Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial

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Summary

Background After hip replacement surgery, prophylaxis following discharge from hospital is recommended to reduce the risk of venous thromboembolism. Our aim was to assess the oral, direct thrombin inhibitor dabigatran etexilate for such prophylaxis.

Methods In this double-blind study, we randomised 3494 patients undergoing total hip replacement to treatment for 28–35 days with dabigatran etexilate 220 mg (n=1157) or 150 mg (1174) once daily, starting with a half-dose 1–4 h after surgery, or subcutaneous enoxaparin 40 mg once daily (1162), starting the evening before surgery. The primary efficacy outcome was the composite of total venous thromboembolism (venographic or symptomatic) and death from all causes during treatment. On the basis of the absolute difference in rates of venous thromboembolism with enoxaparin versus placebo, the non-inferiority margin for the difference in rates of thromboembolism was defined as 7·7%. Efficacy analyses were done by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00168818.

Findings Median treatment duration was 33 days. 880 patients in the dabigatran etexilate 220 mg group, 874 in the dabigatran etexilate 150 mg group, and 897 in the enoxaparin group were available for the primary efficacy outcome analysis; the main reasons for exclusion in all three groups were the lack of adequate venographic data. The primary efficacy outcome occurred in 60 (6·7%) of 897 individuals in the enoxaparin group versus 53 (6·0%) of 880 patients in the dabigatran etexilate 220 mg group (absolute difference –0·7%, 95% CI –2·9 to 1·6%) and 75 (8·6%) of 874 people in the 150 mg group (1·9%, –0·6 to 4·4%). Both doses were thus non-inferior to enoxaparin. There was no significant difference in major bleeding rates with either dose of dabigatran etexilate compared with enoxaparin (p=0·44 for 220 mg, p=0·60 for 150 mg). The frequency of increases in liver enzyme concentrations and of acute coronary events during the study did not differ significantly between the groups.

Interpretation Oral dabigatran etexilate was as effective as enoxaparin in reducing the risk of venous thromboembolism after total hip replacement surgery, with a similar safety profile.

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Introduction

Deep-vein thrombosis diagnosed by contrast venography occurs in up to 20% of patients who have undergone hip replacement surgery, despite routine treatment for 5–11 days with low-molecular-weight heparin, warfarin, or pentasaccharide.[1] The risk of deep-vein thrombosis can be further reduced by continuing treatment with these agents for 1 month after surgery.[1–5] However, most patients do not continue anticoagulant prophylaxis after discharge from hospital,[6,7] and because the duration of hospital stays is falling (mean 3–4 days), only a few patients receive even the minimum 10 days of treatment recommended by the guidelines.[1] By contrast, the use of once-daily oral aspirin after hospital discharge has increased markedly, despite very limited efficacy, presumably because of the convenience of its administration.[6] New oral treatments that do not share the narrow therapeutic index of warfarin[8] and do not need frequent laboratory monitoring and dose adjustment are clearly needed.

There is evidence to suggest that new, orally bioavailable anticoagulants can be used for prevention and treatment of thrombotic disorders.[9,10] Dabigatran etexilate is an oral, direct thrombin inhibitor under investigation for prevention and treatment of venous and arterial thromboembolic disorders. It is the prodrug of the active compound dabigatran, which binds directly to thrombin with a high affinity and specificity.[11,12] Data from a dose-ranging study suggest that the optimum total daily dose for effective and safe prevention of venous thromboembolism in total hip or knee replacement surgery is between 100 mg and 300 mg.[13]

RE-NOVATE—a randomised, double-blind, non-inferiority study—was designed to compare the efficacy and safety of two doses of dabigatran etexilate (220 mg or 150 mg) with the low-molecular-weight heparin enoxaparin, given for 1 month, to reduce the risk of venous thromboembolism after hip replacement surgery.

