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ORIGINAL ARTICLE

A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial

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Summary. *Background*: Dabigatran etexilate is an oral direct thrombin inhibitor undergoing evaluation for the prevention of venous thromboembolism (VTE) following orthopedic surgery. *Methods*: In a multicenter, parallel-group, double-blind study, 1973 patients undergoing total hip or knee replacement were randomized to 6–10 days of oral dabigatran etexilate (50, 150 mg twice daily, 300 mg once daily, 225 mg twice daily), starting 1–4 h after surgery, or subcutaneous enoxaparin (40 mg once daily) starting 12 h prior to surgery. The primary efficacy outcome was the incidence of VTE (detected by bilateral venography or symptomatic events) during treatment. *Results*: Of the 1949 treated patients, 1464 (75%) patients were evaluable for the efficacy analysis. VTE occurred in 28.5%, 17.4%, 16.6%, 13.1% and 24% of patients assigned to dabigatran etexilate 50, 150 mg twice daily, 300 mg once daily, 225 mg twice daily and enoxaparin, respectively. A significant dose-dependent decrease in VTE occurred with increasing doses of dabigatran etexilate ($P < 0.0001$). Compared with enoxaparin, VTE was significantly lower in patients receiving 150 mg twice daily [odds ratio (OR) 0.65, $P = 0.04$], 300 mg once daily (OR 0.61, $P = 0.02$) and 225 mg twice daily (OR 0.47, $P = 0.0007$). Compared with enoxaparin, major bleeding was significantly lower with 50 mg twice daily (0.3% vs. 2.0%, $P = 0.047$) but elevated with higher doses, nearly reaching statistical significance with the 300 mg once-daily dose (4.7%, $P = 0.051$). *Conclusions*: Oral administration of dabigatran etexilate, commenced early in the postoperative period, was effective and safe across a range of doses. Further optimization of the efficacy/safety balance will be addressed in future studies.

Keywords: dabigatran etexilate, deep vein thrombosis, direct thrombin inhibitor, total hip replacement, total knee replacement, venous thromboembolism.

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Introduction

Low-molecular-weight heparins (LMWH) and vitamin K antagonists are routinely used to prevent venous thromboembolism (VTE) following major orthopedic surgery. Both are effective at reducing deep-vein thrombosis (DVT) and pulmonary embolism (PE) [1], although each therapy has limitations. Oral vitamin K antagonists have a narrow therapeutic index and require careful monitoring [2], while LMWH requires parenteral administration.

Dabigatran etexilate is an oral direct thrombin inhibitor (DTI). It is a single chemical entity and the prodrug of the active compound dabigatran which binds to thrombin with high affinity and specificity. The pharmacokinetic profile of dabigatran etexilate in healthy volunteers is characterized by time to peak plasma concentration within 2 h, a biexponential

distribution phase and a terminal half-life of 14–17 h after multiple dose administration [3,4]. An earlier dose escalating study [Boehringer Ingelheim Study in ThROmbosis (BISTRO) I] in patients undergoing total hip replacement (THR) showed dabigatran etexilate to be effective across a range of doses (50–300 mg twice daily) for the prevention of postoperative DVT [5]. A further study using a single 150 mg capsule administered within 3 h of surgery to patients undergoing THR demonstrated an adequate and predictable early postoperative absorption profile (unpublished observations).

The present study explored further the dose–response relationship with regard to efficacy and safety of dabigatran etexilate for prevention of VTE among patients undergoing THR or total knee replacement (TKR). A secondary objective was to compare the efficacy and safety of the different dose regimens of dabigatran etexilate with that of the LMWH, enoxaparin.

Methods

Study design

This was a randomized, parallel-group, double-blind, active controlled study conducted at 60 centers in Europe and two centers in South Africa. On the day before surgery, patients were assigned randomly to five treatment groups, stratified by the study center and surgical procedure (hip or knee replacement), using a computer-generated scheme. Separate medication kits for hip and knee replacement were provided to each site in blocks of 10. Treatment was continued for a total of 6–10 days until mandatory bilateral venography was performed. Continued anticoagulation after this time was at the discretion of the investigator. Patients were assessed at a follow-up visit 4–6 weeks after surgery. The protocol was approved by national independent ethics committees and the study was conducted in accordance with the Declaration of Helsinki.

