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IN FOCUS

Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial

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Summary. *Background:* Oral anticoagulants, such as dabigatran etexilate, an oral, direct thrombin inhibitor, that do not require monitoring or dose adjustment offer potential for prophylaxis against venous thromboembolism (VTE) after total knee replacement surgery. *Methods:* In this randomized, double-blind study, 2076 patients undergoing total knee replacement received dabigatran etexilate, 150 mg or 220 mg once-daily, starting with a half-dose 1–4 h after surgery, or subcutaneous enoxaparin 40 mg once-daily, starting the evening before surgery, for 6–10 days. Patients were followed up for 3 months. The primary efficacy outcome was a composite of total VTE (venographic or symptomatic) and mortality during treatment, and the primary safety outcome was the incidence of bleeding events. *Results:* The primary efficacy outcome occurred in 37.7% (193 of 512) of the enoxaparin group vs. 36.4% (183 of 503) of the dabigatran etexilate 220-mg group (absolute difference, −1.3%; 95% CI, −7.3 to 4.6) and 40.5% (213 of 526) of the 150-mg group (2.8%; 95% CI,−3.1 to 8.7). Both doses were non-inferior to enoxaparin on the basis of the prespecified non-inferiority criterion. The incidence of major bleeding did not differ significantly between the three groups (1.3% vs. 1.5% and 1.3% respectively). No significant differences in the incidences of liver enzyme elevation and acute coronary events were observed during treatment or follow-up. *Conclusions:* Dabigatran etexilate (220 mg or 150 mg) was at least as effective as enoxaparin and had a similar safety profile for prevention of VTE after total knee replacement surgery.

Keywords: dabigatran etexilate, direct thrombin inhibitor, prophylaxis, total knee replacement, venous thromboembolism.

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Introduction

There is considerable interest in developing new, orally available anticoagulants for the prevention and treatment of thrombotic disorders [1,2]. Warfarin, widely prescribed in North America to prevent venous thromboembolism (VTE) after major orthopedic surgery [3,4], has a number of well-documented limitations, which include a narrow therapeutic index, and the need for regular monitoring and frequent dose adjustment [5]. In Europe, the low molecular weight heparins (LMWHs) are more commonly prescribed for thrombosis prevention, but require parenteral administration, which may be an obstacle to optimal patient care, particularly when outpatient dosing is required after early discharge. New oral anticoagulants that require no monitoring and can be administered in a fixed dose without drug–drug and drug–food interactions would clearly offer practical advantages if shown to be safe and effective.

Dabigatran etexilate, a new oral, direct thrombin inhibitor, is the prodrug of the active compound dabigatran, which binds reversibly to thrombin with high affinity and specificity [6,7]. This agent has a rapid onset of action, a predictable and reproducible pharmacodynamic effect, and pharmacokinetic characteristics that permit once-daily dosing [8,9]. In a dose-

ranging study, dabigatran etexilate was effective across a range of doses (50–225 mg twice-daily) for prevention of postoperative VTE after total hip or total knee replacement [10]. Logistic regression analysis showed that a total daily dose of between 100 mg and 300 mg provided the optimal efficacy–safety balance for further evaluation.

The aim of the present study was to establish the efficacy and safety of two doses of dabigatran etexilate (150 mg and 220 mg once-daily), based on a non-inferiority design in comparison with the LMWH enoxaparin, for the prevention of VTE after total knee replacement surgery.

Methods

Study design

This was a randomized, double-blind, active controlled, non-inferiority study conducted at 105 centers in Europe, Australia, and South Africa. The study was approved by national independent ethics committees and conducted in accordance with the Declaration of Helsinki (October 1996 version). On the day before surgery, patients were randomly assigned to one of three treatment groups, using a computer-generated central scheme stratified by study center. Randomization was performed in blocks of six. In each center, the lowest number available was allocated.

Patients

Patients ≥18 years and >40 kg, scheduled for primary elective unilateral total knee replacement who provided signed informed consent, were eligible for study. Exclusion criteria included: any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) within the past month; severe renal insufficiency (creatinine clearance < 30 mL min^{-1}); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; and being female and of childbearing potential. After surgery, any indwelling anesthetic catheter was removed, and subcutaneous injection of trial medication was given at least 4 h later.

