

## A Once-Daily, Oral, Direct Factor Xa Inhibitor, Rivaroxaban (BAY 59-7939), for Thromboprophylaxis After Total Hip Replacement

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**Background**—Rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor—could be an alternative to heparins and warfarin for the prevention and treatment of thromboembolic disorders.

**Methods and Results**—This randomized, double-blind, double-dummy, active-comparator-controlled, multinational, dose-ranging study assessed the efficacy and safety of once-daily rivaroxaban relative to enoxaparin for prevention of venous thromboembolism in patients undergoing elective total hip replacement. Patients (n=873) were randomized to once-daily oral rivaroxaban doses of 5, 10, 20, 30, or 40 mg (initiated 6 to 8 hours after surgery) or a once-daily subcutaneous enoxaparin dose of 40 mg (given the evening before and  $\geq 6$  hours after surgery). Study drugs were continued for an additional 5 to 9 days; mandatory bilateral venography was performed the following day. The primary end point (composite of any deep vein thrombosis, objectively confirmed pulmonary embolism, and all-cause mortality) was observed in 14.9%, 10.6%, 8.5%, 13.5%, 6.4%, and 25.2% of patients receiving 5, 10, 20, 30, and 40 mg rivaroxaban, and 40 mg enoxaparin, respectively (n=618, per-protocol population). No significant dose-response relationship was found for efficacy ( $P=0.0852$ ). Major postoperative bleeding was observed in 2.3%, 0.7%, 4.3%, 4.9%, 5.1%, and 1.9% of patients receiving 5, 10, 20, 30, and 40 mg rivaroxaban, and 40 mg enoxaparin, respectively (n=845, safety population), representing a significant dose-response relationship ( $P=0.0391$ ).

**Conclusions**—Rivaroxaban showed efficacy and safety similar to enoxaparin for thromboprophylaxis after total hip replacement, with the convenience of once-daily oral dosing and without the need for coagulation monitoring. When both efficacy and safety are considered, these results suggest that 10 mg rivaroxaban once daily should be investigated in phase III studies. (*Circulation*. 2006;114:2374-2381.)

**Key Words:** anticoagulants ■ coagulation ■ embolism ■ prevention ■ thrombosis

Currently, low-molecular-weight heparins (LMWHs) and vitamin K antagonists are used routinely for thromboprophylaxis after major orthopedic surgery.<sup>1</sup> Although they effectively reduce the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE),<sup>1</sup> a number of limitations restrict their use. Vitamin K antagonists, although orally administered, have a slow onset of action, interpatient variability, need for frequent monitoring, and potential drug interactions,<sup>1</sup> whereas LMWHs are administered parenterally.

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Rivaroxaban (BAY 59-7939) is an oral, direct Factor Xa (FXa) inhibitor. It has high oral bioavailability (relative bioavailability  $\approx 80\%$ ),<sup>2</sup> a rapid onset of action, and predictable, dose-proportional pharmacokinetics and pharmacodynamics.<sup>2,3</sup> It has a half-life of 5 to 9 hours and is excreted rapidly, predominantly via renal elimination (66% of the total dose, with 36% of the dose excreted unchanged) and also by

Received May 26, 2006; revision received August 10, 2006; accepted September 8, 2006.

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The online-only Data Supplement, which contains a list of the ODIXa-HIP Study Investigators, can be found at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.642074/DC1>.

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.106.642074

the biliary/fecal route.<sup>3-6</sup> Two phase II studies (n=1343) were performed to evaluate the efficacy and safety of a twice-daily regimen of rivaroxaban for 5 to 9 days, relative to the LMWH enoxaparin, for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery.<sup>7,8</sup> A wide (4-fold) dose range of rivaroxaban (total daily doses of 5 to 20 mg) compared favorably with enoxaparin.

Further evidence suggests that rivaroxaban may be suitable for once-daily administration. Phase I studies in healthy subjects showed that single doses of rivaroxaban have pharmacodynamic effects that persist for 24 hours.<sup>2,9,10</sup> Furthermore, via inhibition of Factor Xa activity, rivaroxaban ultimately diminishes thrombin generation. Rivaroxaban significantly inhibited peak and total amounts of thrombin generated and prolonged time to thrombin generation 24 hours after dosing in healthy subjects.<sup>9</sup>

Together, these studies led to the initiation of the Oral, Direct Factor Xa Inhibitor, BAY 59-7939, Given Once Daily in Patients Undergoing Total Hip Replacement (ODIXa-OD-HIP) study. This phase II study was performed to investigate the efficacy and safety of oral rivaroxaban administered once daily relative to that of subcutaneous enoxaparin in patients undergoing elective total hip replacement.