Patients

Consecutive patients aged 18 years or older, weighing at least 40 kg, scheduled for primary elective THR or TKR and who signed an informed consent were eligible for the study. Exclusion criteria included: any bleeding diathesis; coagulation disorders; history of or acute intracranial disease; major surgery or trauma within the last 3 months; cardiovascular disease including uncontrolled hypertension or history of myocardial infarction within the last 6 months; history of stroke; DVT, gastrointestinal or pulmonary bleeding within the last year; known liver disease [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 3 \times$ upper limit of normal (ULN)]; renal disease (serum creatinine $> 1.5 \times$ ULN); use of long-term anticoagulants, antiplatelet drugs (except low-dose aspirin up to 160 mg daily), or fibrinolytics within 7 days prior to surgery (also contraindicated during the treatment period); allergy to radiopaque contrast media; thrombocytopenia (platelet count $< 100 \times 10^9$/L); active malignant disease; current cytostatic treatment or recent treatment with an investigational drug. Women of childbearing potential, those with leg amputations and known alcohol or drug abuse were also excluded.

Treatment schedule

Patients were assigned to either oral dabigatran etexilate with doses of 50 and 150 mg twice daily, 300 mg once daily and 225 mg twice daily, or 40 mg of enoxaparin (Aventis Pharma, Bridgewater, NJ, USA) subcutaneously, once daily. Both study groups received active or matching placebo medications. Each patient received three capsules in the morning and evening and daily subcutaneous injection in the evening. The first dose of dabigatran etexilate was administered 1–4 h after completion of surgery, or as early as possible. The second dose was given on the same day only if it resulted in a dosing interval of at least 8 h. The first subcutaneous injection was given in the evening before surgery and was continued once daily until venography. In some countries, due to differing regional guidelines, the first subcutaneous dose could be started postoperatively.

Concomitant treatment with long-acting non-steroidal anti-inflammatory drugs was prohibited during the treatment period. However, short-acting non-steroidal anti-inflammatory drugs with half lives of less than 12 h, low-dose aspirin and selective cyclo-oxygenase-2 (COX-2) inhibitors were allowed. Antacids could be used, although administration was limited to 2 h prior to or following study drug administration. Elastic compression stockings were allowed, but intermittent pneumatic compression devices were prohibited.

Efficacy assessments

The primary efficacy outcome was the incidence of VTE, being symptomatic, or venographically detected DVT and/or PE detected during the treatment period. Bilateral venography was performed within 12 h of the last dose of oral medication according to a modification of the Rabinov and Paulin technique, requiring at least nine images per leg [6–9]. This required venography to be performed in a semiupright position (preferably 60° elevation from horizontal), using adequate volumes of contrast media (preferably 100 mL per leg), and without use of lower limb tourniquets. Venograms were judged adequate for evaluation if they demonstrated bilaterally complete visualization of all deep veins or if a DVT was found. DVT was diagnosed when a constant intraluminal filling-defect was seen on at least two images. Proximal DVT was defined as DVT in or above the popliteal vein. PE was diagnosed by ventilation–perfusion scintigraphy, pulmonary angiography or spiral computerized tomography (CT) based on accepted criteria for diagnosis [10]. Symptomatic DVT during hospitalization required confirmation by venography. Symptomatic DVT during follow-up were confirmed by ultrasound or venography. All tests for VTE during the treatment period were first evaluated locally and subsequently

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

Safety assessments

The primary safety outcome was major bleeding during the treatment period, defined as clinically overt bleeding associated with ≥ 20 g L^{-1} fall in hemoglobin; clinically overt leading to transfusion of ≥ 2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. Clinically significant bleeding events were defined as: spontaneous skin hematoma ≥ 25 cm^2, wound hematoma ≥ 100 cm^2, epistaxis > 5 min, spontaneous macroscopic hematuria or that lasting > 24 h if associated with an intervention, spontaneous rectal bleeding, gingival bleeding > 5 min, and any other bleeding event judged as clinically significant by the investigator. Minor bleeding events were defined as those not fulfillling the criteria of major or clinically significant bleeding. A composite endpoint of major bleeding and clinically significant bleeding was utilized to assess bleeding events according to the dose administered. Blood loss (perioperative and postoperative) and transfusion volumes were measured during the treatment period. A centralized independent committee classified all bleeding events.