Treatment regimens

Patients were assigned to oral dabigatran etexilate 150 mg or 220 mg once-daily, or enoxaparin (Sanofi-Aventis), 40 mg subcutaneously once-daily. All three groups received one active and one matching placebo treatment that were identical in appearance. Patients received two capsules in the morning and a daily subcutaneous injection in the evening. The first subcutaneous injection was given on the evening before surgery, although in some countries treatment was started postoperatively to reflect local practice. The first dose of dabigatran etexilate was one-half of subsequent doses (one capsule, 75 mg or 110 mg), and was administered 1–4 h after completion of surgery, provided that clinical assessment of perioperative and postoperative bleeding and drainage indicated good hemostasis. If administration was delayed until the day after surgery, then a full dose (two capsules) was administered as the first dose. Treatment was continued for a total of 6–10 days until mandatory bilateral venography. Continuation of anticoagulation after this time was at the discretion of the investigator. Patients were assessed for 3 months after surgery. The treatment period was defined as the time from the first dose to 3 days after the last oral or subcutaneous dose, whichever came later.

Concomitant treatment with low-dose aspirin (< 160 mg) and selective cycloxygenase-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 (proximal DVT and 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 performed within 24 h of the last oral dose, according to a standardized technique described previously [10–13]. Diagnosis of DVT was established as a consistent intraluminal filling defect on at least two venogram images. PE was established by 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 of central review were used in the primary analysis.

The primary safety outcome was the occurrence of bleeding events during study treatment. Major bleeding events, clinically relevant non-major bleeding events and minor bleeding events were defined according to accepted guidelines [14], as reported previously [10]. An independent expert adjudication committee classified all bleeding events. Hematology and clinical chemistry tests were performed before treatment and on the last day of dosing, at 4–6 weeks, and 3 months after surgery. Assessment of liver function was a focus of these tests, with prespecified rules for cessation of study medication and investigation of patients with abnormal values during the

study. All cases of hepatic enzyme abnormalities and suspected cardiovascular events during the study were reviewed by blinded independent expert committees, according to predefined criteria.

Statistical analysis

On the basis of information from a previous comparative study [10], we assumed that the incidence of the primary efficacy outcome would be 1% lower for dabigatran etexilate than for enoxaparin. Using published rates of VTE for enoxaparin [15], and studies that evaluated enoxaparin using the same central adjudication committee as in the present study [10,16,17], we calculated that the rate of VTE for enoxaparin would range from 30% to 48%. On the basis of prior findings [18], we chose a non-inferiority margin of 9.2%; this minimum difference preserves two-thirds of the 95% confidence interval (CI) difference between enoxaparin and placebo. On the basis of these assumptions, we calculated that a study with 500 evaluable patients per group would have 90% power, with a one-sided type I error of 0.025, to reject the hypothesis that the primary outcome with dabigatran etexilate would be 9.2% higher than enoxaparin when the VTE rate with enoxaparin was as high as 48%. Assuming that 25% of patients would not have evaluable venograms, randomization of 2010 patients was required. The safety population consisted of all randomized patients who received at least one dose of study treatment (either subcutaneous injection or oral drug). Patients who were randomized, received at least one subcutaneous injection or one oral dose of study medication, underwent elective total knee replacement surgery and had evaluable centrally adjudicated data for VTE (venography or symptomatic confirmed event) or who died during treatment were included in the primary efficacy analysis. Patients with inadequate or missing mandatory bilateral venography who neither died nor experienced VTE events were excluded from efficacy analyses. The two-sided 95% CI for the absolute difference between each dabigatran etexilate group and enoxaparin was calculated using normal approximation. The rates of the primary efficacy endpoint were analyzed using a combined non-inferiority and superiority test according to the sequential scheme, which tests non-inferiority first [19,20]. If non-inferiority could be shown, the superiority test could then be performed.

Role of the funding source

The planning and management of the study were conducted by the Steering Committee in conjunction with the study sponsor. 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 2183 patients enrolled between November 2004 and March 2006, 2101 were randomized to treatment and 1541 (73%) were included in the primary efficacy analysis (Fig. 1). Patient demographic and surgical characteristics were similar for the three groups (Table 1). The mean time interval between surgery and initiation of dabigatran etexilate treatment was 3.4 h. The median oral treatment duration was 8 days, with 92% of patients receiving treatment for 6–10 days.