## Methods

### Study Design

The ODIXa-OD-HIP study was a randomized, double-blind, double-dummy, active-comparator-controlled, multinational, dose-ranging study to assess the efficacy and safety of oral rivaroxaban (Bayer HealthCare AG, Wuppertal, Germany) administered once daily relative to that of subcutaneous enoxaparin (Clexane/Lovenox, sanofi-aventis, Paris, France) for the prevention of VTE in patients undergoing elective, primary total hip replacement. The study was conducted in accordance with the Declaration of Helsinki. All study documentation was reviewed and approved by local independent ethics committees.

After written, informed consent was obtained, patients scheduled for elective, primary total hip replacement surgery were randomized to receive oral rivaroxaban or subcutaneous enoxaparin. Oral rivaroxaban (5, 10, 20, 30, or 40 mg) was administered 6 to 8 hours after surgery and once daily thereafter (every 24±2 hours) for an additional 5 to 9 days (within 2 hours of food). Enoxaparin 40 mg (0.4-mL prefilled syringes) was administered on the evening before surgery, at least 6 to 8 hours after wound closure in accordance with European practice, and then once daily every evening according to hospital routine for an additional 5 to 9 days. Patients received matching placebo tablets or injections, so that each patient received 2 tablets and an injection every evening. Mandatory bilateral venography was performed the day after the last dose of study drug. Patients attended a clinical follow-up visit 30 to 60 days later. Further thromboprophylaxis after venography was at the discretion of the investigator.

### Patients

Men aged ≥18 years and postmenopausal women scheduled for elective, primary total hip replacement surgery were enrolled. Exclusion criteria included DVT, PE, myocardial infarction, transient ischemic attack, or ischemic stroke during the 6 months before the study. Also excluded were patients with intracerebral, intraocular, or gastrointestinal bleeding in the previous 6 months; patients taking drugs that might have affected the study outcome, such as other anticoagulants, platelet-aggregation inhibitors, or any other drug influencing coagulation (except nonsteroidal antiinflammatory drugs with a half-life <17 hours); patients with severe hypertension,

severe liver or renal impairment, medical conditions that may interfere with the study, or body weight <45 kg; and patients who abuse alcohol or drugs. Intermittent pneumatic compression was not permitted during the treatment period.

## Outcome Measures

### Efficacy

The primary efficacy end point—the composite of the incidence of any DVT (proximal and/or distal); nonfatal, symptomatic, objectively confirmed PE; and all-cause death—was evaluated 6 to 10 days after surgery, or earlier if the patient was symptomatic. Secondary efficacy end points included major VTE (defined as the composite of the incidence of proximal DVT; symptomatic, objectively confirmed PE; and VTE-related death) and symptomatic VTE.

### Safety

The primary safety end point was the incidence of major bleeding, starting after the first postoperative dose of study drug but no later than 2 days after the last dose of study drug. Major bleeding was defined as follows<sup>11</sup>: fatal bleeding; bleeding into a critical organ (including retroperitoneal, intracranial, intraocular, or intraspinal bleeding); bleeding warranting treatment cessation; or clinically overt bleeding associated with a fall in hemoglobin ≥2 g/dL within 24 hours, leading to transfusion of at least 2 units of blood, or leading to reoperation. Other bleeding end points included clinically relevant, non-major bleeding events (defined as multiple-source bleeding; spontaneous hematoma >25 cm<sup>2</sup>; excessive wound hematoma; macroscopic hematuria [spontaneous or lasting >24 hours if associated with an intervention]; spontaneous rectal bleeding; epistaxis, gingival bleeding, or bleeding after venipuncture for >5 minutes; hemoptysis; or hematemesis) and minor bleeding events (those that did not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events). Postoperative blood loss (via drain) and transfusion volumes were documented during the treatment period.

Other safety assessments included hematology and clinical chemistry laboratory tests, including liver function and coagulation tests.

