The oral thrombin inhibitor dabigatran etexilate vs the North American enoxaparin regimen for the prevention of venous thromboembolism after knee replacement surgery: the RE-MOBILIZE trial

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Running title: Dabigatran thromboprophylaxis in knee replacement

Abstract

Background: Dabigatran, an oral once-daily unmonitored thrombin inhibitor, has been tested elsewhere using enoxaparin 40 mg once daily. We used the North American enoxaparin 30 mg bid regimen as the comparator.

Patients/Methods: Double blind, centrally-randomized. Unilateral total knee replacement patients were randomized to receive either once daily oral dabigatran 220 mg, 150 mg, or enoxaparin 30 mg sc bid after surgery, blinded. Dosing stopped at contrast venography, 12-15 days after surgery.

Results: Among 1896 patients, dabigatran 220 mg and 110 mg showed inferior efficacy to enoxaparin (venous thromboembolism rates of 31% [p=0.02 vs enoxaparin], 34% [p<0.001 vs enoxaparin] , and 25%, respectively). Bleeding rates were similar and no drug-related hepatic illness was recognized.

Conclusions: Dabigatran, effective compared to once-daily enoxaparin, showed inferior efficacy to the twice daily North American enoxaparin regimen, probably due to the latter's more intense and prolonged dosing.

Key words: dabigatran etexilate; direct thrombin inhibitor; total knee replacement; prophylaxis; venous thromboembolism

Introduction

A safe and effective oral antithrombotic drug that does not require dosage adjustment and laboratory monitoring could replace injected low molecular weight (LMW) heparins and oral vitamin K antagonists for prevention of venous thromboembolism in high risk situations, such as joint replacement surgery. One such candidate drug is dabigatran etexilate, converted after absorption to the reversible thrombin inhibitor dabigatran. It is 80% renally-excreted and its terminal half-life of about 16 h makes it suitable for once daily administration [1]. Dose-ranging phase 2 studies of dabigatran in hip and knee replacement patients vs the active comparator enoxaparin, the latter injected 40 mg beginning the evening before surgery, [2, 3] led to selection of two dabigatran dosages, 220 mg and 150 mg, for phase 3 testing.

An interesting clinical difference between European and North American prophylactic dosing regimens for antithrombotic drugs for perioperative orthopaedic patients is that historically, European dosing regimens administered these drugs prior to surgery, whereas in North America dosing began postoperatively, sometimes at a higher total daily dosage [4, 5, 6]. Since dabigatran was first investigated in European joint replacement patients, the LMW heparin control therapy, enoxaparin, was begun the evening before the day of surgery at the standard dosage of 40 mg once daily in the phase 2 studies [2, 3]. A phase 3 study similar to the one we report herein was primarily conducted in European knee replacement patients using such a dosage regimen. However, for North American knee replacement patients, we selected as control thromboprophylaxis the North American approved enoxaparin regimen of 30 mg twice daily, begun the morning after surgery. We began oral dabigatran 6-12 h after surgery and continued study drugs until venography at approximately day 13. In the companion European study, oral study drug was begun 1-4 h after surgery and study drug discontinuation and venography occurred days 6-10. We report the results comparing

the two dabigatran dosage regimens with the North American approved dosing of enoxaparin for venous thromboembolism prophylaxis in knee replacement patients.

Methods

Study Design

This was a randomized, double-blind, active controlled, non-inferiority study conducted at 58 centers in the United States, 30 in Canada, 8 in Mexico and 1 in the United Kingdom. The study was approved by Institutional Review Boards and independent ethics committees and conducted in accordance with the Declaration of Helsinki (October 1996 version). All patients gave written informed consent. When hemodynamically stable, patients were randomly assigned to one of 3 treatment groups following surgery. An Interactive Voice Response System was used for randomization in blocks of 6 and was based on an independently generated scheme.

Patients

Patients ≥ 18 years and >40 kg who had undergone primary elective unilateral total knee replacement and provided signed informed consent were eligible for the study. The primary reasons for exclusion included a known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels > 2 x the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant long-acting non-steroidal anti-inflammatory drug therapy or treatment with an anticoagulant during study

drug treatment; active malignant disease; platelet count < 100 x 10^9/L, pregnant, nursing, or pre-menopausal women of child-bearing potential who were not practicing effective birth control, and failure to provide informed consent. Following completion of surgery any indwelling anesthetic catheter was removed and subcutaneous injection of trial medication was administered 12-24 h later.