Efficacy

The primary outcome (total VTE and death) occurred in 36.4% (183 of 503) of patients in the dabigatran etexilate 220-mg group, 40.5% (213 of 526) of the 150-mg group and 37.7% (193 of 512) of the enoxaparin group (Table 2). Both doses of dabigatran etexilate were non-inferior to enoxaparin, as the upper limit of the 95% CI for the absolute difference vs. enoxaparin was less than the prespecified non-inferiority margin of 9.2%; for 220 mg, the difference was −1.3% (95% CI,−7.3 to 4.6), and for 150 mg, the difference was 2.8% (95% CI, −3.1 to 8.7) (Table 2). The testing procedure employed did not show superiority of either dose of dabigatran etexilate over enoxaparin. The findings were consistent with prespecified subgroup analyses by country, age, gender, body mass index, time to first oral dose, and type of anesthesia (data not shown).

The secondary outcome of major VTE and VTE-related mortality occurred in 2.6% and 3.8% of the dabigatran etexilate 220-mg and 150-mg groups, as compared with 3.5% of the enoxaparin group. The absolute difference between each of these dabigatran etexilate doses and enoxaparin (−1.0% and 0.3%, respectively) was consistent with the results of the primary efficacy outcome (Table 2).

Fourteen patients developed symptomatic VTE, including one with fatal PE in the enoxaparin group, during treatment, and a further five patients developed symptomatic events during follow-up (three and two in the dabigatran etexilate 220-mg and 150-mg groups). The composite outcome of total VTE and all-cause mortality during follow-up occurred in 0.6% and 0.4% of patients treated with dabigatran etexilate 220 mg and 150 mg, respectively, and in 0.3% treated with enoxaparin.

Safety

During treatment, major bleeding events occurred in 10 patients (1.5%; 95% CI, 0.7–2.7) in the dabigatran etexilate 220-mg group and in nine patients in both the 150-mg group (1.3%; 95% CI, 0.6–2.4) and the enoxaparin group (1.3%; 95% CI, 0.6–2.4) (Table 3). There was no significant difference in bleeding events between either dose of dabigatran etexilate and enoxaparin ($P = 0.82$ for 220 mg and $P = 1.0$ for 150 mg, respectively). None of the major bleeding events was fatal. Most patients had major bleeding events at the surgical