Methods

Patients

Patients aged 18 years or older, weighing at least 40 kg, who were scheduled for primary elective unilateral total hip replacement were eligible for enrolment. Exclusion

criteria included: any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insufficiency (creatinine clearance less than 30 mL/min); use of long-acting non-steroidal anti-inflammatory drugs (also contraindicated during treatment); childbearing potential; allergy to radiopaque contrast media or heparin; and active malignant disease. If spinal or epidural anaesthesia was done, less than three attempts or non-traumatic placement was required for patient eligibility. After surgery any indwelling anaesthetic catheter was removed and subcutaneous study medication given at least 4 h later.

The study was approved by national independent ethics committees and done in accordance with the principles of the Declaration of Helsinki (October, 1996, version). All patients gave signed informed consent before entry.

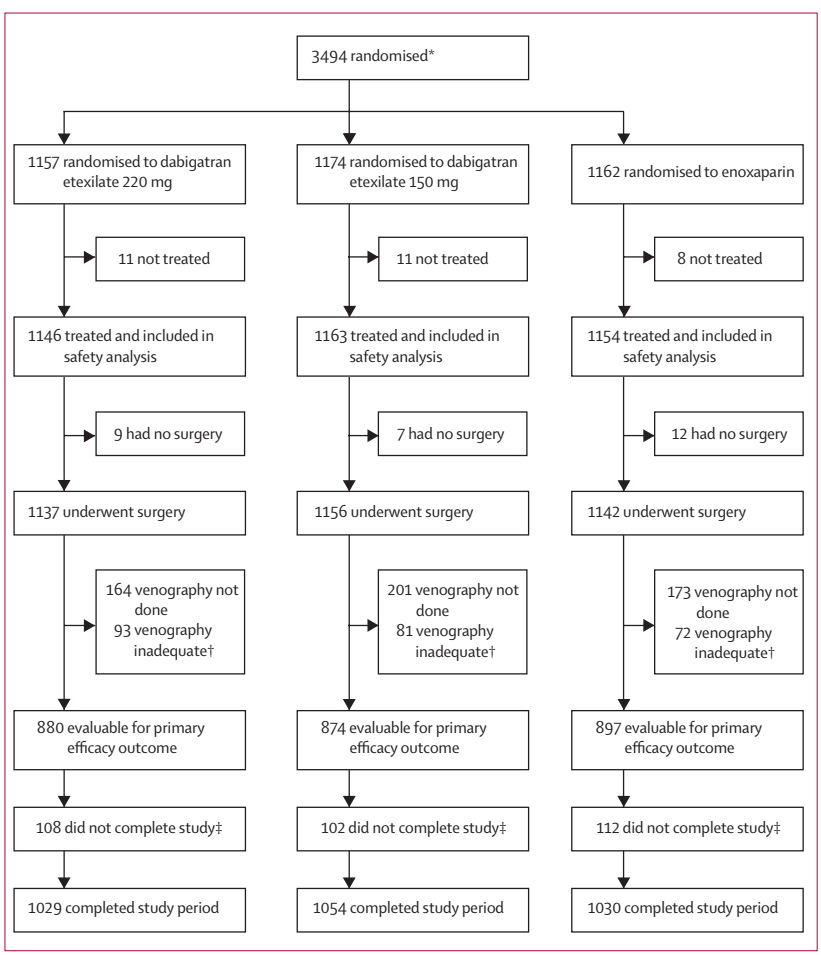

Figure: **Trial profile**
*119 patients were not randomised to treatment since they did not meet the inclusion or exclusion criteria (n=25), withdrew informed consent (n=53), experienced an adverse event before randomisation (n=3), or due to other reasons (n=38). †Venography was considered adequate by the central adjudication committee if films were provided that visualised the proximal and distal deep veins in both legs. If deep-vein thrombosis was seen in any one of the veins visualised, the patient was considered to be suitable for the efficacy outcome even if the venous system was not visualised entirely. ‡The main reasons for premature study discontinuation included consent withdrawal, adverse events, and non-compliance with protocol.