Pharmacokinetic assessments

Plasma concentrations of dabigatran were measured to determine the pharmacokinetic profile of dabigatran in the postoperative setting. Plasma samples were analyzed for quantitative determination of dabigatran concentrations using a validated liquid chromatography–tandem mass spectroscopy method [11]. In a subgroup of 325 patients, dabigatran plasma concentrations were measured on day 1 (day of surgery) and days 4 or 5 pre-dose and then at 0–1, 1–2, 2–4, 4–8 and 12 h post-dose. Maximum plasma concentrations (C_{max}) and time to attain maximum plasma concentrations (t_{max}) were calculated.

Statistical analyses

Based on information from a previous study [5], we assumed that the DVT rate for dabigatran etexilate would range from 24 to 40% (lowest dose) to less than 15% (highest dose). To demonstrate these differences with 90% power at a 5% level of significance, randomization of 2000 patients (400 per treatment group) was required, assuming that 25% of patients would not have evaluable venograms. All statistical analyses were performed on an intention-to-treat basis. The safety population comprised all randomized patients who received at least one subcutaneous injection or one oral dose of study drug. Those patients who also underwent surgery and had centrally adjudicated data on VTE (venography or symptomatic confirmed event) by day 10 were considered for the efficacy analysis.

A logistic regression analysis examined the dose effect of dabigatran etexilate on the primary efficacy outcome. For this analysis, the 150 mg twice-daily and 300 mg once-daily dose groups were pooled. The number of patients with VTE and bleeding parameters was evaluated in each dose group with 95% CI. Between-group efficacy comparisons are presented as odds ratios (OR) with 95% CI. A *post hoc* analysis examined the effect of timing of the first postoperative dose of dabigatran etexilate on efficacy and safety outcomes.

Pharmacokinetic parameters of dabigatran etexilate were calculated using non-compartmental methods and summarized using descriptive statistics. A logistic regression model was developed to examine the relationship between C_{max} and the primary efficacy and safety outcomes.

Results

Patients

Of the 2039 patients enrolled between November 2002 and August 2003, 1973 were randomized to either dabigatran etexilate (1576) or enoxaparin (397) (Fig. 1). Of these, 24 were not treated. The safety population comprised 1949 patients who received at least one dose of study drug. Two hundred and fifteen patients discontinued treatment early, 99 due to an adverse event. The efficacy population comprised 1464 patients.

Patient demographic and surgical characteristics were similar for all five treatment groups (Table 1). The mean age was 66 years (range 20–93 years), and 61% of the patients were female. Two-thirds of patients underwent THR (68%) and a third TKR (32%). Regional anesthesia was used in 73% of operations. The mean time interval between surgery and first dose of dabigatran etexilate was 2.6 h. The median duration of treatment was 7 days. One patient in the dabigatran etexilate group did not have any assessment during the treatment period. After the treatment period, nine (0.6%) of 1557 patients in the dabigatran etexilate group and 3 (0.8%) of 392 patients in the enoxaparin group were lost to follow-up at 4–6 weeks.

Efficacy results

The incidence of centrally adjudicated VTE events are summarized in Table 2. There was a significant dose dependent decrease in the frequency of VTE with increasing doses of dabigatran etexilate ($P < 0.0001$). This occurred for both distal and proximal DVT, and among the two surgical groups. The lowest rate of VTE (13.1%) and proximal DVT (1.7%) occurred in the highest dose group (225 mg twice daily). Correspondingly, the highest rate of VTE (28.5%) and proximal DVT (5%) occurred in the lowest dose group (50 mg twice daily). There was no significant difference in VTE between 300 mg once daily and 150 mg twice daily (OR 0.94, 95% CI 0.60–1.47).

Compared with enoxaparin, VTE was significantly lower in patients receiving 150 mg twice daily (17.4% vs. 24.0%, OR 0.65, 95% CI 0.43–0.98, $P = 0.04$), 300 mg once daily (OR