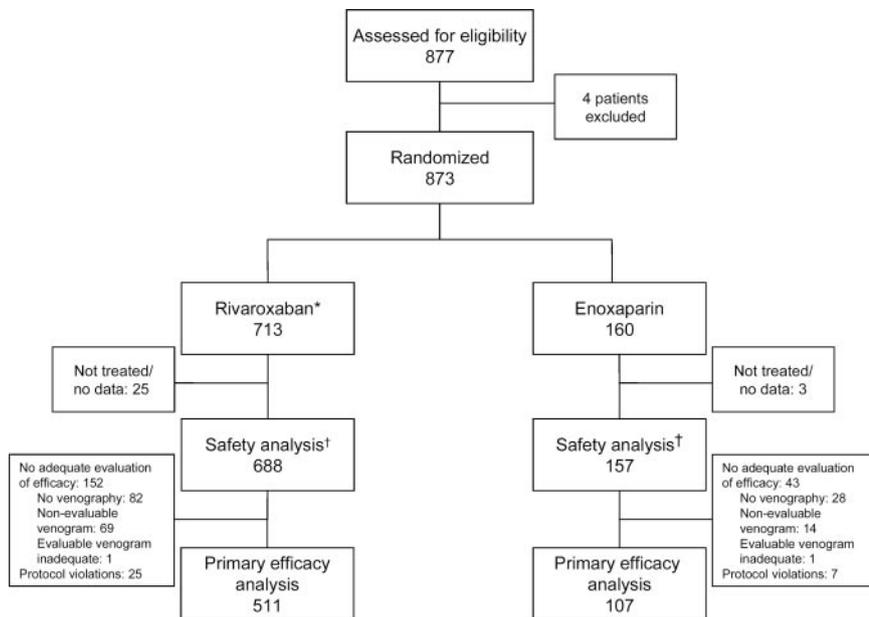
### Assessments

Patients were screened for DVT with standardized, mandatory, bilateral venography the day after their last dose of study drug (ie, 6 to 10 days after surgery), or sooner if signs and symptoms were present.<sup>11</sup> The venography method used was the Rabinov and Paulin technique,<sup>12-14</sup> with a standardized methodology in which a minimum of 9 films were used for each leg, each from a different projection. All venograms were assessed centrally by the Venography Adjudication Committee (Department of Radiology, Östra Hospital, Gothenburg, Sweden). Symptomatic PE was confirmed by pulmonary angiography, spiral computed tomography, or perfusion/ventilation lung scintigraphy plus chest radiography. In cases of death, an autopsy was performed if possible. All symptomatic VTEs and deaths occurring during the treatment or follow-up period were assessed centrally by the VTE Adjudication Committee (Central Clinic, Östra Hospital, Gothenburg, Sweden). All bleeding events were assessed centrally by the Bleeding Event Adjudication Committee. All adjudication committees were independent and blinded to treatment allocation.

An independent Data and Safety Monitoring Board continuously monitored efficacy and safety in this study. The Data and Safety Monitoring Board could unblind patients' study drug allocation and, in cases of insufficient efficacy or unacceptable safety, recommend amendment of the study protocol, which included discontinuation of the study or a treatment arm, according to prespecified criteria.

### Sample Size Calculation

According to the initial study protocol, patients were randomized evenly (1:1:1:1) to receive 1 of 4 doses of rivaroxaban (10, 20, 30, or 40 mg once daily [OD]) or enoxaparin (40 mg OD). However, after the study was initiated, the results of 2 phase IIb studies investigating twice-daily doses of rivaroxaban became available and showed that rivaroxaban 2.5 mg twice daily was more effective than



**Figure 1.** Flow of patients through the ODIxa-OD-HIP study. \*Patients were randomized to receive 1 of 5 doses of rivaroxaban (5, 10, 20, 30, or 40 mg OD). †Patients eligible for the safety analysis had at least 1 dose of study drug and data allowing safety assessment.

anticipated in patients who had undergone major orthopedic surgery.<sup>7,8</sup> As a result, a 5-mg OD dose of rivaroxaban was included in the protocol after the study was initiated. On the basis of event rates of the primary efficacy end point of 10% to 25%, and assuming a linear trend in the dose–response relationship and a 23% invalidity rate, 135 subjects were required in each dose group to provide 90% power to detect a dose trend in the primary efficacy analysis. To achieve similar numbers of patients in each dose group despite the late start of the 5-mg OD dose group, patients were randomized 2:1:1:1:1 to 5, 10, 20, 30, and 40 mg rivaroxaban OD and 40 mg enoxaparin, respectively.

## Statistical Analysis

### Efficacy

The primary efficacy analysis—to determine a trend in the dose–response relationship between rivaroxaban and the primary efficacy end point—was performed in the per-protocol (PP) population with a logistic regression model, including the total daily dose of rivaroxaban and the country in which the patient was treated as explanatory variables. An identical supportive analysis was performed in the intention-to-treat (ITT) population.