Procedures

The RE-NOVATE study was done at 115 centres in Europe, Australia, and South Africa. On the day before surgery, patients were randomly assigned to one of three treatment groups, stratified by study centre with a central computer generated scheme. Randomisation was prepared in blocks of six, with the lowest number allocated sequentially. Patients were assigned to once-daily oral dabigatran etexilate 220 mg or 150 mg, or enoxaparin (Sanofi-Aventis) 40 mg subcutaneously. All three groups received one active and one placebo medication identical in appearance to the other active treatment. Patients received two capsules in the morning and a subcutaneous injection in the evening. Subcutaneous treatment was started the evening before surgery, although some countries started postoperatively to reflect local practice. The first dabigatran etexilate dose was halved (one capsule, 110 mg or 75 mg) and given 1–4 h after surgery, provided there was evidence of good haemostasis. If administration was delayed until the day after surgery, a full dose was given, followed by a second dose at least 12 h later. Treatment was continued for 28–35 days until mandatory bilateral venography. The treatment period was the time from first dose to 3 days after the last dose of the study drug.

Concomitant administration of low-dose aspirin (less than 160 mg) and selective cyclo-oxygenase-2 inhibitors was allowed during treatment. Elastic compression stockings were permitted, but intermittent pneumatic compression devices were prohibited.

The primary efficacy outcome was the composite of total venous thromboembolic events (venographic or symptomatic deep-vein thrombosis or symptomatic pulmonary embolism) and all-cause mortality during treatment. The prespecified secondary efficacy outcomes were the composite of major venous thromboembolism (proximal deep-vein thrombosis and pulmonary embolism) and venous thromboembolism-related mortality, proximal deep-vein thrombosis, and the individual components of the primary efficacy outcome. Bilateral venography was done within 24 h of the last oral dose, as described previously.[13–16] Deep-vein thrombosis was confirmed by a consistent intraluminal filling defect on at least two venogram images. Pulmonary embolism was established by ventilation-perfusion scintigraphy, pulmonary angiography, spiral chest CT, or by autopsy. Symptomatic deep-vein thrombosis was confirmed by compression ultrasound or venography. Diagnostic tests for venous thromboembolic events were initially assessed locally,

then by an independent central adjudication committee blinded to treatment allocation. The results of the independent committee were used in the primary analysis.

The primary safety outcome was the occurrence of bleeding events during treatment. Major bleeding events, clinically relevant non-major bleeding events, and minor bleeding events were defined according to accepted guidelines,[17] as reported previously,[13] and classified by an independent, expert adjudication committee. Haematology and clinical chemistry testing was done before treatment, at hospital discharge, on the last day of dosing, and 2 and 3 months after surgery. Liver function was a focus of safety assessment,[18] with prespecified rules for treatment withdrawal and follow-up tests. Independent committees, masked to treatment allocation, reviewed cases with hepatic enzyme abnormalities and suspected cardiovascular events according to predefined criteria.

Statistical analysis

The study was powered for separate comparisons between enoxaparin and each dabigatran etexilate dose. We assumed that the frequency with which the primary efficacy outcome would occur would be equal across the three groups. In the absence of placebo-controlled trials with enoxaparin given for 28–35 days, we used a pooled analysis of published rates of venous thromboembolism for enoxaparin versus placebo given for 8–14 days.[19–21] This showed an absolute difference in rates of 32·8% (95% CI 23·2–42·6), from which we chose a conservative non-inferiority margin of 7·7%, which preserves two-thirds of the 95% CI difference between enoxaparin and placebo. From recent studies that assessed enoxaparin with the same venogram adjudication committee,[13,22,23] we calculated that a study with 720 assessable patients per group would have at least 95% power, with a one-sided type I error of 0·025, to reject the hypothesis that the primary outcome with dabigatran etexilate would be 7·7% higher than enoxaparin when the rate of thromboembolism with enoxaparin was up to 20%. Assuming that 35% of patients would not have assessable venograms, randomisation of 3330 patients was required.