Treatment Regimens

Eligible, consenting patients were assigned to receive oral dabigatran etexilate 220 mg or 150 mg once daily, or enoxaparin (Sanofi-Aventis), 30 mg subcutaneously twice daily. All 3 groups received one active and one placebo treatment (i.e., double-dummy blinding). Patients received 2 capsules in the morning as well as a subcutaneous injection; they received a subcutaneous injection in the evening. The first dose of dabigatran etexilate was one-half of subsequent doses (one capsule, 110 or 75 mg) and was administered 6-12 hours after completion of surgery, provided clinical assessment of peri- and post-operative bleeding and drainage indicated adequate haemostasis. If administration was delayed until the day after surgery, a full dose (2 capsules) was administered as the first dose the morning following surgery. The first subcutaneous injection was given 12-24 hours following surgery, usually on the morning following the day of surgery. Treatment was continued for a total of 12-15 days, followed by mandatory bilateral venography performed within 12 hours of the last administration of medication. Administration of antithrombotics after this time was left to the discretion of the investigator. Patients were followed for 3 months after surgery. The treatment period was defined as the time from the first dose until 3 days following the last oral or subcutaneous dose, whichever came later.

Concomitant treatment with low dose aspirin (<160 mg) and selective

cyclooxygenase-2 (COX-2) inhibitors was allowed during the treatment period. Elastic compression stockings were permitted but intermittent pneumatic compression devices were prohibited.

Outcome Measures

The primary efficacy outcome was the composite of total VTE events (symptomatic or venographic deep vein thrombosis [DVT] and/or symptomatic pulmonary embolism [PE]) and all-cause mortality during treatment. Secondary efficacy outcomes included a composite of major VTE, defined as proximal DVT, PE, and VTE-related mortality; proximal DVT; the incidence of total VTE and all-cause mortality during follow-up; and the individual components of the primary outcome. Bilateral venography was to be performed within 12 h of the last oral dose, according to a standardized technique described previously [2, 7, 8, 9]. Diagnosis of DVT was considered established if there was a consistent intraluminal filling defect on at least two venogram images. PE was diagnosed by a high-probability result on ventilation-perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy. Symptomatic DVT during treatment and follow-up was confirmed by compression ultrasound or venography. Diagnostic tests for VTE events were initially evaluated locally and subsequently reviewed by an independent central adjudication committee blinded to treatment allocation. The results from the central assessment were used in the primary analysis.

The primary safety outcome was the incidence of bleeding events occurring during study treatment. Major bleeding events, clinically relevant non-major bleeding events and minor bleeding events were defined according to accepted guidelines [10]. An independent expert adjudication committee classified all bleeding events (criteria in

Table 1). Hematology and clinical chemistry tests were performed before treatment, on the last day of dosing and, if clinically indicated, at 4 to 6 weeks and 3 months after surgery. Total bilirubin, ALT, and AST levels were measured on the last day of treatment, at 4 to 6 weeks and 3 months after surgery. There were pre-specified rules for cessation of study medication in patients with abnormal values of ALT, AST or total bilirubin. Patients were evaluated for liver disease if either ALT or AST (greater than 2 times ULN) was found to be elevated concurrently with total bilirubin (greater than 1.5 times ULN). All cases of hepatic enzyme abnormalities and suspected cardiovascular events during the study were reviewed by blinded independent expert committees, utilizing predefined criteria.

Statistical Analysis

An upper limit of 9.2% for the 95% CI for the risk difference found between dabigatran and enoxaparin treatments for the primary efficacy outcome was chosen as the margin for non-inferiority. If this margin were not exceeded, dabigatran would have preserved at least two-thirds of the superiority of enoxaparin over placebo demonstrated in a previous study [11]. It was determined that a study with 1950 evaluable patients (650 per group) would have 90% power, with a type I error of 0.025, to reject the hypothesis that the primary outcome with dabigatran would be 9.2% higher than enoxaparin if the VTE rate were as high as 48%. Assuming that 25% of patients would not have evaluable venograms, randomization of 2610 patients was required. The safety population comprised all randomized patients who received at least one dose of study treatment (either subcutaneous injection or oral drug). Patients with evaluable centrally adjudicated data for VTE (venography or an objectively confirmed symptomatic event) or who died during treatment were included in the primary efficacy analysis. The 95% CI for the absolute difference between each dabigatran group and enoxaparin was calculated

using normal approximation. Analysis was performed on an intention-to-treat basis.