A similar analysis, using logistic regression with the total daily dose of rivaroxaban as a covariate, was performed in the PP population to determine a trend in the dose–response relationship between rivaroxaban and major VTE (a secondary efficacy end point; because of the expected low incidence of major VTE, country effects were not considered in this analysis).

The PP population comprised patients who had received at least one dose of study medication and had data allowing assessment of safety (ie, the safety population), who had undergone surgery, had an adequate VTE assessment (adequate bilateral venography 6 to 10 days after surgery, or confirmed DVT, PE, or death up to 10 days after surgery) performed no later than 36 hours after the last dose of study drug, and who did not show any major protocol violations. All tests were 2 sided, with a type I error rate of  $\alpha=5\%$ .

### Safety

The incidence of major bleeding was analyzed in the safety population with a logistic regression model, including the total daily dose of rivaroxaban as a covariate. In addition, each dose of rivaroxaban was compared with enoxaparin with the Fisher exact test. All statistical analyses were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Study Population

Between November 2004 and July 2005, 877 patients were enrolled in this study, at 48 centers in 11 countries (Europe and Israel); 873 patients were randomized to receive rivaroxaban or enoxaparin (Figure 1; for further details, see the Data Supplement Figure). Twenty-one randomized patients did not receive study drug (18 in the rivaroxaban dose groups and 3 in the enoxaparin group). Of the remaining 852 patients, 695 received rivaroxaban (128, 142, 140, 143, and 142 patients received 5, 10, 20, 30, and 40 mg OD, respectively) and 157 received enoxaparin. The safety population comprised 845 patients (7 patients withdrew from the study before surgery). The primary analysis was performed in the PP population, which comprised 618 patients: 511 patients receiving rivaroxaban (94, 113, 106, 104, and 94 patients in the 5-, 10-, 20-, 30-, and 40-mg OD dose groups, respectively) and 107 patients receiving enoxaparin (Figure 1). A total of 29% of all randomized patients (255/873) were excluded from the primary efficacy analysis. The main reason for exclusion was inadequate evaluation of efficacy, which occurred in 195 patients, 110 of whom did not undergo bilateral venography, and venograms were considered inadequate for interpretation in 83 patients. In 2 patients, venography was performed before the prespecified time window, ie, before the fifth postoperative day. Other reasons for exclusion included protocol violations, such as violating the time interval between doses of study drug and taking prohibited medications.

All groups were well balanced with respect to age, sex, weight, body mass index, and the duration of surgery (Table 1). Almost all patients were white; there were 3 nonwhite patients (2 Asian, 1 Hispanic). The mean interval between

**TABLE 1. Baseline Characteristics and Surgery Details for Study Patients (Safety Population; n=845)**

Characteristics	Rivaroxaban					Enoxaparin
	5 mg OD (n=128)	10 mg OD (n=142)	20 mg OD (n=139)	30 mg OD (n=142)	40 mg OD (n=137)	40 mg OD (n=157)
Age, mean (range), y	64.8 (28–84)	64.0 (27–87)	65.0 (27–93)	65.4 (31–86)	64.7 (27–83)	65.6 (30–89)
Female, n (%)	72 (56)	89 (63)	82 (59)	73 (51)	81 (59)	101 (64)
Weight, mean (range), kg	76.6 (45–118)	75.6 (45–111)	75.7 (47–120)	78.4 (49–130)	77.6 (50–126)	74.9 (45–116)
Body mass index, mean (range), kg/m <sup>2</sup>	27.4 (17–46)	26.9 (18–49)	27.1 (18–41)	27.5 (20–43)	27.5 (19–40)	27 (16–39)
Surgery details						
Cemented hip prosthesis, n (%)	37 (28.9)	55 (38.7)	50 (36.0)	58 (40.8)	57 (41.6)	64 (40.8)
Duration of surgery, mean±SD, min	85±33	89±30	85±31	89±34	89±31	84±28
Type of anesthesia						
General, n (%)	64 (50)	49 (35)	42 (30)	56 (39)	42 (31)	60 (38)
Regional,* n (%)	62 (48)	93 (65)	96 (69)	84 (59)	95 (69)	97 (62)

\*Spinal and epidural anesthesia.

surgery and first oral dose of rivaroxaban was 7 hours. The mean duration of treatment was 7 days for rivaroxaban and 8 days for enoxaparin—the difference is explained by the initiation of enoxaparin on the day before surgery and the initiation of rivaroxaban after surgery.