The safety population consisted of all randomised patients who received at least one dose of study drug. Patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, underwent elective total hip replacement surgery, and had assessable adjudicated data on venous thromboembolism (venography or symptomatic event) or died during treatment were included in the primary efficacy analysis. Patients with inadequate or missing mandatory bilateral venography who neither died nor experienced venous thromboembolic events were excluded from efficacy analyses (ie, efficacy analyses were done by a modified intention-to-treat basis). The two-sided 95% CI for the absolute difference between each dabigatran etexilate dose and enoxaparin was calculated with a normal approximation.

This trial is registered with ClinicalTrials.gov, number NCT00168818.

Role of the funding source

The steering committee was responsible for the study design, in conjunction with the study sponsor. Data collection and analysis were done by the sponsor. An independent data and safety board monitored the study. The steering committee had overall responsibility for the integrity and completeness of the data, accuracy and interpretation of the data analysis, and content of the manuscript. All authors had full access to all the data in the medical report. The steering committee had final responsibility for the decision to submit for publication.

Results

Of 3613 patients enrolled between December, 2004, and April, 2006, 3494 were randomised. Of the randomised patients, 2651 (76%) were included in the primary efficacy analysis (figure). Demographic and surgical characteristics of the three groups were much the same (table 1). Dabigatran etexilate was initiated a mean of 3·4 h after surgery. Overall, median treatment duration was 33 days, with 87% of patients receiving treatment for 28–35 days.

	Dabigatran etexilate		Enoxaparin
	220 mg	150 mg	
Number treated	1146	1163	1154
Age (years)	65 (10)	63 (11)	64 (11)
Sex (female)	636 (56%)	667 (57%)	651 (56%)
Weight (kg)	79 (15)	79 (15)	78 (15)
Creatinine clearance (mL/min)*	89 (29)	90 (31)	89 (30)
History of deep-vein thrombosis or pulmonary embolism	40 (3%)	29 (2%)	30 (3%)
Treated and operated	1137 (99%)	1156 (99%)	1142 (99%)
Type of anaesthesia†			
General alone	293 (26%)	276 (24%)	278 (24%)
Neuraxial alone‡	746 (66%)	766 (66%)	773 (68%)
Combination§	95 (8%)	110 (10%)	90 (8%)
Duration of surgery (min)	85 (29)	85 (29)	87 (29)
Time to first oral dose (h)¶	3·3 (−4·0 to 22·7)	3·5 (−3·6 to 46·4)	3·4 (−3·4 to 37·8)‖
Duration of hospital stay (days)**	9 (7 to 12)	9 (7 to 12)	9 (7 to 12)
Duration of treatment (days)††	32 (1 to 47)	33 (1 to 44)	33 (1 to 47)
Duration of study including follow-up (days)††	94 (1 to 450)	94 (1 to 400)	94 (1 to 392)

Data are mean (SD) or n (%), unless otherwise specified. *Calculated with the Cockcroft–Gault formula. †Patients may have had more than one type of anaesthetic. Data available for 1134, 1152, and 1141 patients, respectively. ‡Includes spinal and epidural anaesthesia. §Peripheral nerve block plus general or neuraxial. ¶Time from operation to first postoperative dabigatran etexilate dose. Data are mean (range). ‖Placebo capsule. **Data are median (IQR). Time from surgery until day of discharge, data available for 1136, 1155, and 1140 patients respectively. ††Data are median (range).