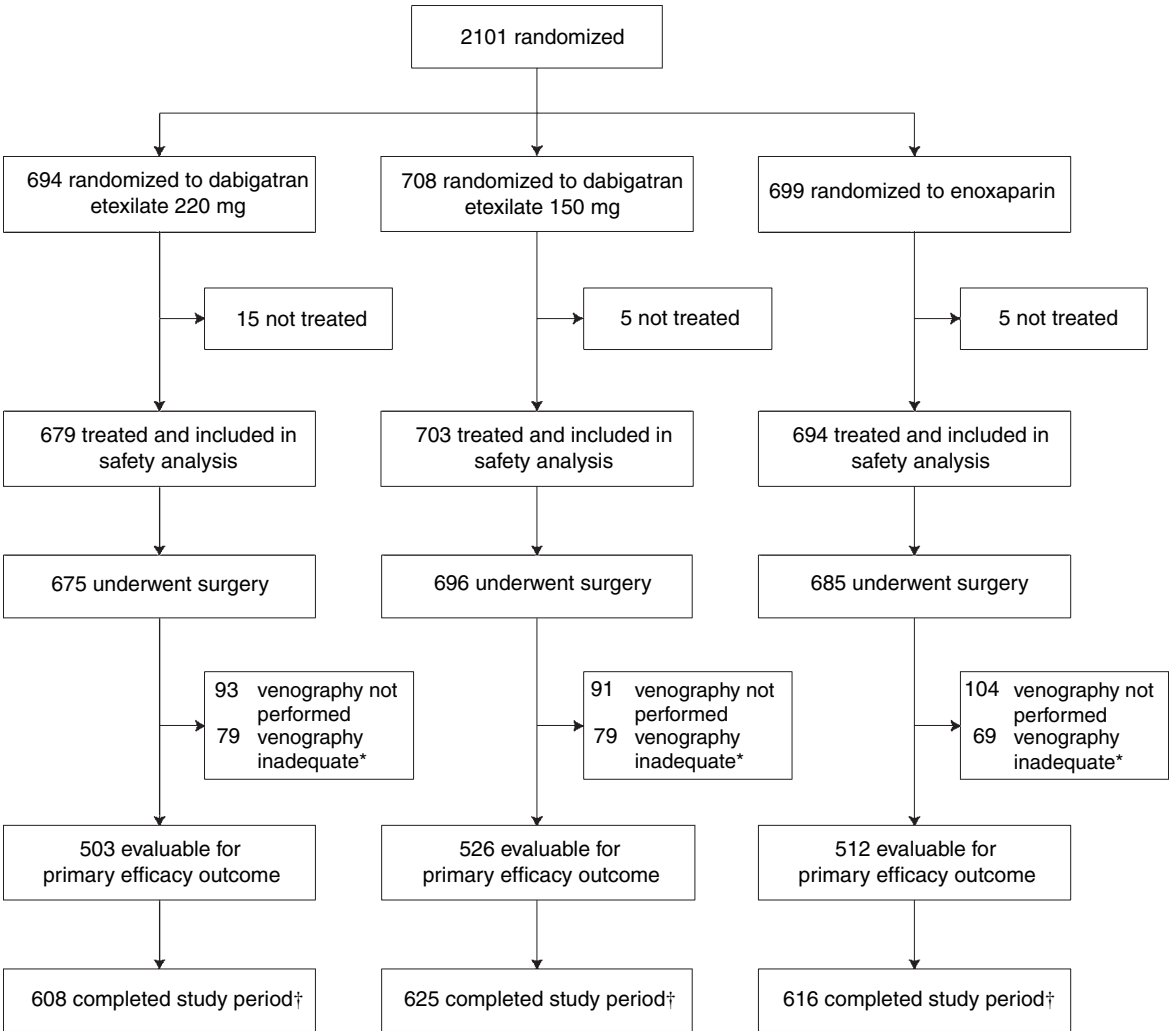

Fig. 1. Randomization and progression of patients in the trial. *Venography was considered adequate by the central adjudication committee if films were provided visualizing the proximal and distal deep veins in both legs. If deep vein thrombosis was seen in any one of the veins visualized, the patient was considered to be suitable for the efficacy outcome even if the venous system was not visualized entirely. †The main reasons for premature study discontinuation included consent withdrawal, adverse events, and non-compliance with protocol.

Table 1 Characteristics of treated and operated patients

Characteristic	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin
Treated (*n*)	679	703	694
Age (years)*	67 ± 9	68 ± 9	68 ± 9
Weight (kg)*	82 ± 15	83 ± 15	82 ± 15
Female gender [*n* (%)]	441 (65)	451 (64)	478 (69)
Treated and operated (*n*)	675	696	685
Type of anesthesia [*n* (%)]†			
General alone	149 (22)	167 (24)	152 (22)
Neuraxial alone‡	331 (49)	325 (47)	330 (48)
Combination§	195 (29)	204 (29)	202 (30)
Duration of surgery (min)	91 ± 28	91 ± 30	90 ± 28
Time to first oral dose (h) [mean (range)]¶	3.5 (0.2–27.4)	3.3 (−12.6 to 38.0)	3.6 (−4.3 to 38.8)**
Active treatment duration (days) [median (range)]	8 (2–14)	8 (1–12)	7 (1–13)

*Plus/minus values are means ± SD. †Patients may have had more than one type of anesthetic. Data missing for one patient in the enoxaparin group. ‡Includes spinal and epidural anesthesia. §Peripheral nerve block plus general or neuraxial anesthesia. ¶Time from operation to first postoperative dabigatran etexilate dose. **Placebo capsule.

Table 2 Efficacy outcomes during treatment period

Parameter	Dabigatran etexilate		Enoxaparin
	220 mg	150 mg	
Primary outcome* (*n*/*N*)	183/503	213/526	193/512
% (95% CI)	36.4 (32.2–40.6)	40.5 (36.3–44.7)	37.7 (33.5–41.9)
Absolute difference vs. enoxaparin (95% CI)	−1.3 (−7.3 to 4.6)	2.8 (−3.1 to 8.7)	
P-value for non-inferiority vs. enoxaparin†	0.0003	0.017	
Total asymptomatic DVT (*n*/*N*)‡	181/503 (36.0%)	208/524 (39.7%)	184/511 (36.0%)
Proximal	13/506 (2.6%)	18/525 (3.4%)	16/510 (3.1%)
Distal only	168/503 (33.4%)	190/524 (36.3%)	168/511 (32.9%)
Symptomatic DVT (*n*/*N*)‡	1/675 (0.1%)	3/696 (0.4%)	8/685 (1.2%)
Symptomatic PE (*n*/*N*)‡	0/675	1/696 (0.1%)	1/685 (0.1%)§
Death (*n*/*N*)	1/675 (0.1%)	1/696 (0.1%)¶	1/685 (0.1%)§
Major VTE†† and VTE-related mortality (*n*/*N*)**	13/506	20/527	18/511
% (95% CI)	2.6 (1.2–3.9)	3.8 (2.2–5.4)	3.5 (1.9–5.1)
Absolute difference vs. enoxaparin (95% CI)	−1.0 (−3.1 to 1.2)	0.3 (−2.0 to 2.6)	
P-value for difference vs. enoxaparin†	0.38	0.82	