Because multiple hypotheses (e.g., two dabigatran dosages) were being tested without a p-value penalty, testing of the hypotheses was ordered. Proof of a hypothesis could not be claimed if the previous hypothesis were not proven. The order of testing was (1) non-inferiority of the 220 mg dabigatran treatment group, (2) non-inferiority of the 150 mg treatment dabigatran group, (3) superiority of the 220 mg dabigatran treatment group, (4) superiority of the 150 mg dabigatran treatment group.

Role of the Funding Source

The planning and management of the study were conducted by the Steering Committee in conjunction with the sponsor, Boehringer Ingelheim. The sponsor was responsible for data collection and statistical analysis. Interpretation of the data and preparation and submission of the manuscript were performed by the Steering Committee who had full access to all data. The study was monitored by an independent data and safety monitoring board.

RESULTS

Patients

Of 3016 patients enrolled between Nov 2004 and June 2006, 2615 were randomized and 2596 received treatment (Figure 1). Patient demographic and surgical characteristics were similar for the 3 groups (Table 2). Patients' mean age was 66 years, 58% were women, and general anaesthesia was used in 53% of operations. The mean interval between surgery end and initiation of blinded oral study drug administration was 10 h. Enoxaparin treatment was initiated a mean of 20 h after surgery. The median treatment duration was 14 days, with 92% of patients receiving 12-15 days of treatment and between 90% (for enoxaparin) and 92% (for dabigatran) of patients completing study drug treatment as planned; 3 months of study observation were completed for 94% (for dabigatran 220 mg), 95% (for dabigatran 150 mg), and 94% (for enoxaparin). Figure 1 shows reasons for discontinuations.

Efficacy

1896 (73.0%) patients were included in the primary efficacy analysis. The reasons for exclusion from the analysis were similar across treatment groups (Table 3); the most common reason was non-evaluability of the contrast venograms. The primary outcome (total VTE and death) occurred in 31.1% (188 of 604) of patients in the dabigatran 220 mg group, 33.7% (219 of 649) of the 150 mg group and 25.3% (163 of 643) of the enoxaparin group (Table 4). Both dabigatran dosage regimens failed to show non-inferiority to enoxaparin, as the upper limit of the 95% CI for the absolute difference versus enoxaparin was higher than the pre-specified non-inferiority margin of 9.2%. For 220 mg, the risk difference was 5.8% (95% CI: 0.8 to 10.8; p-value=0.0234) and for 150 mg, the risk difference was 8.4% (95% CI: 3.4 to 13.3; p-value=0.0009)

compared to enoxaparin. The largest component of the primary endpoint for all three groups was distal DVT: 27.6% (dabigatran 220 mg), 30.5% (dabigatran 150 mg) and 23.0% (enoxaparin).

The secondary outcome of major VTE and VTE-related mortality occurred in 3.4% (21 of 618) and 3.0% (20 of 656) of the dabigatran 220 mg and 150 mg groups, respectively, compared with 2.2% (15 of 668) in the enoxaparin group. The risk difference between dabigatran 220 mg and enoxaparin was 1.2% (95% CI : -0.7 to 3.0; p=0.21) and between dabigatran 150 mg and enoxaparin was 0.8% (95% CI: -0.9 to 2.5; p= 0.36).

During treatment, symptomatic DVT was confirmed in 7, 6 and 5 patients in the dabigatran 220 mg, dabigatran 150 mg, and enoxaparin group, respectively. PE was confirmed in 6 (dabigatran 220 mg) and 5 patients (enoxaparin). Two patients died: 1 in the dabigatran 220 mg group in whom fatal PE could not be ruled out and 1 not associated with PE in the dabigatran 150 mg group.

Safety

Major bleeding events were uncommon during treatment and not significantly different among the 3 groups: 0.6% (5/857) for dabigatran 220 mg, 0.6% (5/871) for dabigatran 150 mg, and 1.4% (12/868) for enoxaparin (Table 5). None of the bleeding events was fatal. Bleeding at the surgical site was the most common major bleeding event (dabigatran 220 mg: 2 of 5; dabigatran 150 mg: 3 of 5; enoxaparin: 11 of 14). The rates of minor (clinically relevant non-major) bleeding were similar in the 3 groups (Table 5).