Table 1: **Characteristics of treated and operated patients**

	Dabigatran etexilate		Enoxaparin
	220 mg	150 mg	
Primary efficacy outcome*	53/880 (6·0%, 4·5 to 7·6%)	75/874 (8·6%, 6·7 to 10·4%)	60/897 (6·7%, 5·1 to 8·3%)
Absolute difference *vs* enoxaparin	–0·7% (–2·9 to 1·6%)	1·9% (–0·6 to 4·4%)	..
p value for non-inferiority *vs* enoxaparin†	<0·0001	<0·0001	..
Total asymptomatic deep-vein thrombosis‡	40/874 (4·6%)	63/871 (7·2%)	56/894 (6·3%)
Proximal	18/905 (2·0%)	28/885 (3·2%)	32/914 (3·5%)
Distal only	22/874 (2·5%)	35/871 (4·0%)	24/894 (2·7%)
Symptomatic deep-vein thrombosis‡	6/1137 (0·5%)	9/1156 (0·8%)	1/1142 (0·1%)
Symptomatic pulmonary embolism‡	5/1137 (0·4%)	1/1156 (0·1%)§	3/1142 (0·3%)
Death¶	3/1137 (0·3%)	3/1156 (0·3%)§	0/1142 (0%)
Major venous thromboembolism|| and venous thromboembolism-related mortality**	28/909 (3·1%, 2·0 to 4·2%)	38/888 (4·3%, 2·9 to 5·6%)	36/917 (3·9%, 2·7 to 5·2%)
Absolute difference *vs* enoxaparin	–0·8% (–2·5 to 0·8%)	0·4% (–1·5 to 2·2%)	..
p value for difference *vs* enoxaparin†	0·33	0·71	..

Data are n/N (%), n/N (%, 95% CI), or absolute difference (95% CI). *Total venous thromboembolism and all-cause mortality. †p values are for the comparison of each dabigatran group compared with enoxaparin, calculated with Fisher's exact test. ‡Includes events that occurred within 3 days of last dose of study medication. Patients could have events included in more than one category. §Fatal pulmonary embolism, same patient. ¶Venous thromboembolism could not be excluded in one patient in the dabigatran etexilate 220 mg group and two patients in the dabigatran etexilate 150 mg group. ||Includes proximal deep-vein thrombosis and pulmonary embolism. **Includes all deaths where venous thromboembolism cannot be excluded.

Table 2: **Efficacy outcomes during the treatment period**

Table 2 shows the number of patients in each group that experienced the primary outcome. Both doses of dabigatran etexilate were non-inferior to enoxaparin, since the upper limit of the CI for the absolute difference versus enoxaparin was less than the prespecified non-inferiority margin of 7·7% (table 2). Results were consistent in predefined subgroup analyses by age, sex, body-mass index, time to first oral dose, and duration of treatment (data not shown). There was no significant difference in the absolute difference of major venous thromboembolism and venous thromboembolism-related mortality with either dose of dabigatran etexilate versus enoxaparin during the treatment period (table 2). One fatal pulmonary embolism 4 days after surgery occurred in the dabigatran etexilate 150 mg group. During follow-up, a further three patients developed symptomatic events (one in each group).

Table 3 shows the occurrence of bleeding events during treatment. There was no significant difference in the frequency of major bleeding events during treatment between both dabigatran etexilate doses and enoxaparin (p=0·44 for 220 mg and p=0·60 for 150 mg, respectively). There were two fatal bleeding events. One patient in the 220 mg group developed retroperitoneal bleeding

	Dabigatran etexilate		Enoxaparin (n=1154)
	220 mg (n=1146)	150 mg (n=1163)	
Number of patients with major bleeding*	23 (2·0%, 1·3 to 3·0%)	15 (1·3%, 0·7 to 2·1%)	18 (1·6%; 0·9 to 2·5%)
Fatal	1	1	0
In a critical organ	0	0	0
Clinically overt associated with 20 g/L or more fall in haemoglobin†	18	12	12
Clinically overt leading to transfusion of two or more units of packed cells or whole blood†	21	8	16
Warranting treatment cessation	1	1	1
Leading to re-operation	2	3	3
Onset of major bleeding events‡			
Onset before the first oral dose	13/23 (56·5%)	7/15 (46·7%)	8/18 (44·4%)§
Onset after the first oral dose	10/23 (43·5%)	8/15 (53·3%)	10/18 (55·6%)§
Number of patients with clinically relevant non-major bleeding‡	48 (4·2%)	55 (4·7%)	40 (3·5%)
Number of patients with minor bleeding‡	70 (6·1%)	72 (6·2%)	74 (6·4%)

Data are n (%, 95% CI). For all bleeding outcomes, none of the differences between each dabigatran etexilate dose and enoxaparin were significant. *Patients may have been included in more than one category. †In excess of that expected by the investigator. ‡Data are n/N (%). §Placebo capsule.

