Dabigatran Etexilate Prevents Venous Thromboembolism After Total Knee Arthroplasty in Japanese Patients With a Safety Profile Comparable to Placebo

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Abstract: We assessed the efficacy, safety, and dose-response of dabigatran etexilate (DAB) in preventing venous thromboembolism (VTE) in Japanese patients undergoing total knee arthroplasty (TKA). Five hundred twelve patients received DAB (110, 150, or 220 mg) or placebo once daily for 11 to 14 days, starting the day after surgery. The primary efficacy end point was the incidence of total VTE and all-cause mortality; the primary safety end point was incidence of major, clinically relevant, and minor bleeding events. Total VTE and all-cause mortality were lower in patients receiving DAB (39.6%, 32.7%, and 24.0%) than placebo (56.4%). There was no difference in the incidence of major bleeding between the DAB and placebo groups. Overall, DAB reduced the incidence of VTE in Japanese patients undergoing TKA, with a comparable safety profile vs placebo. **Keywords:** dabigatran etexilate, direct thrombin inhibitor, total knee arthroplasty, venous thromboembolism.
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Venous thromboembolism (VTE) is a potentially serious complication of major orthopedic surgery and is particularly common after total knee arthroplasty (TKA) and total hip arthroplasty (THA) [1,2]. As a result, aggressive thromboprophylaxis using drugs such as low-molecular-weight heparin (LMWH) is recommended and widely used throughout the world in patients undergoing these and similar major orthopedic procedures [2]. Recently, enoxaparin and fondaparinux have been approved for parenteral thromboprophylaxis in patients after TKA or THA in Japan. At the time of the study, LMWH or fondaparinux was not approved for this indication in Japan, so thromboprophylaxis comprised intermittent pneumatic compression or use of low-dose unfractionated heparin. However, the efficacy of the dose of unfractionated heparin used in Japan (less than half of that used in Western countries) had not been proven. Hence, as there was no standard drug available at the time in Japan for the primary prevention of VTE after orthopedic surgery, a randomized, parallel-group, placebo-controlled study was performed.

The importance of VTE in Japanese patients is increasingly recognized [3-5]. Although the incidence of VTE in Japanese patients was at one point thought to be low, it is now a major health issue and recent data have suggested that the risk is similar to their white counterparts when undergoing orthopedic surgery of the lower limbs (49%-80% and 41%-85% after TKA, and 23%-43% and 42%-57% after THA in Japanese and white patients, respectively) [2,6,7]. In recognition of the risk of VTE in Japanese patients after orthopedic surgery, guidelines for preventing VTE were introduced in 2004. However, approvals of anticoagulant therapies for thromboprophylaxis were not granted until April 2007 (fondaparinux) and January 2008 (LMWH). Our study was initiated in 2005 at a time when the efficacy of several anticoagulants was being investigated in the

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Japanese population, and when a new agent, dabigatran etexilate, was also entering phase III clinical trials.

Dabigatran etexilate is a novel, reversible, selective, oral, direct thrombin inhibitor [7,8] with a rapid onset of action, predictable pharmacodynamic effects, and pharmacokinetic characteristics that allow once-daily dosing [9,10]. Currently under investigation for the prevention of VTE in a variety of thromboembolic indications, this agent has already shown efficacy at least equivalent to that of enoxaparin in preventing VTE in white patients after TKA (the RE-MODEL trial [11]) and THA (the RE-NOVATE trial [12]) when administered at doses of 150 and 220 mg. Based on these findings, dabigatran etexilate was approved in Europe for prevention of VTE after orthopedic surgery [13]. In view of the current lack of data on VTE prevention in Japanese patients and possible differences in body weight and pharmacokinetics between Japanese and white subjects, the aim of the present study was to compare the efficacy and safety of 3 doses of dabigatran etexilate (110, 150, and 220 mg) with that of placebo, as well as to evaluate its dose-response, when used for the prevention of VTE in Japanese patients undergoing primary elective TKA.

Patients and Methods

Study Design

This was a double-blind, multicenter, randomized, parallel-group, placebo-controlled study conducted at 38 centers in Japan. The study was performed in accordance with the Declaration of Helsinki (October 1996 version), with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and with the Japanese GCP (Ministry of Health and Welfare Ordinance No. 28, March 1997). Before participation in the trial, written informed consent was obtained from each patient. Patients were randomly assigned to 1 of 4 treatment groups using a computer-generated scheme stratified by study center. Randomization was performed in blocks of 4.