Other observations

Serious adverse events (SAEs) occurred in 6.9% of dabigatran 220 mg patients, 6.5% of dabigatran 150 mg patients, and 5.2% of enoxaparin patients. Neither hepatitis nor hepatotoxicity was identified as an SAE in the study. Whereas about 96% of patients had a baseline ALT in the normal range, 5%, 5%, and 13% of patients developed ALT levels above the normal range by the time of last study drug dosing in the dabigatran 220 mg, dabigatran 150 mg, and enoxaparin groups, respectively. The proportion of patients with an ALT > 3 times the upper limit of normal during the study was 0.7%, 1.0% and 0.9% for the dabigatran 220 mg, 150 mg and enoxaparin groups, respectively. Two dabigatran 220 mg patients and 2 enoxaparin patients had ALT> 3 times the upper limit of normal together with a serum total bilirubin > 2 times the upper limit of normal. One dabigatran 220 mg patient and both enoxaparin patients had cholelithiasis convincingly diagnosed and treated. The other dabigatran etexilate 220 mg patient was diagnosed with cholangiocarcinoma.

Cardiac SAEs during blinded prophylaxis occurred in 9 dabigatran 220 mg patients, 10 dabigatran 110 mg patients, and 9 enoxaparin patients.

Discussion

The safety of once-daily unmonitored, unadjusted oral dabigatran appeared similar to that of enoxparin in this thromboembolism prophylaxis trial. However, the dabigatran dosage regimens evaluated failed to meet the prospectively set criteria for non-inferior efficacy.

A similar study to the one we report herein, the RE-MODEL study, was conducted concurrently primarily in European centers, with Australian and South African knee replacement centers also participating, . RE-MODEL employed as comparator therapy once daily 40 mg enoxaparin, with dosing begun the evening prior to surgery, earlier initiation (1-4 h) of blinded oral study drug after surgery, and earlier discontinuation of study drug concomitant with earlier contrast venography between post-operative days 6-10 [13]. In RE-MODEL and a phase 2 study of similar design in knee replacement patients [2,13], dabigatran at the same or similar dosages appeared efficacious. It is interesting to consider the multiple possible factors that might explain why both dabigatran dosages tested in this trial appeared. Table 6 compares selected relevant differences and similarities of our RE-MOBILIZE and the mostly European RE-MODEL trials.

Outcome interpretation was blinded in all studies and performed nearly contemporaneously by the same adjudicators, minimizing the likelihood that it explains the differing results. The enoxaparin and dabigatran dosing regimens were clearly different, however. Enoxaparin was dosed in our study at a 50% higher daily dosage than in the RE-MODEL study and both enoxaparin and dabigatran were dosed a mean of 5 days longer (13 vs 8 days, respectively). Previous analysis suggested that prolonging enoxaparin dosing to 12 days may increase efficacy compared to shorter enoxaparin dosing, even in knee replacement patients [12]. The lower thromboembolism rates seen in the current study compared with the rates in the RE-

MODEL study are consistent with that hypothesis (Table 6).

Another difference in our study from RE-MODEL was our somewhat later start of dabigatran, protocol-prescribed to start 6-12 h after surgery, compared to 1-4 h post-operatively in RE-MODEL. Actual mean times for the first dabigatran dose were 10 h in our study and 4 h post-operatively in RE-MODEL, respectively. However, since prior pharmacokinetic analyses [1] suggest that a substantial number of patients experience reduced plasma peak concentrations and bioavailability of dabigatran on the day of surgery, the contribution of our slightly delayed administration of the first dose to the different efficacy outcomes determined nearly 2 weeks later is uncertain.

The role of chance in explaining our results must also be taken into account. Although the chance of type 1 error in our study's efficacy findings was quite low, the possibility of type 2 error, i.e., that dabigatran at 220 mg might truly be non-inferior within the 9.2% margin but that other results would be found, was 10%. However, our upper margins were 10.8% and 13.3% (vide supra).

The number of patients with symptomatic thromboembolism or death was similar in all 3 treatment groups. However, the incidence of these outcomes in practice may be higher than in studies in which patients are protocol-mandated to have screening bilateral venography at a time earlier than when thrombosis may become clinically evident. Hence, whether a knee replacement patient receiving one of the 3 regimens but not venography might face a heightened risk of thromboembolism or death in usual clinical practice is uncertain.

