

Dabigatran etexilate for prevention of venous thromboembolism

John E. Eikelboom¹; Jeffrey I. Weitz^{1,2}

¹Department of Medicine, McMaster University and Henderson Research Centre, Hamilton, Ontario, Canada; ²Department of Biochemistry and Medical Sciences, McMaster University, Hamilton, Ontario, Canada

Venous thromboembolism (VTE) is a major public health problem that affects several hundred thousand North Americans (1) and several million persons worldwide each year. In the United Kingdom, there are more deaths from VTE in hospitalized patients each year than there are from breast cancer and road accidents combined (2), and one of every 10 deaths in the European Union has been associated with VTE (3). To reduce this enormous burden of disease, we must identify patients at risk and provide them with effective thromboprophylaxis. One such high-risk patient group is that undergoing hip or knee arthroplasty.

Low-molecular-weight heparins (LMWH), such as enoxaparin, fondaparinux and vitamin K antagonists (VKA), such as warfarin, are widely used for VTE prevention in patients undergoing hip or knee arthroplasty. Because the risk of VTE persists beyond the time of hospital discharge, the 2008 American College of Chest Physicians (ACCP) guidelines recommend thromboprophylaxis for up to 35 days in patients undergoing hip arthroplasty and for at least 10 days in those undergoing knee arthroplasty (4). Despite these recommendations, many patients do not receive thromboprophylaxis after they are discharged from hospital (5). With the progressive shortening of hospital stays after hip or knee arthroplasty, this means that thromboprophylaxis is only being given for four or five days, which places these patients at risk of fatal pulmonary embolism. The major barrier to the use of LMWH or fondaparinux out-of-hospital is their need for daily subcutaneous administration (6), while the use of VKA is limited by the necessity for coagulation monitoring and dose adjustment.

Dabigatran etexilate is a new oral direct thrombin inhibitor that has recently been licensed in Europe and Canada for thromboprophylaxis after hip or knee arthroplasty. A prodrug, dabigatran etexilate is rapidly absorbed and converted in the liver to dabigatran, the active moiety. Dabigatran circulates with a half-life of 12–17 hours, which permits once-daily oral administration, and is excreted unchanged by the kidneys. With a low potential for drug-drug interactions and a predictable anticoagulant effect, dabigatran etexilate can be given in fixed doses without coagulation monitoring (7).

Dabigatran etexilate has been compared with enoxaparin for thromboprophylaxis after hip or knee arthroplasty in three phase III trials. Two different doses of dabigatran etexilate were evaluated in these trials; 220 or 150 mg once-daily, starting with a half dose of 110 or 75 mg on the first day. In this issue of *Thrombosis and Haemostasis*, Wolowacz et al. (8) report the results of a meta-analysis of these three trials. The authors focused on the higher dose dabigatran etexilate regimen because this is the regimen recommended for most patients; the lower-dose regimen is reserved for patients with a higher risk of bleeding, such as those over 75 years of age or with a creatinine clearance of less than 50 ml/min. The European-approved dose of enoxaparin, 40 mg once-daily with the first dose given in the evening prior to surgery, was used as the comparator in the RE-MODEL and RE-NOVATE trials (9, 10), while the North American-approved dose of enoxaparin, 30 mg twice-daily starting 12 to 24 hours after surgery, was the comparator in the RE-MOBILIZE trial (11).

The pooled results from the three trials, which included a combined total of 8,210 patients undergoing hip or knee arthroplasty, revealed no statistically significant differences between dabigatran etexilate and enoxaparin for the primary efficacy outcome of total VTE and all-cause mortality (relative risk [RR] 1.06; 95% confidence interval [CI]: 0.94–1.18) or for the secondary efficacy outcome of major VTE, a composite of pulmonary embolism, proximal deep-vein thrombosis and VTE-related mortality (RR 0.92; 95% CI: 0.66–1.29). There also were no significant differences in safety outcomes between dabigatran etexilate and enoxaparin, including major bleeding (RR 0.99; 95% CI: 0.63–1.54) and clinically relevant bleeding (RR 1.15; 95% CI: 0.88–1.50), nor was there statistical evidence of heterogeneity amongst the trials for either efficacy or safety. In the RE-MOBILIZE trial, which used the twice-daily enoxaparin regimen, dabigatran was statistically inferior to enoxaparin for the primary efficacy endpoint of total VTE and all-cause mortality, but the rates of symptomatic VTE and bleeding were similar (11).

