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.

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