional extension of up to 84 weeks. The trial was terminated when 252 patients were randomized, due to excesses in both thromboembolic and bleeding events in the dabigatran group.

Baseline characteristics were well balanced between the two treatment groups. The majority of patients were treated within 7 days after valve replacement (79%) with the rest randomized 3 months post surgery. The mean patient age was 56 years. The valve location was aortic (n=172; 68%), mitral (n=71; 28%), and both in 9 patients (4%). In patients within 7 days of valve replacement surgery, the median time to administration of the first dose of study drug was 6 days in the dabigatran arm and 5 days in the warfarin arm. Thereafter, the median time to achievement of target INR was a further 7 days (interquartile range [IQR] 5-12) in the warfarin arm versus the median time to target dabigatran level of 8 (IQR 7-23) days.

The composite of death or a first major thromboembolic event (stroke, SE, TIA, or MI) occurred in 9% of the dabigatran group and 5% of the warfarin group (HR, 1.94; 95% CI, 0.64 to 5.86; p=0.24). Bleeding occurred significantly more frequently in dabigatran (27%) versus warfarin patients (12%; HR, 2.45; 95% CI, 1.23 to 4.86; p=0.01; Table 1). All of the major bleeding episodes in this early post-valve replacement population were pericardial, with numerically more occurring with dabigatran (n=7; 5%) versus warfarin (n=2; 3%).

In explaining the negative study results, Prof. Van der Werf suggested three possible explanations: inadequate dabigatran blood levels, play of chance with relatively few events in the warfarin group, or a difference between the mechanism of dabigatran and warfarin.

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].