Table 3: **Bleeding events during the treatment period**

	Dabigatran etexilate		Enoxaparin (n=1154)
	220 mg (n=1146)	150 mg (n=1163)	
Adverse events during treatment			
Serious adverse events	89 (8%)	91 (8%)	82 (7%)
Total with adverse events	879 (77%)	895 (77%)	892 (77%)
Adverse events leading to treatment discontinuation	74 (6%)	88 (8%)	66 (6%)
Adverse events during treatment with an incidence of ≥3% or difference of ten or more events between any treatment group*			
Nausea	238 (21%)	258 (22%)	289 (25%)
Vomiting	194 (17%)	186 (16%)	191 (17%)
Constipation	146 (13%)	141 (12%)	150 (13%)
Pyrexia	123 (11%)	142 (12%)	162 (14%)
Wound secretion	102 (9%)	96 (8%)	63 (5%)
Hypotension	81 (7%)	77 (7%)	83 (7%)
Insomnia	77 (7%)	88 (7%)	80 (7%)
Peripheral oedema	65 (6%)	81 (7%)	56 (5%)
Anaemia	47 (4%)	39 (3%)	44 (4%)
Dizziness	38 (3%)	38 (3%)	49 (4%)
Wound complication	40 (3%)	37 (3%)	47 (4%)
Deep-vein thrombosis	33 (3%)	55 (5%)	36 (3%)
Diarrhoea	30 (3%)	49 (4%)	36 (3%)
Blister	40 (3·5)	43 (4%)	30 (3%)
Headache	37 (3%)	37 (3%)	39 (3%)
Urinary retention	25 (2%)	25 (2%)	35 (3%)
Post-procedural haematoma	17 (1%)	34 (3%)	26 (2%)
Dyspepsia	22 (2%)	12 (1%)	17 (1%)
Tachycardia	9 (0·8%)	15 (1%)	5 (0·4%)
Dysuria	4 (0·3%)	8 (0·7%)	14 (1%)
Haemorrhage	12 (1%)	2 (0·2%)	11 (1%)

Data are n (%). *According to MedDRA, descending total frequency.

Table 4: **Adverse events**

presumed secondary to an arteriovenous malformation, resulting in hypovolaemic shock and death. One patient in the 150 mg group who received eight doses of study medication had an ischaemic bowel resected but died 1 week later from septicaemia and gastrointestinal bleeding. 51 (91%) of the 56 major bleeding events occurred at the surgical site. There was no bleeding into a critical organ. Three bleeding events (one in each group) required treatment discontinuation. There were eight re-operations due to bleeding. Major bleeding events started before the first oral dose in 57% of patients in the 220 mg group, 47% of those in the 220 mg and 150 mg group, and 44% of those who received enoxaparin. Mean blood loss volumes during and after surgery, wound drainage volumes, need for transfusion, and mean transfusion volumes were similar across the groups (data not shown).