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism. *Total VTE and all-cause mortality. †*P*-values are for the comparison of each dabigatran etexilate dose vs. enoxaparin, calculated with Fisher's exact test. ‡Includes events that occurred within 3 days of last dose of study medication. Patients may have events included in more than one category. §Fatal PE, same patient. ¶Death where VTE could not be excluded. **Includes all deaths where VTE cannot be excluded. ††Includes proximal DVT and PE.

Table 3 Bleeding events during the treatment period*

Bleeding event	Dabigatran etexilate		Enoxaparin (n = 694)
	220 mg (n = 679)	150 mg (n = 703)	
Major bleeding (no. of patients) (%; 95% CI)†	10 (1.5; 0.7–2.7)	9 (1.3; 0.6–2.4)	9 (1.3; 0.6–2.4)
Fatal (*n*)	0	0	0
In a critical organ (*n*)	0	1‡	0
Clinically overt associated with 20 g l^{-1} or more fall in hemoglobin (*n*)§	7	7	7
Clinically overt leading to transfusion of two or more units of packed cells or whole blood (*n*)§	8	6	5
Warranting treatment cessation (*n*)	2	0	0
Leading to reoperation (*n*)	3	1	1
Clinically relevant non-major bleeding [no. of patients (%)]	40 (5.9)	48 (6.8)	37 (5.3)
Minor bleeding [no. of patients (%)]	60 (8.8)	59 (8.4)	69 (9.9)

CI, confidence interval. *For all bleeding outcomes, none of the differences between each dabigatran etexilate dose and enoxaparin was statistically significant. †Patients may have been included in more than one category. One patient in the dabigatran etexilate 220-mg group had two events. ‡Patient suffered a bloody puncture during spinal anesthesia; no active study medication was administered. §In excess of that expected by the investigator.

site [25 of 28 (89%)]. There was one bleed into a critical organ (dabigatran etexilate 150-mg group), and two bleeding events in patients treated with dabigatran etexilate 220 mg required treatment discontinuation. Five reoperations were required due to bleeding (three in the dabigatran etexilate 220-mg group, and one each in the other two groups). Mean blood loss volumes during and after surgery, wound drainage volumes, need for transfusion and mean transfusion volumes were similar across the treatment groups (data not shown).

Other observations

Adverse events leading to treatment discontinuation occurred in 3.7%, 3.7% and 4.6%, respectively, of the dabigatran etexilate 220-mg and 150-mg groups and the enoxaparin group. Moderate liver enzyme elevation (ALT levels $> 3 \times$ ULN) was reported in 2.8%, 3.7% and 4.0% of these groups (Appendix S1). One patient in the dabigatran etexilate 150-mg group had an ALT value $> 3 \times$ ULN together with a 2-fold increase in bilirubin. A definitive diagnosis could not be made, and the liver enzymes returned to the normal range within 4 weeks. It is of note that this patient developed a similar enzyme elevation (ALT $> 3 \times$ ULN together with a $>$ 2-fold increase in bilirubin) 1 year later, when she underwent replacement of the contralateral knee, at which time she was not participating in any trial. During follow-up, in two and five patients in the dabigatran 220-mg and 150-mg groups, and in three patients in the enoxaparin group, ALT was $> 3 \times$ ULN for the first time. In all cases, the abnormalities returned to baseline or the ULN with additional follow-up.

Adjudicated acute coronary events (confirmed unstable angina, myocardial infarction and cardiac death) occurred in

three and seven patients in the dabigatran etexilate 220-mg and 150-mg groups and in four patients in the enoxaparin group during treatment, and in one patient in the dabigatran etexilate 150-mg group and in two patients in the enoxaparin group, during follow-up.