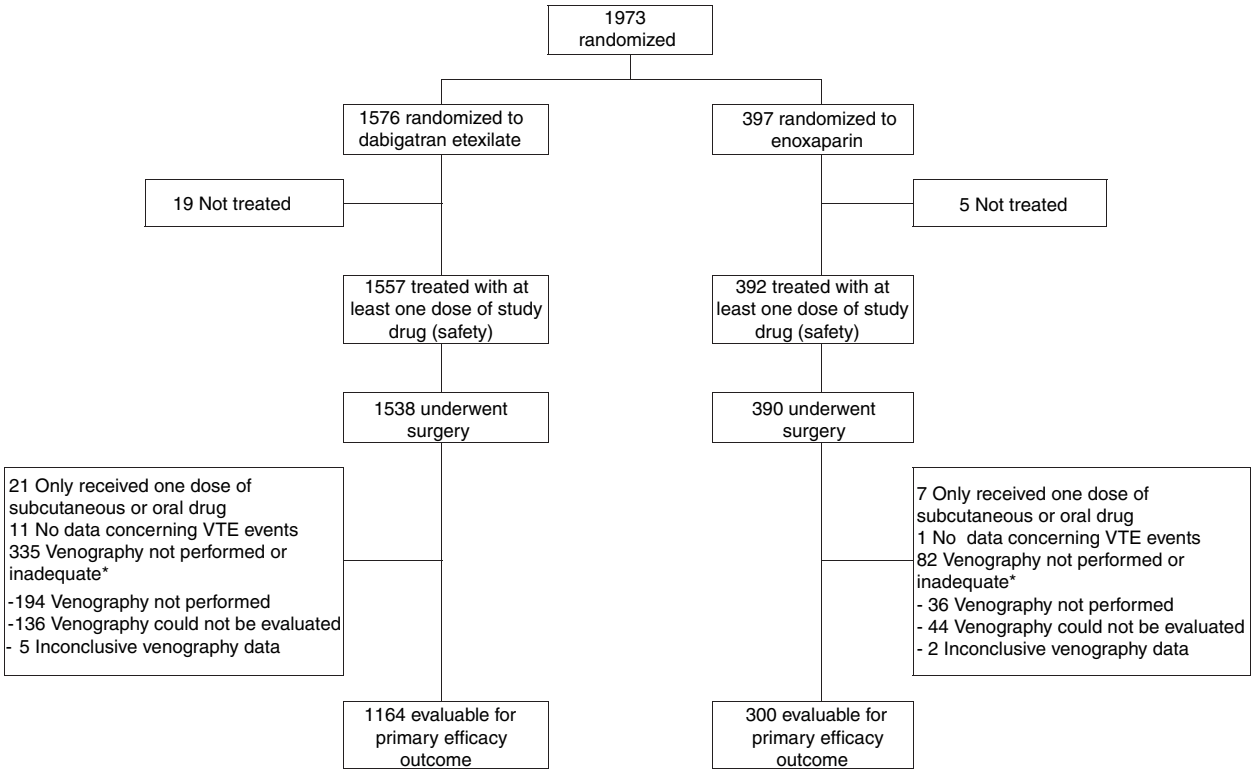

Fig. 1. Trial profile. VTE, venous thromboembolism. *Venography was considered adequate by the central adjudication committee if films were provided visualizing the proximal and distal deep veins in both legs. If deep vein thrombosis was seen in any one of the veins visualized, the patient was considered to be suitable for the efficacy outcome even if the venous system was not visualized entirely.

Table 1 Baseline characteristics of all treated patients

Characteristic	Dabigatran etexilate groups				Enoxaparin 40 mg qd	Total
	50 mg bid	150 mg bid	300 mg qd	225 mg bid		
N	389	390	385	393	392	1949
Age, year, mean (range)	66.1 (31–88)	65.9 (34–89)	66.5 (21–88)	65.9 (33–93)	65.0 (20–86)	65.9 (20–93)
Weight, kg, mean (range)	79 (46–125)	79 (44–130)	79 (43–128)	79 (44–130)	79 (47–125)	79 (43–130)
Female sex						
n (%)	223 (57.3)	252 (64.6)	246 (63.9)	229 (58.3)	241 (61.5)	1191 (61.1)
Operated and treated						
n (%)	380 (97.7)	385 (98.7)	380 (98.7)	386 (98.2)	390 (99.5)	1921 (98.6)
Type of surgery, *n*						
Total hip replacement	258	263	253	264	268	1306
Total knee replacement	122	122	127	122	122	615
Type of anesthesia, *n* (%)						
General	100 (26.3)	105 (27.3)	98 (25.8)	106 (27.5)	109 (27.9)	518 (27.0)
Epidural, spinal or both	280 (73.7)	280 (72.7)	282 (74.2)	280 (72.5)	281 (72.1)	1403 (73.0)
Duration of surgery (h)						
Mean	1.4	1.5	1.4	1.4	1.5	1.4
Range	0.5–3.9	0.5–5.4	0.5–3.9	0.5–3.6	0.4–4.6	0.4–5.4
Time to first oral dose (h)*						
Mean	2.6	2.7	2.6	2.7	2.6	2.6
Range	− 2.9–10.4	− 15.1–20.2	− 2.7–8.0	0.3–26.9	− 6.2–15.9	− 15.1–26.9

bid, twice daily; *n*, number of patients; *N*, number of patients treated; qd, once daily. *Time from operation to first postoperative dabigatran etexilate administration.