Both doses of dabigatran etexilate had a similar adverse event profile to enoxaparin (table 4). Moderate increases in the concentration of alanine aminotransferase (more than three times the upper limit of the normal range) at any time post-baseline were seen in slightly more patients in the enoxaparin group (60 of 1122 patients [5%]) than with either dose of dabigatran (34 of 1117 patients on 220 mg [3%] and 34 of 1124 patients on 150 mg [3%]; p=0·0081 for 220 mg *vs* enoxaparin and p=0·0061 for 150 mg *vs* enoxaparin; webtable). Besides one patient with acute cholangitis, no clinical signs or symptoms were attributed to these abnormalities. All alanine aminotransferase concentrations returned to baseline or the upper limit of normal with additional follow-up. In one case, a 37-year-old patient in the group receiving 150 mg of dabigatran in whom the baseline alanine aminotransferase concentration was 1·7 times the upper limit of normal had not returned to baseline or the upper limit of normal after 2 years of follow-up. This patient's alanine aminotransferase concentration was recorded as being greater than three times the upper limit of normal only once during the 2 years, and has since returned to baseline levels. One patient in each of the dabigatran etexilate groups had raised concentrations of alanine aminotransferase and a two-fold increase in bilirubin concentration. One of these patients was diagnosed with acute cholangitis but a definitive diagnosis was not made in the other patient. At all time points during treatment, the occurrence of raised liver enzymes with either dose of dabigatran etexilate was consistently lower than with enoxaparin.

See **Online** for webtable

Adjudicated acute coronary events (confirmed unstable angina, myocardial infarction, and cardiac death) were seen in five patients in the dabigatran etexilate 220 mg group, in eight patients in the dabigatran etexilate 150 mg group, and in nine patients in the enoxaparin group during treatment, and in three patients in the enoxaparin group during follow-up.

Discussion

Our results show that oral dabigatran etexilate, 220 mg or 150 mg once daily, given for a median of 33 days, was non-inferior to enoxaparin for reducing the risk of total venous thromboembolism and all-cause mortality after total hip replacement surgery. There was no significant difference in the rates of major venous thromboembolism and thrombosis-related death with either dose of dabigatran etexilate versus enoxaparin. Furthermore, the frequency of bleeding was low and comparable between the three groups. Thus, treatment with dabigatran etexilate is as effective as enoxaparin after total hip replacement for the prevention of venous thromboembolism, with a similar safety profile.

The frequency of asymptomatic deep-vein thrombosis with enoxaparin in this study (6·3%) was similar to that reported (7·7%) in a meta-analysis of nine studies of extended-duration thromboprophylaxis with low-molecular weight or unfractionated heparin in hip replacement patients, involving systematic assessment of venous thromboembolism.[2] As expected, the overall

frequency of venographic or symptomatic venous thromboembolism was markedly reduced compared with previous studies of short-duration prophylaxis (5–11 days). For enoxaparin, studies that used the same venogram definition and adjudication committee reported at that time point a frequency of between 14·9% and 19·4%.[13,22,23] Although not a direct comparison, extending prophylaxis with dabigatran etexilate from a median of 7 days in an earlier dose-ranging study (frequency of deep-vein thrombosis about 13%) to 33 days in the present study reduced the occurrence of venous thromboembolism by about 50%.[13] Similarly, the rate of symptomatic venous thromboembolism during treatment was low (0·4–0·9%) and comparable with that reported with other anticoagulants administered for a similar duration.[4,5,24] The low occurrence of symptomatic events in our study should be interpreted with caution, since the study was not powered to investigate these low-frequency events. The overall higher rate of symptomatic events seen in the two dabigatran etexilate groups (0·9%) compared with enoxaparin (0·4%) is likely to be due to chance in view of a lack of internal consistency between the occurrence of deep-vein thrombosis and pulmonary embolism events in the three treatment groups.

The lowest frequency of pulmonary embolism occurred in the dabigatran etexilate 150 mg group, by direct contrast with that seen for symptomatic deep-vein thrombosis, where the highest rate was noted. There were six deaths during treatment in the two dabigatran etexilate groups versus none in the enoxaparin group. The investigators deemed that none of the deaths were related to study treatment. Although the true frequency of late post-treatment symptomatic events (1–3 months) cannot be documented accurately because of the screening procedure, the very low number of events seen during follow-up suggest that a 4–5-week treatment period could be an appropriate duration of prophylaxis in patients undergoing hip replacement surgery.