Discussion

This study showed that oral dabigatran etexilate (150 mg or 220 mg once-daily), initiated at half-dose in the early postoperative period (mean 3.4 h) and continued at full dose for 6–10 days, was non-inferior to enoxaparin 40 mg once-daily, started the night before surgery, for the prevention of VTE after total knee replacement surgery. There was no difference between the two doses of dabigatran etexilate and enoxaparin with respect to the primary safety outcome (bleeding) or the incidence of adverse events during treatment and follow-up.

Overall, the incidence of the primary efficacy outcome (primarily VTE) in this study was similar to that observed in previous studies, including those with dabigatran etexilate and enoxaparin. Although the rate for VTE with enoxaparin in the current study (38%) was at the lower end of the expected range – in previous knee replacement studies using the same venogram technique and adjudication committee, the incidence of VTE was 44–46% [10,16,17] – it was within the predicted range for VTE (30–48%) and the prespecified non-inferiority margin used in sample size calculations.

The safety of anticoagulation is probably the most important concern for orthopedic surgeons, especially after knee replacement, when bleeding into the replaced joint can have catastrophic consequences for clinical outcome [21]. In this study, the rates of major bleeding with all treatments were low (1.3–1.5%); for enoxaparin, the rate was consistent with the findings of a previous dose-ranging study (1.6%), which used the same definition of bleeding and the same adjudication committee [10]. Reducing the first dose of dabigatran etexilate in this study as compared with most doses in the earlier dose-ranging study improved the safety profile of the drug, with bleeding rates nearly identical to those of enoxaparin. This is a particularly important finding for a new anticoagulant likely to be initiated early in the postoperative period.

The benefit–risk balance of anticoagulant use for prevention of VTE after major orthopedic surgery is dependent on a number of inter-related issues, in particular dose and timing of administration in relation to the operation. Transatlantic differences seen with the use of LMWHs (once-daily preoperatively vs. twice-daily postoperatively with initiation at a higher dose) are now decreasing, with the development of new anticoagulants focused on oral, once-daily administration initiated early in the postoperative period [1]. The initiation of anticoagulation after surgery offers specific advantages for those patients who may be admitted to hospital on the day of their surgery in addition to the benefits associated with the increasing use of regional anesthesia during these procedures [3]. Studies of new agents generally show that, when given in an appropriate schedule, primary efficacy and safety findings essentially do not differ from those with the comparator LMWH (usually enoxaparin), as also demonstrated in this study. This understanding was fundamental in the choice of a non-inferiority design for this study.

In this study, there was no increase in the incidence of liver enzyme elevation associated with dabigatran etexilate as compared with enoxaparin, during either treatment or extended follow-up. The one patient who met the definition of severe liver injury (an ALT $> 3 \times$ ULN and a bilirubin $> 2 \times$ ULN) [22] was noted to have a similar liver enzyme elevation while undergoing a subsequent knee replacement off study medication, suggesting that the abnormality observed was anesthetic-related. Given the similar pattern and degree of transaminase elevations observed in the study with dabigatran as compared with enoxaparin, it is likely that these changes are benign and related to either the surgical procedure or associated anesthesia. Similarly, the incidence of acute coronary-related events was low and did not differ between the three treatment groups. This latter finding, taken together with the lack of any significant difference in the incidence of PE or death during follow-up, suggests that there is no evidence of any rebound effect on coagulation after completion of dabigatran etexilate treatment.

In conclusion, the findings of this study suggest that oral once-daily dabigatran etexilate, at the doses investigated, is a well-tolerated alternative to enoxaparin for the prevention of VTE after total knee replacement. These findings, in conjunction with the other results from the large, phase III development program in elective hip and knee replacement surgery [23,24], will help to define the optimal dose and overall safety profile of dabigatran etexilate.

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Disclosure of conflict of interests

B. I. Eriksson, O. E. Dahl, N. Rosencher, A. A. Kurth, C. N. van Dijk, S. P. Frostick, P. Kälebo and H. R. Büller participated as investigators, consultants or both for Boehringer Ingelheim. A. V. Christiansen, S. Hantel, R. Hettiarachchi and J. Schnee are employees of Boehringer Ingelheim. This study was sponsored by Boehringer Ingelheim, Copenhagen, Denmark.