Patients

Male and female patients were eligible for inclusion in the trial if they met the following criteria: age of at least 20 years; weight of 40 kg or higher; primary, unilateral, elective TKA; and provision of signed, informed consent. Exclusion criteria were as follows: any bleeding diathesis; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; clinically relevant bleeding or gastric/duodenal ulcer within the last 6 months; history of hemorrhagic stroke or acute intracranial bleeding; history of VTE or preexisting condition requiring anticoagulant therapy; severe liver disease or elevated aspartate aminotransferase or alanine aminotransferase (ALT) levels to more than 2 times the upper limit of normal range (ULN); significant renal disease; treatment with anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs with $t_{1/2}$ of more than 12 hours within 7 days before TKA; anticipated requirement for intermittent pneumatic compression of lower limb; pregnancy or women of child-bearing potential; history of thrombocytopenia; previous leg amputation; and active malignant disease.

Treatment Regimens

Patients were randomly assigned to oral dabigatran etexilate 110, 150, or 220 mg once daily, or placebo once daily. All 4 groups received 2 capsules per day (1 verum and 1 placebo capsule [dabigatran etexilate 110 mg], 2 verum capsules [dabigatran etexilate 2 × 75 mg or 2 × 110 mg, respectively], or 2 placebo capsules [placebo]); verum and placebo capsules were identical in appearance. The first oral dose was administered as early as possible on the day after surgery (or at least 2 hours after removing the indwelling catheter and confirming the absence of abnormal bleeding from the drainage sites). The second dose was administered 8 hours or more after the first, with subsequent daily doses being administered at 08:00 AM (±1 hour). All capsules had to be taken with at least 100 mL of water and could be taken before or after a meal. Treatment continued for 11 to 14 days after surgery; at the end of treatment, bilateral venography was performed. A follow-up examination was conducted 7 to 10 days after the last administration of trial medication; the clinical trial was considered completed for each patient if no abnormal findings were noted at this time.

The concomitant use of elastic compression stockings and dressings was allowed. Postoperative use of intermittent pneumatic compression was not permitted. The concomitant use of anticoagulants and antiplatelet agents was also prohibited until at least 24 hours after the last administration of study drug.

Endpoint Measures

The primary efficacy end point was a composite of total VTE events (symptomatic/venographic proximal or distal deep venous thrombosis [DVT] and/or pulmonary embolism [PE]) and all-cause mortality during treatment. Secondary efficacy end points included a composite of major VTE (proximal DVT and PE) and VTE-related mortality; total DVT; symptomatic DVT; symptomatic PE; proximal DVT; and death. Bilateral venography was performed within 12 hours of the last dose of study medication. Symptomatic DVT was confirmed by venous duplex ultrasound, high-speed contrast computed tomography, or venography, whereas PE was confirmed by pulmonary scintigraphy, pulmonary angiography, or contrast computed tomography. Diagnostic tests for VTE were evaluated centrally by an independent adjudication committee blinded to treatment allocation. The rules for adjudication were the

same as those in the other 3 pivotal phase III trials (RE-MODEL [11], RE-MOBILIZE [14], and RE-NOVATE [12]). The results of the adjudication were used in the primary efficacy analysis.

The primary safety end point was the occurrence of bleeding events during study treatment. Bleeding events were classified as major, clinically relevant, or minor, according to the accepted European guidelines [15]. Surgical wound site bleeding was included in the bleeding event. Two medical experts reviewed all cases of bleeding. Hematology and clinical chemistry tests were performed before treatment (visit 1), on the last day of dosing (visit 4), and 7 to 10 days after the last day of dosing (visit 5) if clinically significant abnormal changes were noted at visit 4. These tests paid particular attention to liver function, with prespecified rules for patient monitoring and/or termination of study medication if abnormal hepatic enzyme or bilirubin levels were found during the treatment period. Information on adverse events was also collected.