The incidence of major bleeding, clinically relevant non-major bleeding, and the combination appeared similar in our 3 patient groups. There were no symptomatic or drug-related hepatic injuries in any treatment group in this study.

Enoxaparin administered 40 mg the evening before surgery and once daily thereafter has never been prospectively compared to enoxaparin given 30 mg twice daily

starting the morning after surgery. A comparison of enoxaparin 40 mg once daily and 30 mg twice daily, both begun after surgery in hip replacement patients---who have a markedly different VTE risk from knee replacement patients---showed efficacy failure rates of 14% vs 11%, respectively, a difference that was not statistically significant with the sample size employed [4]. The weight of evidence from our study and RE-MODEL seems to suggest that the twice-daily 30 mg enoxaparin regimen continued for 12 days may provide superior protection against VTE compared to the once daily enoxaparin regimen, irrespective of the continent on which the surgery occurs. For patients at highest risk, this information may be important.

We found the dabigatran dosing regimens tested to have inferior efficacy to the North American postoperative enoxaparin regimen when all were continued for a mean of 12 days. Our results do not allow us to recommend one dabigatran dosage over another. However, our results do not inherently conflict with those of the European study showing non-inferiority of different dabigatran prophylaxis regimens compared to a different enoxaparin prophylaxis regimen.

Addendum

Contribution of authors

J Ginsberg, B L Davidson, P C Comp, C W Francis, R J Friedman, M H Huo, J Lieberman, J E Muntz, G E Raskob, and J A Caprini were active members of the Steering Committee, were responsible for the study design and for monitoring study conduct, and contributed to writing and revising the manuscript.

M L Clements and J Schnee represented the sponsor and were responsible for overseeing the study and data collection. S Hantel also represented the sponsor and was the study statistician responsible for the analyses. All contributed to writing and revising the manuscript.

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Table 1. Safety criteria for major and minor bleeding

Major bleeding

- Fatal bleeding
- Clinically overt bleeding in excess of expected and associated with a fall of 2 g Hb/mL and/or leading to transfusion of ≥ 2 units packed cells or whole blood
- Symptomatic retroperitoneal, intracranial, intraocular, or intraspinal bleeding
- Bleeding requiring treatment cessation and/or operation

Minor bleeding (i.e., clinically relevant non-major bleeding)

- Spontaneous skin hematoma > 25 sq cm
- Wound hematoma > 100 sq cm
- Spontaneous nose bleed or gingival bleed lasting longer than 5 min,
- Spontaneous rectal bleed creating more than a spot on toilet paper
- Macroscopic hematuria either spontaneous or, if associated with an intervention (eg Foley catheter), lasting longer than 24 h
- Other bleeding event considered clinically relevant by the investigator not qualifying as a major bleed

Table 2 Patient demographic and surgical characteristics

Characteristic	Dabigatran etexilate		Enoxaparin
	220 mg	150 mg	
Treated – n	857	871	868
Age – yr*	66.2 ± 9·5	65.9 ± 9.5	66·3 ± 9.6
Weight – kg*	88.4 ± 19.1	87.6 ± 20·0	88·0 ± 19.2
Female gender – no. (%)	486 (56.7)	507 (58·2)	504 (58.1)
Creatinine clearance at screening (ml/min)*	83.6 (30.1)	82.3(30.0)	82.9(29.5)
General anesthesia (%)	453(52.9)	470(54.0)	449(51.7) †
Spinal anesthesia (%)	397(46.3)	399(45.8)	412(47.5)
Other anesthesia (%)	7 (0.8)	2 (0.2)	7 (0.8)
Duration of surgery – min*	91 ± 28	91 ± 30	90 ± 28
Time to first oral dose – h – mean* ‡	9.6 (3.4)	9.5 (3.4)	9.7(3.8) §
Treatment duration – days – median (range)	14 (1 to 18)	14 (2 to 33) ¶	14 (1 to 18)

* Mean ± SD.

†Patients may have had more than one type of anaesthetic. Data missing for 2 patients in the enoxaparin group.

‡Time from operation to first post-operative dabigatran etexilate dose.

§Placebo dose.