0.61, 0.40–0.92, $P = 0.02$) and 225 mg twice daily (OR 0.47, 0.30–0.73, $P = 0.0007$). This superior efficacy was similar in both surgical groups. Overall, no significant difference in VTE or proximal DVT was seen between 50 mg twice daily and enoxaparin (28.5% vs. 24%, $P = 0.24$; and 5% vs. 5.6%, $P = 0.57$).

A *post hoc* analysis of the incidence of VTE according to timing of the first dose of dabigatran etexilate showed a

Table 2 Efficacy outcomes during the treatment period

Characteristic	Dabigatran etexilate groups				Enoxaparin 40 mg qd	Total
	50 mg bid	150 mg bid	300 mg qd	225 mg bid		
Total population						
VTE evaluable patients*	302	282	283	297	300	1464
Patients with VTE (%)	86 (28.5)	49 (17.4)	47 (16.6)	39 (13.1)	72 (24.0)	293 (20.0)
(95% CI)	(23.5–33.9)	(13.1–22.3)	(12.5–21.5)	(9.5–17.5)	(19.3–29.2)	(18.0–22.2)
Patients with DVT (%)†	86 (28.5)	47 (16.8)	47 (16.6)	39 (13.1)	72 (24.0)	291 (19.9)
Proximal DVT	15 (5.0)	9 (3.3)	6 (2.1)	5 (1.7)	17 (5.6)	52 (3.6)
Distal DVT	79 (26.2)	43 (15.4)	43 (15.2)	36 (12.1)	67 (22.3)	268 (18.3)
Composite proximal DVT/PE	15 (5.0)	11 (4.0)	6 (2.1)	5 (1.7)	17 (5.6)	54 (3.7)
Total hip replacement						
VTE evaluable patients*	208	201	191	204	208	1012
Patients with VTE (%)	49 (23.6)	27 (13.4)	25 (13.1)	17 (8.3)	31 (14.9)	149 (14.7)
(95% CI)	(18.0–29.9)	(9.0–18.9)	(8.7–18.7)	(4.9–13.0)	(10.4–20.5)	(12.6–17.1)
Patients with DVT (%)†	49 (23.6)	26 (13.0)	25 (13.1)	17 (8.3)	31 (14.9)	148 (14.6)
Proximal DVT	12 (5.7)	8 (4.0)	3 (1.5)	4 (2.0)	11 (5.2)	38 (3.7)
Distal DVT	42 (20.2)	22 (11.0)	22 (11.6)	14 (6.9)	26 (12.5)	126 (12.5)
Composite proximal DVT/PE	12 (5.7)	9 (4.5)	3 (1.5)	4 (2.0)	11 (5.2)	39 (3.8)
Total knee replacement						
VTE evaluable patients*	94	81	92	93	92	452
Patients with VTE (%)	37 (39.4)	22 (27.2)	22 (23.9)	22 (23.7)	41 (44.6)	144 (31.9)
95% CI	(29.4–50.0)	(17.9–38.2)	(15.6–33.9)	(15.5–33.6)	(34.2–55.3)	(27.6–36.4)
Patients with DVT (%)†	37 (39.4)	21 (26.3)	22 (23.9)	22 (23.4)	41 (44.6)	143 (31.6)
Proximal DVT	3 (3.4)	1 (1.3)	3 (3.4)	1 (1.1)	6 (6.6)	14 (3.2)
Distal DVT	37 (39.4)	21 (26.3)	21 (22.8)	22 (23.4)	41 (44.6)	142 (31.4)
Composite proximal DVT/PE	3 (3.4)	2 (2.6)	3 (3.4)	1 (1.1)	6 (6.6)	15 (3.4)

bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; qd, once daily; VTE, venous thromboembolism. *Evaluable patients for the total VTE population only. †Patients with more than one DVT are shown in both distal and proximal categories.

consistent finding in all dose groups. VTE was significantly lower among patients administered their first oral dose of dabigatran etexilate within 2 h postoperatively [70/498 (14.1%)] compared with when it was given beyond 2 h [121/539 (22.4%), $P = 0.0005$].