Statistical Analysis

We calculated that a total of 400 evaluable patients would be needed to demonstrate the superior efficacy of dabigatran etexilate 150 and 220 mg over placebo with a power of 80% or higher. Assuming that 20% of patients would not have evaluable venograms, randomization of 500 patients was required. The safety population consisted of all randomized patients who received at least 1 oral dose of study medication and underwent surgery. The primary efficacy analysis set included all randomized patients who received at least one oral dose of study medication, underwent surgery, had an evaluable venogram for distal and proximal DVT or had confirmed symptomatic DVT or PE, or died. The primary analyses were pairwise comparisons between each dabigatran etexilate group and the placebo group; the 2-sided 95% confidence interval (CI) of the rate difference between each of the dabigatran etexilate groups and the placebo group was calculated using the normal approximation of 2 independent binomial distributions. The same analyses (without the hierarchical tests) were conducted for major VTE and VTE-related mortality; only the incidences are presented for total DVT, proximal DVT, symptomatic DVT, PE, and death. The pattern of dose-response of the rate of total VTE plus all-cause mortality among dabigatran etexilate and placebo groups was investigated by means of a maxi-

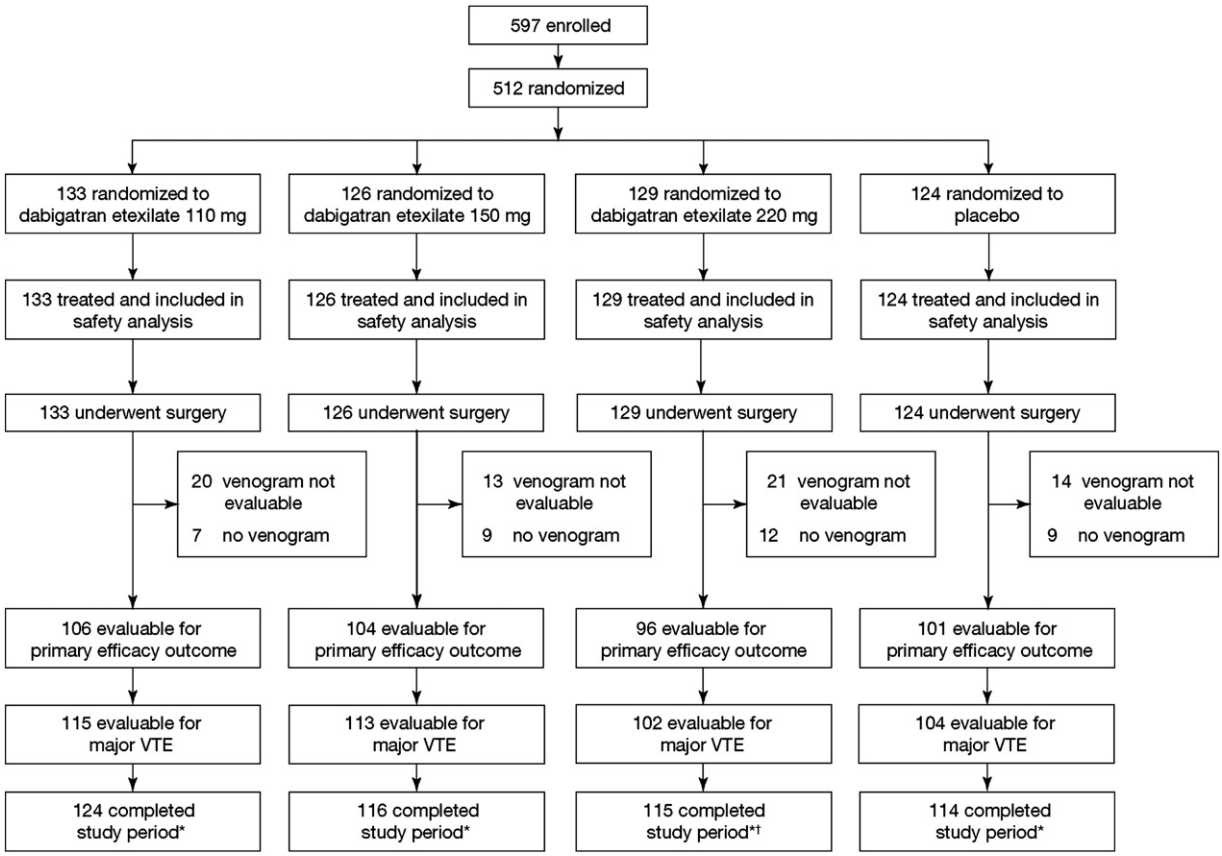

Fig. 1. Randomization and progression of patients in the trial. *The main reasons for premature study discontinuation included adverse events and withdrawal of consent. †One patient completed study medication but did not receive follow-up examination because of withdrawal of consent.