Anticoagulation-related bleeding is the primary safety concern in this population, since major bleeding into the replaced joint can have a detrimental effect on clinical outcome.[25] Generally, few major bleeding events were reported. The frequency of such events with dabigatran etexilate (1·3–2·0%) was lower than that seen in a previous dose-ranging study (3·8–4·7%), possibly a result of the reduced first dose on the day of surgery (110 mg or 75 mg *vs* initial doses of 150 mg to 300 mg used previously), when most bleeding events occur.[13] Notably, about half of all major bleeding events started before treatment. There were no major bleeding events reported after hospital discharge in the dabigatran etexilate groups, indicating safety of use in an outpatient setting. Data from frequent liver function monitoring suggest that the risk of hepatic dysfunction with dabigatran etexilate is low during a 4–5-week treatment period and for the following 2 months. Similarly, the frequency of acute coronary events was low and much the same with all treatments. Although the safety and adverse event data are reassuring in that there does not seem to be a difference between dabigatran etexilate and enoxaparin, due to the rarity of these events, much larger datasets need to accrue before any definitive statements can be made.

24% of the patients in this study were not available for assessment for the primary efficacy outcome, an inevitable consequence of the study design adopted for this study and the use of venography to detect asymptomatic deep-vein thrombosis at the end of the treatment period. Large proportions of non-assessable patients are an unavoidable result of the use of venography, whereby patients either do not undergo the procedure or the venogram is inadequate and cannot be adjudicated by a central blinded committee. The number of patients not assessable for the primary outcome in this study is consistent with that reported in previous studies that used venographic deep-vein thrombosis as an endpoint, and lower than the 35% predicted at commencement of the study.[26] Although this approach could be considered to be a methodological weakness of our study, since symptomatic events are fairly rare and difficult to detect clinically after hip replacement surgery, we adopted the approach of the American College of Chest Physicians[1] consensus statement and the European Health Authorities,[17] which recommend the use of a composite endpoint combining clinical events with asymptomatic venographic deep-vein thrombosis. Venographic deep-vein thrombosis is recognised to be a valid surrogate when comparing antithrombotic regimens in the same patient population.[27] In support of the main study findings, we did sensitivity analyses for the primary efficacy endpoint, using best and worst case scenarios (all treatment success or all treatment failure, data not shown) to ensure that missing data, which was comparable between the three treatment groups, did not affect the power of trial or bias any estimation of the treatment effect. Additionally, separate assessments of clinical endpoints showed results consistent with the primary efficacy outcome and none of the patients excluded from the primary efficacy analysis experienced a symptomatic event or died.

The US Hip and Knee Registry covering the 6-year period up to 2002, reported trends for increasing duration of prophylaxis and shorter hospital stays (decreasing to 3·7 days for total hip replacement).[6] These findings highlight the shifting burden of thromboprophylaxis from in-hospital to out-of-hospital, and focus on the need for anticoagulant prophylaxis that is easy to use at home. In our study, more than 70% of doses of dabigatran etexilate were administered out-of-hospital. Good compliance, as assessed by investigator, was seen, with a satisfactory adverse event profile.

On the basis of the ease of once-daily dosing and there being no need for coagulation monitoring, dabigatran etexilate can be considered to be an attractive alternative

to other thromboprophylaxis regimens for patients undergoing total hip replacement surgery. These findings, in conjunction with other results from the large, phase III development programme in total hip and knee replacement surgery,[28,29] will help define the optimum dosage regimen for dabigatran etexilate.

Contributors

BIE was the principal investigator and coordinated the study. OED, NR, AAK, CNvD, SPF, MHP, RH, SH, JS, and HRB all participated in the planning and execution of the study and contributed to the development of the study report. RH was responsible for the overall planning and conduct of the study for the sponsor. SH was responsible for the statistical analysis. All authors (except MHP) were members of the RE-NOVATE steering committee and participated in the writing of the manuscript. All authors have seen and approved the final version of the manuscript.

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Conflict of interest statement

BIE, OED, NR, AAK, CNvD, SPF, MHP, and HRB participated as investigators, consultants, or both, for Boehringer Ingelheim. JS, RH, and SH are employees of Boehringer Ingelheim.

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