How do the results of the trials with dabigatran etexilate compare with those evaluating other new oral anticoagulants in the

Correspondence to:
Dr. Jeffrey Weitz
Henderson Research Centre
711 Concession Street
Hamilton, Ontario
L8V 1C3, Canada
Tel.: +1 905 574 8550, Fax: +1 905 575 2646
E-mail: jweitz@thrombosis.hhsc.org

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Table 1: Comparison of the pharmacological features of dabigatran etexilate with those of rivaroxaban and apixaban.

Feature	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Dosing	Fixed, once daily	Fixed, once daily	Fixed, twice daily
Bioavailability (%)	6	80	50
Coagulation monitoring	No	No	No
Half-life (h)	12–17	5–9	12
Renal clearance (%)	80	65	25
Interactions	P-gp inhibitors*	Combined P-gp and CYP3A4 inhibitors†	Potent CYP3A4 inhibitors†
Approved indications	VTE prevention	VTE prevention	None
Trials ongoing	AF, ACS, VTE treatment	AF, ACS, VTE treatment	AF, ACS, VTE prevention and treatment

AF, atrial fibrillation; ACS, acute coronary syndromes; *P-gp, P-glycoprotein; VTE, venous thromboembolism. Includes verapamil, clarithromycin and quinidine. Quinidine is contraindicated in patients receiving dabigatran etexilate. † Includes ketoconazole, macrolide antibiotics (e.g., clarithromycin) and protease inhibitors (e.g., atazanavir).

setting of hip or knee arthroplasty? Favorable results also have been achieved with rivaroxaban and apixaban, oral direct factor Xa inhibitors. Table 1 compares the pharmacological properties of these agents with those of dabigatran etexilate. At a once-daily dose of 10 mg, a 35-day course of rivaroxaban was superior to enoxaparin (40 mg once-daily) administered for up to 35 days (12, 13). When thromboprophylaxis was given for 10–14 days after knee arthroplasty, rivaroxaban (10 mg once-daily) was superior to enoxaparin used in either the 40 mg once-daily or the 30 mg twice-daily regimen (13, 14). In the same patient population, a twice-daily 2.5 mg dose of apixaban had efficacy similar to that of enoxaparin given at a dose of 30 mg twice-daily. Based on the results with rivaroxaban, the drug has recently been licensed in Canada for thromboprophylaxis after hip or knee arthroplasty and has been recommended for approval in Europe. Apixaban is not yet approved, and additional phase III trials with this agent and with other oral factor Xa and thrombin inhibitors are underway. Head-to-head trials comparing dabigatran etexilate with rivaroxaban or apixaban have not been done. Therefore, direct evidence of their relative efficacy and safety is lacking.

Are there any safety concerns with dabigatran etexilate? Unlike ximelagatran, which was withdrawn because of its potential hepatic toxicity, there is no evidence that dabigatran is associated with hepatic side-effects. RE-VOLUTION, the global clinical trial program evaluating dabigatran etexilate, will include more than 38,000 patients. The RE-LY trial, which is comparing dabigatran etexilate with warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation (AF), has enrolled more than 18,000 patients treated for a minimum of a year.

With follow-up nearing completion, this trial will provide robust evidence of the long-term safety of dabigatran etexilate.

How will the results with dabigatran etexilate in patients undergoing hip or knee arthroplasty alter clinical practice? The randomized comparisons with enoxaparin provide clear evidence that dabigatran etexilate, like rivaroxaban and apixaban, is effective for VTE prevention in this setting. Although these new oral agents may eventually replace LMWH and fondaparinux, it is likely that the parenteral agents will continue to be used while patients remain in hospital. Where the new oral anticoagulants will make the most difference is in the out-of-hospital management of these high-risk patients. By streamlining out-of-hospital anticoagulation, these drugs will increase the uptake of practice guidelines, which recommend extended thromboprophylaxis after hip or knee arthroplasty.

What does the future hold for the new oral anticoagulants? The major unmet need is to simplify long-term anticoagulation therapy by replacing warfarin. How will dabigatran etexilate fare against warfarin for prevention of stroke and systemic embolism in patients with AF or for secondary prevention in patients with VTE? (16). The results of the RE-LY AF treatment trial are expected in September of 2009, while the results of the RECOVER and RE-MEDY trials, which are comparing dabigatran etexilate with warfarin for the initial and long-term treatment of VTE, also are expected in 2009. In the meantime, the findings with dabigatran etexilate, rivaroxaban and apixaban in orthopaedic surgery highlight the promise of the new oral anticoagulants and bring us one step closer to finding a replacement for warfarin.

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