Table 1. Characteristics of Treated and Operated Patients

Characteristic	Dabigatran Etexilate			
	110 mg	150 mg	220 mg	Placebo
Treated and operated, n	133	126	129	124
Mean age, y (SD)	71.3 (7.9)	70.9 (7.7)	72.7 (6.8)	71.3 (8.5)
Mean weight, kg (SD)	61.4 (11.7)	59.8 (11.1)	60.3 (10.7)	60.8 (11.2)
Female sex, n (%)	106 (79.7)	105 (83.3)	109 (84.5)	105 (84.7)
Type of anesthesia, n (%)				
General	100 (75.2)	97 (77.0)	96 (74.4)	92 (74.2)
Nongeneral	33 (24.8)	29 (23.0)	33 (25.6)	32 (25.8)
Mean duration of surgery, min (SD)	110.8 (46.2)	109.2 (44.2)	108.9 (44.2)	108.8 (46.9)
Mean volume of blood loss during surgery, mL (SD)	90.5 (128.0)	67.5 (96.0)	77.3 (130.6)	82.8 (132.0)
Mean time to first oral dose after surgery, h (SD)	21.6 (3.5)	21.7 (3.3)	21.4 (3.2)	21.9 (4.9)
Mean treatment duration, d (SD)	12 (2.5)	12 (2.4)	11.8 (2.9)	12.1 (2.7)

mum contrast method using 3 types of contrast in the Cochran-Armitage test (no adjustment of α was made because of the exploratory nature of this analysis). For major bleeding events and any bleeding events, the incidence and its 95% CI were calculated.

Results

Patients

Of 597 patients enrolled between October 2005 and April 2007, 512 were randomized to treatment and 407 were included in the primary efficacy analysis (Fig. 1). Patient demographic and surgical characteristics were similar between the 4 groups (Table 1). The mean volume of blood loss during surgery was 90.5, 67.5, 77.3, and 82.8 mL in the dabigatran etexilate 110, 150, and 220 mg and placebo groups, respectively. The mean time interval between surgery and initiation of study treatment was 21.6 hours and the mean duration of study treatment was 13 days, with 92% of patients receiving treatment for at least 10 days. Reasons for the discontinuation of treatment were as follows: adverse events (n = 7) and withdrawal of consent (n = 3) in the placebo group; adverse events (n = 9) in the dabigatran etexilate 110-mg group; adverse events (n = 9) and withdrawal of consent (n = 1) in the dabigatran etexilate 150-mg group; and adverse events (n = 10), withdrawal of consent (n = 2), and other (n = 1) in the dabigatran etexilate 220-mg group.

Efficacy

The incidence of primary end point (total VTE and all-cause mortality) was 39.6% (42/106) of patients in the dabigatran etexilate 110-mg group, 32.7% (34/104) in the dabigatran etexilate 150-mg group, 24.0% (23/96) in the dabigatran etexilate 220-mg group, and 56.4% (57/101) in the placebo group. All 3 doses of dabigatran etexilate showed a statistically significant lower incidence of total VTE and all-cause mortality than placebo ($P = .0155$, $P = .0006$, and $P < .0001$ for the dabigatran etexilate 110-, 150-, and 220-mg groups, respectively, vs placebo), resulting in absolute risk reductions of 16.8%, 23.7%, and 32.5% (Table 2) and relative risk reductions of 29.8%, 42.1%, and 57.5%, respectively. There was a pronounced ($P < .0001$) dose-response effect of dabigatran etexilate.

The incidence of the secondary end point (major VTE and VTE-related mortality) was 1.7% (2/115), 1.8% (2/