During the treatment period five patients developed symptomatic VTE, which was more common in the patients undergoing TKR [four of 452 (0.9%)] compared with those undergoing THR [one of 1012 (0.1%)]. Two events were PE, occurring in the 150 mg group [two of 282 (0.7%)]. Two DVT occurred in the 50 mg group (both undergoing TKR), with one DVT in the enoxaparin group undergoing TKR. During the follow-up period, a further five patients developed symptomatic VTE (three in THR and two in TKR). These events occurred in the 50 mg (one DVT, one PE), 150 mg (one DVT) and 300 mg (two DVT) groups. Of the 295 DVT, 248 (85%) occurred in the operated leg.

Safety results

The frequency of bleeding events is shown in Table 3. Most major bleeding events occurred on the day of surgery [33 of 58 (57%)] with the majority at the surgical site [52 of 58 (90%)]; no case of bleeding into a critical organ was observed. Four patients (one in each of the three highest dabigatran etexilate groups and one in the enoxaparin group) required reoperation due to bleeding. Across the dabigatran etexilate doses, major bleeding episodes were significantly higher in the 150 and 225 mg twice-daily and 300 mg once-daily dosage groups compared with the 50 mg twice daily group (analysis not shown). The increase in bleeding was irrespective of the surgical procedure. Clinically significant bleeding and the composite endpoint of major and clinically significant bleeding showed similar results compared with the primary safety outcome.

Compared with enoxaparin, major bleeding was significantly lower in the 50 mg twice-daily dose group (0.3% vs. 2.0%, $P = 0.047$), while showing a non-significant trend for increased bleeding in those receiving 150 mg twice daily (4.1%, $P = 0.10$), 225 mg twice daily (3.8%, $P = 0.15$) and 300 mg once daily (4.7%, $P = 0.051$).

A *post hoc* analysis of bleeding events in relation to timing of the first administration of dabigatran etexilate was performed for patients receiving their first oral dose either 0–2 h, 2–4 h or more than 4 h postoperatively. No significant correlation between the timing of the first dose and bleeding events was demonstrated for any dose. Major bleeding occurred in 18/628 (2.9%) when given 0–2 h, 22/688 (3.2%) when given 2–4 h ($P = 0.75$), and in 9/185 (4.9%) when given > 4 h ($P = 0.24$).

Mean transfusion volumes were lowest in patients receiving 50 mg twice daily (689 mL) and highest in the 225 mg twice-daily group (839 mL) (Table 4). Bleeding warranting treatment discontinuation, as judged by the adjudication committee, was distributed evenly across the higher dabigatran etexilate dose groups (six in the 150 mg group, 10 in the 300 mg group, six in the 225 mg group), with no significant difference compared with enoxaparin (five events). No deaths occurred during the

Table 3 Safety outcomes

Characteristic	Dabigatran etexilate groups				Enoxaparin 40 mg qd
	50 mg bid	150 mg bid	300 mg qd	225 mg bid	
Total population	389	390	385	393	392
Major bleeding, *n* (%; 95% CI)	1 (0.3; 0.0–1.4)	16 (4.1; 2.4–6.6)	18 (4.7; 2.8–7.3)	15 (3.8; 2.2–6.2)	8 (2.0; 0.9–4.0)
Clinically significant bleeding, *n* (%)	9 (2.3)	16 (4.1)	19 (4.9)	20 (5.1)	10 (2.6)
Composite major or clinically significant bleeding, *n* (%)	10 (2.6)	32 (8.2)	32 (8.3)	33 (8.4)	18 (4.6)
Minor bleeding, *n* (%)	18 (4.6)	31 (7.9)	37 (9.6)	38 (9.7)	25 (6.4)
Total hip replacement	265	266	258	270	270
Major bleeding, *n* (%)	0	10 (3.8)	12 (4.7)	12 (4.4)	6 (2.2)
Clinically significant bleeding, *n* (%)	5 (1.9)	11 (4.1)	12 (4.7)	15 (5.6)	7 (2.6)
Composite major or clinically significant bleeding, *n* (%)	5 (1.9)	21 (7.9)	21 (8.2)	26 (9.6)	13 (4.8)
Minor bleeding, *n* (%)	11 (4.2)	23 (8.6)	22 (8.5)	28 (10.4)	14 (5.2)
Total knee replacement	124	124	127	123	122
Major bleeding, *n* (%)	1 (0.8)	6 (4.8)	6 (4.7)	3 (2.4)	2 (1.6)
Clinically significant bleeding, *n* (%)	4 (3.2)	5 (4.0)	7 (5.5)	5 (4.1)	3 (2.5)
Composite major or clinically significant bleeding, *n* (%)	5 (4.0)	11 (8.8)	11 (8.6)	7 (5.7)	5 (4.1)
Minor bleeding, *n* (%)	7 (5.6)	8 (6.5)	15 (11.8)	10 (8.1)	11 (9.0)

bid, twice daily; *n*, number of patients with event; qd, once daily. Patients with both major and clinically significant bleeding were only counted once in the composite outcome.

