Oral Thrombin Inhibitor Dabigatran Etexilate vs North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery

The RE-MOBILIZE Writing Committee*

Abstract: Dabigatran, an oral once-daily unmonitored thrombin inhibitor, has been tested elsewhere using enoxaparin 40 mg once daily. We used the North American enoxaparin 30 mg BID regimen as the comparator. This was a double-blind, centrally randomized trial. Unilateral total knee arthroplasty patients were randomized to receive oral dabigatran etexilate 220 or 150 mg once daily, or enoxaparin 30 mg SC BID after surgery, blinded. Dosing stopped at contrast venography, 12 to 15 days after surgery. Among 1896 patients, dabigatran 220 and 110 mg showed inferior efficacy to enoxaparin (venous thromboembolism rates of 31% [$P = .02$ vs enoxaparin], 34% [$P < .001$ vs enoxaparin], and 25%, respectively). Bleeding rates were similar, and no drug-related hepatic illness was recognized. Dabigatran, effective compared to once-daily enoxaparin, showed inferior efficacy to the twice-daily North American enoxaparin regimen, probably because of the latter's more intense and prolonged dosing. **Key words:** Dabigatran etexilate, direct thrombin inhibitor, total knee arthroplasty, prophylaxis, venous thromboembolism.

A safe and effective oral antithrombotic drug that does not require dosage adjustment and laboratory monitoring could replace injected low-molecular-weight heparins and oral vitamin K antagonists for prevention of venous thromboembolism in high-risk situations, such as joint arthroplasty. One such

Jeffrey S. Ginsberg, MD, Bruce L. Davidson, MD, MPH, Philip C. Comp, MD, PhD, Charles W. Francis, MD, Richard J. Friedman, MD, Michael H. Huo, MD, Jay R. Lieberman, MD, James E. Muntz, MD, Gary E. Raskob, PhD, Mary L. Clements, PhD, Stefan Hantel, PhD, Janet M. Schnee, MD, Joseph A. Caprini, MD.

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See Appendix for Committee Members' affiliations.

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This study registered as 1160.24 at www.clinicaltrials.gov.

Reprint requests: Bruce L. Davidson, MD, MPH, Weill Cornell Medical College-Qatar, 575 Lexington Avenue, Suite 670, New York, NY 10022.

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candidate drug is dabigatran etexilate, converted after absorption to the reversible thrombin inhibitor dabigatran. It is 80% renally excreted and its terminal half-life of about 16 hours makes it suitable for once-daily administration [1]. Dose-ranging phase 2 studies of dabigatran in hip and knee arthroplasty patients vs the active comparator enoxaparin, the latter injected 40 mg beginning the evening before surgery, [2,3] led to selection of 2 dabigatran dosages, 220 and 150 mg, for phase 3 testing.

An interesting clinical difference between European and North American prophylactic dosing regimens for antithrombotic drugs for perioperative orthopedic patients is that historically, European dosing regimens administered these drugs before surgery, whereas in North American dosing began postoperatively, sometimes at a higher total daily dosage [4-6]. Because dabigatran was first investigated in European joint arthroplasty patients, the low-molecular-weight heparin control therapy, enoxaparin, was begun the evening before the day of surgery at the standard dosage of 40 mg once daily in the phase 2 studies [2,3]. A phase 3 study similar to the one we report herein was primarily conducted in European knee arthroplasty patients using such a dosage regimen. However, for North American knee arthroplasty patients, we selected as control thromboprophylaxis the North American approved enoxaparin regimen of 30 mg twice daily, begun the morning after surgery. We began oral dabigatran 6 to 12 hours after surgery and continued study drugs until venography at approximately day 13. In the companion European study, oral study drug was begun 1 to 4 hours after surgery, and study drug discontinuation and venography occurred at days 6 to 10. We report the results comparing the 2 dabigatran dosage regimens with the North American approved dosing of enoxaparin for venous thromboembolism prophylaxis in knee arthroplasty patients.

Methods

Study Design

This was a randomized, double-blind, active controlled, noninferiority study conducted at 58 centers in the United States, 30 in Canada, 8 in Mexico, and 1 in the United Kingdom. The study was approved by institutional review boards and independent ethics committees and conducted in accordance with the Declaration of Helsinki (October 1996 version). All patients gave written informed consent. When hemodynamically stable, patients were randomly assigned to 1 of 3 treatment groups after surgery. An Interactive Voice Response System was used for randomization in blocks of 6 and was based on an independently generated scheme.

Patients

Patients 18 years or older and weighing more than 40 kg who had undergone primary elective unilateral total knee arthroplasty and provided signed informed consent were eligible for the study. The primary reasons for exclusion included a known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months; history of acute intracranial disease or hemorrhagic stroke; gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months; severe liver disease; aspartate or alanine aminotransferase (AST, ALT) levels higher than 2× the upper limit of the normal range (ULN) within the last month; severe renal insufficiency (creatinine clearance <30 mL/min); need for concomitant long-acting nonsteroidal anti-inflammatory drug therapy or treatment with an anticoagulant during study drug treatment; active malignant disease; platelet count less than 100×10^9/L, pregnant, nursing, or premenopausal women of child-bearing potential who were not practicing effective birth control; and failure to provide informed consent. After completion of surgery, any indwelling anesthetic catheter was removed and subcutaneous injection of trial medication was administered 12 to 24 hours later.

Treatment Regimens

Eligible, consenting patients were assigned to receive oral dabigatran etexilate 220 or 150 mg once daily, or enoxaparin (Sanofi-Aventis), 30 mg SC twice daily. All 3 groups received one active and one placebo treatment (ie, double-dummy blinding). Patients received 2 capsules in the morning as well as a subcutaneous injection; they received a subcutaneous injection in the evening. The first dose of dabigatran etexilate was one half of subsequent doses (one capsule, 110 or 75 mg) and was administered 6 to 12 hours after completion of surgery, provided clinical assessment of perioperative and postoperative bleeding and drainage indicated adequate hemostasis. If administration was delayed until the day after surgery, a full dose (2 capsules) was administered as the first dose the morning after surgery. The first subcutaneous injection was given 12 to 24 hours after surgery, usually on the morning