Table 2. Summary of Efficacy Endpoints During the Treatment Period

Parameter	Dabigatran Etexilate			
	110 mg	150 mg	220 mg	Placebo
Primary end point*, n/N	42/106	34/104	23/96	57/101
% (95% CI) †	39.6 (30.3 to 48.9)	32.7 (23.7 to 41.7)	24.0 (15.4 to 32.5)	56.4 (46.8 to 66.1)
Risk difference vs placebo, % (95% CI) †	−16.8 (−30.2 to −3.4)	−23.7 (−37.0 to −10.5)	−32.5 (−45.4 to −19.6)	–
P vs placebo	.0155	.0006	<.0001	–
Secondary end points				
Major VTE ‡ and VTE-related mortality, n/N	2/115	2/113	0/102	6/104
Total DVT, n/N (%)	42/106 (39.6)	34/104 (32.7)	23/96 (24.0)	57/101 (56.4)
Symptomatic DVT, n/N (%)	1/133 (0.8)	2/126 (1.6)	1/129 (0.8)	2/124 (1.6)
Symptomatic PE, n/N	0/133	0/126	0/129	0/124
Death, n/N	0/133	0/126	0/129	0/124
Proximal DVT, n/N	2/115 (1.7)	2/113 (1.8)	0/102 (0)	6/104 (5.8)

n indicates number of patients; N, total number of evaluable patients.
* Total VTE and all-cause mortality.
† Confidence interval based on normal approximation of independent binomial distribution.
‡ Includes proximal DVT and PE.

Table 3. Summary of Bleeding Events During the Treatment Period *

	Dabigatran Etexilate			
Bleeding Event	110 mg (n = 133)	150 mg (n = 126)	220 mg (n = 129)	Placebo (n = 124)
Patients with major bleeding, n (%; 95% CI) †	1 (0.8; 0.0-4.1)	0 (0)	3 (2.3; 0.5-6.6)	1 (0.8; 0.0-4.4)
No. of major bleeding events	2	0	4	1
Fatal	0	0	0	0
In a critical organ	0	0	0	0
Associated with ≥2 g/dL fall in hemoglobin ‡	0	0	0	0
Requiring transfusion of ≥4.5 U of blood ‡	0	0	1	0
Warranting treatment cessation	2	0	4	1
Leading to reoperation	0	0	1	0
Patients with clinically relevant bleeding, n (%)	0 (0)	1 (0.8)	2 (1.6)	3 (2.4)
Patients with minor bleeding, n (%)	12 (9.0)	12 (9.5)	9 (7.0)	6 (4.8)
Patients with any bleeding, n (%; 95% CI) †	13 (9.8; 4.7-14.8)	13 (10.3; 5.0-15.6)	14 (10.9; 5.5-16.2)	10 (8.1; 3.3-12.9)

N indicates total number of evaluable patients; n, number of patients.
* There were no significant differences in bleeding end points between any dabigatran etexilate group and placebo.
† Confidence interval based on the F distribution method.
‡ In excess of that expected by investigator.

113), and 0% (0/102) of patients in the dabigatran etexilate 110-, 150-, and 220-mg groups, respectively, and in 5.8% (6/104) of placebo-treated patients. The difference between the dabigatran etexilate 220-mg group and the placebo group was statistically significant ($P = .0138$).

The greatest contribution to total VTE and all-cause mortality was from asymptomatic DVT detected by venography, which was identified in 41 patients in the dabigatran etexilate 110-mg group, 32 in the dabigatran etexilate 150-mg group, 22 in the dabigatran etexilate 220-mg group, and 55 patients receiving placebo. Symptomatic DVT was detected in 1, 2, 1, and 2 patients in each of the 4 treatment groups, respectively. As no patients had PE or died during the treatment period, total DVT occurred at exactly the same incidence as total VTE plus all-cause mortality (the primary end point), and the incidence of proximal DVT was the same as that for major VTE plus VTE-related mortality.

Safety

During treatment, 5 patients experienced 7 major bleeding events: 1 patient (0.8%) in the dabigatran etexilate 110-mg group (2 events), no patients in the dabigatran etexilate 150-mg group, 3 patients (2.3%) in the dabigatran etexilate 220-mg group (4 events), and 1 patient (0.8%) in the placebo group (1 event) (Table 3). None of the 7 major bleeding events was fatal, but all required treatment cessation and one led to reoperation (dabigatran etexilate 220-mg group). Of the 5 patients with major bleeding events, 3 major bleeding events (60%) occurred at the surgical site (1 event in each of the dabigatran etexilate 220-mg, dabigatran etexilate 110-mg, and placebo groups), and 4 occurred at other locations (hematoma of left arm, hematemesis, melena, and subcutaneous hemorrhage in left thigh). No significant differences in the incidence of any bleeding events (major, clinically relevant, or minor) were noted between the dabigatran etexilate and placebo groups (Table 3). Wound drainage volumes and the number of patients who required a transfusion were similar across all 4 groups (data not shown).