¶ One patient in the dabigatran 150 mg group received half the required daily oral dose, 75 mg qd, for 33 days

Table 3. Analysis: reasons for inclusion or exclusion [N (%)]

	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 30 mg bid	Total
Randomized	862	877	876	2615
Randomized and treated	857 (100.0)	871 (100.0)	868 (100.0)	2596 (100.0)
Total Included in analysis*	604 (70.5)	649 (74.5)	643 (74.1)	1896 (73.0)
Evaluable for total DVT by venogram	593 (69.2)	645 (74.1)	637 (73.4)	1875 (72.2)
Evaluable for Symptomatic DVT	7 (0.8)	3 (0.3)	2 (0.2)	12 (0.5)
Evaluable for PE or death	4 (0.5)	1 (0.1)	4 (0.5)	9 (0.3)
Total excluded from analysis*	253 (29.5)	222 (25.5)	225 (25.9)	700 (27.0)
Unevaluable venogram for total DVT	133 (15.5)	105 (12.1)	110 (12.7)	348 (13.4)
No venogram performed and symptomatic DVT unconfirmed	12 (1.4)	10 (1.1)	13 (1.5)	35 (1.3)
No venogram following premature discontinuation of study med	45 (5.3)	37 (4.2)	50 (5.8)	132 (5.1)
No venogram but completed treatment	63 (7.4)	70 (8.0)	52 (6.0)	185 (7.1)

*: Each patient is only included in one category.

Table 4. Summary of components of the primary efficacy outcome

	Dabigatran etexilate 220mg	Dabigatran etexilate 150mg	Enoxaparin
Treated	857	871	868
Treated and operated	857	871	868
Included in analysis	604 (100.0)	649 (100.0)	643 (100.0)
Total VTE/death during treatment*			
Total (%)	188 (31.1)	219 (33.7)	163 (25.3)
Distal DVT (%)	167 (27.6)	198 (30.5)	148 (23.0)
Proximal DVT (%)	14 (2.3)	20 (3.1)	10 (1.6)
Nonfatal PE (%)	6 (1.0)	0 (0.0)	5 (0.8)
Death VTE cannot be ruled out (%)	1 (0.2)	0 (0.0)	0 (0.0)
Death not associated with VTE (%)	0 (0.0)	1 (0.2)	0 (0.0)
Symptomatic DVT, PE or death during follow up*†	5	6	6

* Treatment period: from administration of first dose of study medication and ending 3 days after administration of last dose of study medication. Follow-up is from the end of treatment period to the conclusion of subject participation

† Dabigatran etexilate 220mg: 2 sympt.DVT, 2 PE, 1 death; Dabigatran etexilate 150mg: 4 sympt.DVT, 0 PE, 2 death; Enoxaparin: 2 sympt.DVT, 2 PE, 2 death.

Note: patients were counted only once in the most severe category in the subcategories of DVT, PE and death.

Table 5. Patients with bleeding events

	Dabigatran 220mg	Dabigatran 150mg	Enoxaparin
Treated	857	871	868
During treatment period			
Major bleed (%)	5 (0.6)	5 (0.6)	12 (1.4)
Bleeding site and criteria*			
Surgical site	2	3	11
Intra-occular	1	0	0
Other site	2	2	3
Fatal bleeding	0	0	0
Bleed leading to re-operation	0	0	1
Bleed requiring treatment cessation	0	0	1
Clinically relevant non-major bleed (%)	23 (2.7)	22 (2.5)	21 (2.4)
Post-treatment study bleeding			
Major bleed (%)	1 (0.1)	2 (0.2)	0
Clinically relevant non-major bleed	6 (0.7)	5 (0.5)	3 (0.3)

* Some patients are listed by more than 1 criterion

Table 6. Comparison of factors for enoxaparin-treated patients in North American RE-MOBILIZE and European RE-MODEL dabigatran etexilate knee replacement trials

	RE-MOBILIZE	RE-MODEL
N	868	694
Study centers	Primarily N.America	Europe, Australia, S.Africa
Enoxaparin dosing	30 mg bid	40 mg qd
Start time	12-24 h after surgery	evening prior to surgery
Mean time to first sc injection in relation to surgery	20 h	-14 h
Mean days of treatment	13	8
Total VTE rate in Enox arm	25%	36%
Proportion of VTE that was asymptomatic	153/163 (93.3%)	184/193 (95.3%)
Symptomatic VTE or death	10/163 (6.1%)	9/193 (5.5%)
Major Bleeding Events	12/868 (1.4%)	9/694 (1.3%)
Clinically relevant, non-major bleeding events	21/868 (2.4%)	37/694 (5.3%)