Table 4 Blood loss and transfusions

Characteristic	Dabigatran etexilate groups				Enoxaparin 40 mg qd
	50 mg bid	150 mg bid	300 mg qd	225 mg bid	
Total population	389	390	385	393	392
Volume of blood loss, ml, mean (SE)					
During surgery	392 (19)	406 (19)	381 (17)	410 (19)	417 (19)
Post-op drainage	688 (24)	707 (25)	706 (25)	714 (24)	649 (23)
Blood transfusion					
Patients requiring transfusion, *n* (%)	1 (0.3)	21 (5.4)	19 (4.9)	16 (4.1)	14 (3.6)
Mean transfusion volume, ml, mean (SE)	689 (43)	761 (42)	792 (42)	839 (61)	703 (32)
Total hip replacement	698 (56)	794 (55)	830 (51)	878 (79)	707 (39)
Total knee replacement	661 (45)	674 (48)	690 (71)	726 (55)	688 (58)

bid, twice daily; n, number of patients with event; qd, once daily; SE, standard error.

treatment period, while during the follow-up period two deaths occurred in patients with active malignancy (50 mg and 225 mg dose groups). Fatal PE could not be excluded as a cause of death in one of these patients.

Pharmacokinetic parameters

Following initial oral administration of dabigatran etexilate 1–4 h (mean 2.6 h) after surgery, plasma concentrations of dabigatran increased slowly and in proportion to the dose (median t_{max} of 3.7–4.5 h) to reach mean peak plasma concentrations of 24.5–132 ng mL^{-1}. Once steady state conditions were reached (days 4–5) mean peak plasma concentrations were higher (48.0–271 ng mL^{-1}) and occurred earlier (t_{max} 2.3–2.9 h) compared with administration on the day of surgery.

A logistic regression analysis model of C_{max} following administration of the first dose showed a strong correlation with efficacy and safety outcomes (Fig. 2). Within the range of clinically relevant (major plus clinically significant) bleeding events seen in the study (2–5%), there was a strong correlation with C_{max} with narrow CIs. A 5% rate of clinically relevant bleeding corresponded to a predicted C_{max} of dabigatran of 40 ng mL^{-1}. At this plasma concentration, the first dose of dabigatran etexilate is predicted to be 75 mg with a DVT rate of 13%.

Adverse events

A total of 98 patients reported 160 serious adverse events during the treatment period, 24 of whom were judged attributable to the study drug by the investigators (none in the 50 mg group, four in the 150 mg group, 12 in the 300 mg group, six in the 225 mg group, two in the enoxaparin group). The liver enzymes AST and ALT increased during treatment in all dose groups. These elevations were all mild and were not associated with any increase in bilirubin levels. ALT increases judged to be of possible clinical significance (3 × ULN) were lower in the dabigatran etexilate groups [five of 344 (1.5%) to

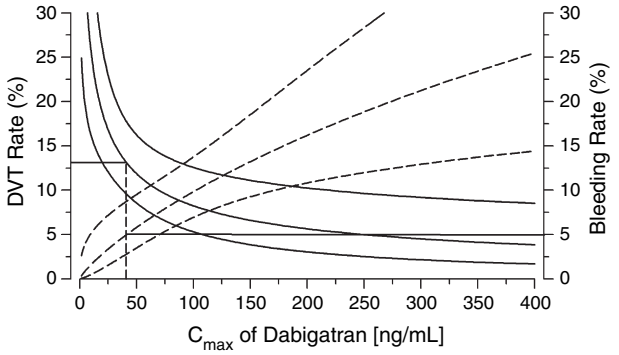

Fig. 2. Logistic regression analysis of C_{max} on day 1 vs. efficacy and safety. DVT, deep vein thrombosis; C_{max}, maximum plasma concentrations. Logistic regression of DVT (solid curves) and clinically relevant (major plus clinical significant) bleeding (dashed curves) illustrating their correlation with maximum plasma concentrations of dabigatran following administration of the first dose of dabigatran etexilate. The median percentage of events and corresponding 95% CI are demonstrated. A 5% rate of clinically relevant bleeding (solid horizontal line) corresponds to a predicted dabigatran plasma concentration of 40 ng mL^{-1} and a DVT rate of 13%. Data were obtained from patients participating in the pharmacokinetic substudy ($n = 351$).