Other Observations

There were no significant differences between dabigatran etexilate and placebo groups in the incidence of any adverse events (71.4%, 68.3%, 72.1%, and 75.0% for

Table 4. Summary of Adverse Events During the Treatment Period *

	Dabigatran Etexilate			
Adverse Event	110 mg (n = 133)	150 mg (n = 126)	220 mg (n = 129)	Placebo (n = 124)
Patients with any adverse event, n (%)	95 (71.4)	86 (68.3)	93 (72.1)	93 (75.0)
Patients with an adverse event leading to treatment discontinuation, n (%)	7 (5.3)	9 (7.1)	9 (7.0)	7 (5.6)
Patients with a serious adverse event †, n (%)	3 (2.3)	3 (2.4)	2 (1.6)	2 (1.6)
Patients with ALT increases >2× ULN observed within 2-10 d postsurgery, n (%)	1 (0.8)	1 (0.8)	0	2 (1.6)
Patients with total bilirubin increases >1.5× ULN, n (%)	1 (0.8)	0	1 (0.8)	1 (0.8)

N indicates total number of evaluable patients; n, number of patients.
* There were no significant differences in adverse events between any dabigatran etexilate group and placebo.
† In 4 of 10 patients, serious adverse events were considered drug related (abnormal liver function [placebo, dabigatran etexilate 150 mg], hematemesis [dabigatran etexilate 220 mg], wound hemorrhage [dabigatran etexilate 220 mg]; all of them recovered.

dabigatran etexilate at 110, 150, 220, and also placebo, respectively). Most adverse events were of mild or moderate severity. The numbers of patients experiencing adverse events leading to treatment discontinuation or serious adverse events are given in Table 4. Alanine aminotransferase increases of more than 2 times ULN were observed within 2 to 10 days after surgery in one patient from each of the dabigatran etexilate 110-mg and 150-mg groups and in 2 placebo-treated patients; total bilirubin increases of more than 1.5 times ULN were observed in one patient from each of the dabigatran etexilate 110 mg, dabigatran etexilate 220 mg, and placebo groups (Table 4). The cutoff level for total bilirubin was lower than a 2 times increase to exclude any possibility of Hy's law and to ensure a rigorous safety check. No patients experienced an ALT increase of more than 2 times ULN together with an increase in bilirubin levels of more than 1.5 times ULN.

Discussion

Although VTE has traditionally been considered to primarily affect patients in Western countries [1], it is now thought that Japanese patients face a similarly high risk of VTE development after major orthopedic procedures. For example, the incidence of VTE is 49% to 80% and 41% to 85% after TKA, and 23% to 43%, and 42% to 57% after THA in Japanese and white patients, respectively [2,6,7]. In a population of general surgery patients in Western countries, there was a 19% incidence of DVT and a 1.6% incidence of PE, with 0.9% of patients experiencing fatal PE. In Japan, there was a 23.7% incidence of DVT and a 0.6% incidence of PE in a population of abdominal surgery patients [16]. The paucity of established thromboprophylactic measures emphasizes the urgent need for safe, effective, and convenient anticoagulant treatments for Japanese patients undergoing major orthopedic surgery.

The aim of the current study was to evaluate the safety and efficacy of dabigatran etexilate (110, 150, and 220 mg) in the prevention of VTE in Japanese patients undergoing elective TKA. Because there was no standard approved drug available in Japan for the primary prevention of VTE after orthopedic surgery at the time of this trial, an active control was not included. This study was conducted using as a comparator best standard of care available in Japan at the time. Since the study was initiated, alternative thromboprophylactic treatments have become available. Comparative studies are needed to judge the relative efficacy and safety of these treatments in a Japanese population. Although enoxaparin and fondaparinux have since been approved for use in Japan, both are administered parenterally and therefore there is still an unmet need for an oral thromboprophylactic agent. Inclusion of a dabigatran etexilate dose lower (110 mg) than that used in the RE-MODEL [11]) and RE-MOBILIZE [14]) trials ensured a thorough evaluation of dabigatran etexilate dose-response in Japanese patients and allowed for possible differences in body weight between Japanese and white subjects.