Supplementary Material

The following supplementary material is available for this article:

Appendix S1. Frequency of elevated alanine aminotransferase values for treated patients.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1538-7836.2007.02748.x

Appendix. RE-MODEL Study Group Committees and Investigators

Steering Committee

B. I. Eriksson (Study Chair), Göteborg, Sweden; O. E. Dahl, London, UK; C. N. van Dijk, The Netherlands; S. P. Frostick, Liverpool, UK; A. A. Kurth, Frankfurt, Germany; N. Rosencher, Paris, France; R. Hettiarachchi, Boehringer Ingelheim, Alkmaar, The Netherlands (non-voting member); J. Schnee, Boehringer Ingelheim, Ridgefield, CT, USA (non-voting member). The following were ad-hoc members of the Steering committee: H. R. Büller, Amsterdam, The Netherlands; A. V. Christiansen, Boehringer Ingelheim, Copenhagen, Denmark; E. Hwang, Boehringer Ingelheim, Ridgefield, CT, USA; M. Iovino, Boehringer Ingelheim, Alkmaar, The Netherlands; L.-E. Lins, Boehringer Ingelheim, Stockholm, Sweden.

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Investigators

These recruited at least one patient (number of patients randomized in each country is included in parentheses).

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Denmark (146 patients, five centers) J. Bagger (Amager, Kbh S), B. R. Duus (Bispebjerg, Kbh NV), M. R. Lassen (Hørsholm), S. Mikkelsen (Silkeborg), C. Tørholm (Gentofte).

Finland (162 patients, four centers) P. Jokipii (Seinäjoki), J. Leppilahti (Oulu), M. Pesola (Jyväskylä); H. Väänänen (Helsinki).

France (122 patients, nine centers) I. Alawwa (Roubaix), D. Baylot (Saint Etienne), P. Catoire (La Rochelle), E. Gaertner (Strasbourg), E. Lepelley (Poitiers), E. Mazuir (Paris), P. Mertl (Amiens), P. Narchi (Soyaux), V. Souron (Annecy).

Germany (224 patients, nine centers) W. Birkner (Rheinfelden), B. Fink (Markgröningen), H.-M. Fritsche (Garmisch-Partenkirchen), A. Halder (Sommerfeld), W. Hein (Halle), A. Kurth (Frankfurt), G. Salzmann (Wiesbaden), H. Schmelz (Bad Mergentheim), R. Schmidt (Erlangen).

Hungary (183 patients, six centers) L. Bucsi (Székesfehérvár), G. Dósa (Gyula), E. Lenart (Kecskemét), A. Sárváry (Budapest), J. Toth (Békéscsaba), K. Toth (Szeged).

Italy (43 patients, six centers) B. Borghi (Bologna), A. Ghirarduzzi (Reggio Emilia), D. Imberti (Piacenza), F. Piovella (Pavia), R. Quintavalla (Parma), G. Scannapieco (Treviso)

The Netherlands (217 patients, six centers) R. Albers (Hilversum), C. N. Van Dijk (Amsterdam), P. Nolte (Hoofddorp), R. Slappendel (Nijmegen), A. D. Verburg (Sittard), C. Verheyen (Zwolle).

Poland (11 patients, four centers) B. Franczuk (Kraków), K. Kwiatkowski (Warszawa), T. Niedzwiecki (Kraków), L. Siuda (Kielce).

South Africa (51 patients, three centers) D. Adler (Johannesburg), I. Dymond and C. Smith (Johannesburg), R. Routier (Randburg).

Spain (200 patients, 11 centers) E. Gómez-Barrena (Madrid), E. García-Cimbrelo (Madrid), L. Peidro-Garcés (Barcelona), M. De Frías-González (Madrid), J. A. Hernández-Hermoso (Barcelona), A. Sanz-Laguna (Madrid), A. D. Delgado-Martínez (Jaén), A. Navarro-Quilis (Barcelona), F. Gomar-Sancho (Valencia), R. Canosa-Sevillano (Madrid), L. Lopez-Duran Stern (Madrid).

Sweden (197 patients, nine centers) L. Ahnfelt (Falköping), C. Andersson (Linköping), B. Edshage (Kungälv), B. I. Eriksson (Göteborg), A. Folestad (Mölndal), H. Laestander (Varberg), B. Paulsson (Lidköping), S. Ponzer (Stockholm), A. Wykman (Halmstad).

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