10 of 327 (3.1%)] compared with enoxaparin [26 of 352 (7.4%)]. There were no cases of clinically relevant thrombocytopenia. No difference in other adverse events was seen between groups during the treatment or follow-up period.

Discussion

In this study, all doses of dabigatran etexilate commenced early in the postoperative period were effective in preventing VTE following major joint replacement surgery. This treatment effect was dose dependent and consistent in patients undergoing both THR and TKR. Bleeding was also dose dependent with higher doses of dabigatran etexilate showing an increase in all bleeding parameters. Evidence of a dose relationship for efficacy and safety therefore achieved the main objective of this study. Furthermore, the three highest doses of dabigatran etexilate were significantly more effective than enoxaparin.

Bleeding is recognized to be a potential complication with the use of any anticoagulant in patients undergoing surgery. The improved efficacy of the higher doses of dabigatran etexilate compared with enoxaparin were associated with higher rates of major bleeding. In particular, only the 50 mg twice-daily dose of dabigatran etexilate showed significantly lower rates of major bleeding compared with enoxaparin. Higher doses were associated with a 2-fold increase in major bleeding events compared with enoxaparin, suggesting that the optimal total daily dose for dabigatran etexilate is between 100 and 300 mg per day.

A *post hoc* analysis of efficacy and bleeding according to timing of the first dose of dabigatran etexilate showed that VTE was lower among patients receiving their first dose within 2 h postoperatively without any associated increase in major or clinically significant bleeding. Possible reasons for this lack of increased bleeding may be the oral route of administration of dabigatran etexilate, which results in slower absorption and reduced maximal plasma concentrations compared with steady state conditions. This contrasts with results for the DTI melagatran [12,13], and the factor Xa inhibitor fondaparinux [14] where the first dose is administered subcutaneously close to surgery. Both therapies demonstrate superior efficacy compared with LMWH, although being compromised by an increase in bleeding events. This may be related to the more rapid systemic bioavailability and higher peak concentrations observed with parenteral administration of these agents [15,16].

As noted in the BISTRO I study [5], and now confirmed in this larger cohort study, once-daily dosing of 300 mg dabigatran etexilate shows almost identical efficacy and bleeding rates compared with twice-daily dosing of 150 mg. These once- and twice-daily dosing regimens resulted in identical overall drug exposure at steady state but, as expected, a larger peak–trough difference was observed with once-daily administration of the same daily dose. When plasma concentration data were combined with clinical outcomes of clinically relevant bleeding (major plus clinically significant) and VTE events, the optimal efficacy–safety balance for different dosing regimens of dabigatran etexilate was predicted by a theoretical logistic regression model. Using this model, maximal plasma concentrations following administration of the first dose showed a strong correlation with the efficacy and safety outcomes. This model will be utilized to help select doses in upcoming phase III studies.

In summary, this study demonstrates a dose relationship for both efficacy and safety following postoperative administration of dabigatran etexilate. Furthermore, the three higher doses of dabigatran etexilate, commenced within 1–4 h postoperatively, were significantly more effective than enoxaparin (40 mg once daily) starting preoperatively, although appearing to result in an increase in bleeding events.

Author contributions

Bengt Eriksson was the principal investigator and coordinated the study. Ola Dahl, Harry Büller, Rohan Hettiarachchi, Nadia Rosencher, Marie-Laure Bravo, Lennart Ahnfelt, Franco Piovella, Joachim Stangier, Peter Kälebo, and Paul Reilly all participated in the planning and execution of the study and contributed to the development of the study report. Rohan Hettiarachchi was responsible for the overall planning and conduct of the study for the sponsor. Marie-Laure Bravo was responsible for the statistical analysis. All authors were members of the BISTRO II steering committee (except Peter Kälebo) and participated in the writing of the manuscript.

Declaration of conflicts of interest

R. Hettiarachchi, M-L. Bravo, J. Stangier and P. Reilly are all employees of Boehringer Ingelheim. B. Eriksson, O. Dahl, H. Büller, N. Rosencher, L. Ahnfelt, F. Piovella, and P. Kälebo were all investigators during the study and received grants for enrolling patients.

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