All 3 doses of dabigatran etexilate produced a significantly lower incidence of total VTE and all-cause mortality than placebo: 56.4% for placebo vs 39.6% for dabigatran etexilate 110 mg, 32.7% for dabigatran etexilate 150 mg, and 24.0% for dabigatran etexilate 220 mg. Asymptomatic DVT, detected by venography, accounted for most of the events observed; symptomatic DVT was experienced by 6 patients. A significant, inverse linear relationship ($P < .0001$) was found between dabigatran etexilate dose and the primary end point of total VTE.

These results compare favorably with the 2 multinational phase III trials in white patients undergoing elective TKA [11,14]; the incidence of total VTE plus all-cause mortality in the RE-MODEL trial was 40.5% for dabigatran etexilate 150 mg and 36.4% for dabigatran etexilate 220 mg [11]; in RE-MOBILIZE, rates of VTE plus all-cause mortality were 33.7% and 31.1% for dabigatran etexilate 150 and 220 mg, respectively [14].

The incidence of major bleeding associated with anticoagulant therapy is the primary concern for any orthopedic surgeon, especially for TKA where postoperative bleeding into the joint can have significant and disastrous impacts on the success of the procedure [17]. Importantly, the rates of major bleeding events in the current study were low, with no significant differences in the incidence of any bleeding events between the dabigatran etexilate doses or placebo groups. These safety findings are consistent with those of the RE-MODEL and RE-MOBILIZE trials, and also with those of a multinational phase III study that compared dabigatran etexilate 150 and 220 mg with enoxaparin for VTE prevention after THA in white patients (RE-NOVATE [12]).

This study used the same criteria for classifying bleeding events as RE-MODEL, RE-MOBILIZE, and RE-NOVATE, in which the frequency of major bleeding associated with any dose of dabigatran etexilate was similar to or lower than any dose of the active comparator, enoxaparin [11,12,14]. Interestingly, the overall number of major bleedings at the surgical site is lower in this study (43%) than in RE-MODEL (89%), or RE-NOVATE (91%), possibly because of the later initiation of dabigatran etexilate treatment. Furthermore, there is no loss of efficacy in the current trial when compared with RE-MODEL or RE-MOBILIZE, even with the later treatment initiation. However, data from the current analysis cannot be considered as conclusive evidence of the benefits of later treatment initiation, and further trials are needed to strengthen and confirm this observation.

There was no increase in the incidence of liver enzyme elevation associated with dabigatran etexilate compared

with placebo, during treatment or at follow-up. No patients experienced an ALT increase of more than 2 times ULN together with an increase in bilirubin levels of more than 1.5 times ULN.

The findings of the current study, along with those of the RE-MODEL, RE-MOBILIZE, and RE-NOVATE studies, suggest that dabigatran etexilate has a favorable benefit-risk profile when used for the prevention of VTE after TKA or THA in Japanese and white patients. However, assessment of the benefit-risk balance of any anticoagulant also depends on a number of interrelated issues [11,17]. For example, as 45% to 80% of all symptomatic VTE events occur after hospital discharge [2], the duration of thromboprophylactic therapy is an important consideration. The Seventh American College of Chest Physicians Guidelines on Prevention of VTE [2] recommends continuing treatment for at least 10 days after TKA. In the current study, dabigatran etexilate was administered for 11 to 14 days, with 92% of patients receiving treatment for 10 days or more. Early indications suggest that a longer treatment period with dabigatran etexilate might be associated with a greater reduction in VTE events (pooled data from RE-MODEL and RE-MOBILIZE showed that the DVT rates decreased significantly with a longer duration of treatment of dabigatran etexilate 220 mg once daily and 150 mg twice daily [$P < .005$]). Deep venous thrombosis rates for 220 mg dabigatran etexilate once daily for 6 vs 15 days were 40% (95% CI, 34%-45%) and 27% (95% CI, 24%-31%), and for 150 mg dabigatran etexilate once daily 42% (95% CI, 37%-48%) and 32% (95% CI, 28-36%), respectively [18].

We conclude that once daily oral dabigatran etexilate, when administered at the 3 doses studied from the day after surgery, is well tolerated and effective in preventing VTE in Japanese patients undergoing elective TKA. No increased risk of major bleeding was found with any of the doses evaluated vs placebo. These results will help to further define and clarify the role of dabigatran etexilate in VTE prevention after major orthopedic surgery.

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