**Efficacy Outcomes**

The primary efficacy end point (composite of any DVT, PE, and all-cause death) was observed in 14.9%, 10.6%, 8.5%, 13.5%, and 6.4% of patients receiving 5, 10, 20, 30, and 40 mg rivaroxaban OD, respectively, compared with 25.2% of patients receiving enoxaparin (Table 2). Although there was a tendency toward a lower incidence of the primary efficacy end point with increasing doses of rivaroxaban (Table 2, Figure 2), statistical analysis did not detect a trend in this dose–response relationship (P=0.0852). Similar results were obtained in the ITT population (data not shown). No rivaroxaban dose arm was discontinued because of lack of efficacy.

No deaths were reported during the study (treatment and follow-up). Although there were no PEs reported in the PP

population (Table 2), there was a PE in a patient in the ITT population who received 40 mg rivaroxaban OD, and one in a patient receiving 10 mg rivaroxaban OD who was only eligible for the safety analysis. There was one report of symptomatic DVT during the treatment period (1 distal DVT in the enoxaparin group [PP population]), and 3 during the follow-up period (2 proximal DVTs: 20 mg and 40 mg rivaroxaban; and 1 PE: 40 mg rivaroxaban).

The observed incidence of the secondary efficacy end point, major VTE (composite of proximal DVT, PE, and VTE-related death), was similar to enoxaparin in all rivaroxaban dose groups, except the 5-mg OD group, in which the incidence was 8.5%, compared with 2.8% for enoxaparin (Table 2). Statistical analysis demonstrated a significant trend in the dose–response relationship between rivaroxaban and major VTE (P=0.0072).

**Safety Outcomes**

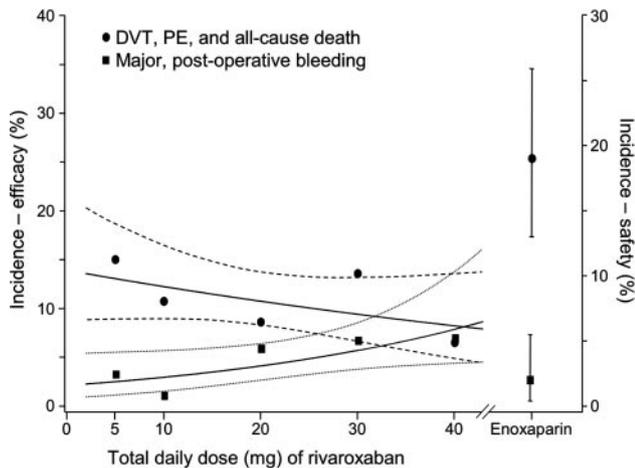
The primary safety end point—major postoperative bleeding—was observed in 2.3%, 0.7%, 4.3%, 4.9%, and 5.1% of patients receiving 5, 10, 20, 30, and 40 mg rivaroxaban OD,

**TABLE 2. Efficacy End Points and Their Composites (PP Population; n=618)**

Parameter	Rivaroxaban					Enoxaparin
	5 mg OD (n=94)	10 mg OD (n=113)	20 mg OD (n=106)	30 mg OD (n=104)	40 mg OD (n=94)	40 mg OD (n=107)
Primary efficacy end point,* n (%)	14 (14.9)	12 (10.6)	9 (8.5)	14 (13.5)	6 (6.4)	27 (25.2)
95% CI	8.4, 23.7	5.6, 17.8	4.0, 15.5	7.6, 21.6	2.4, 13.4	17.3, 34.6
DVT, n (%)	14 (14.9)	12 (10.6)	9 (8.5)	14 (13.5)	6 (6.4)	27 (25.2)
Proximal, n (%)	8 (8.5)	3 (2.7)	1 (0.9)	2 (1.9)	1 (1.1)	3 (2.8)
Distal only, n (%)	6 (6.4)	9 (8.0)	8 (7.5)	12 (11.5)	5 (5.3)	24 (22.4)
PE, n (%)	0	0	0	0	0	0
Death, n (%)	0	0	0	0	0	0
Major VTE,† n (%)	8 (8.5)	3 (2.7)	1 (0.9)	2 (1.9)	1 (1.1)	3 (2.8)
95% CI	3.7, 16.1	0.6, 7.6	0.0, 5.1	0.2, 6.8	0.0, 5.8	0.6, 8.0

\*Components of primary efficacy end point: any DVT; nonfatal, symptomatic, objectively confirmed PE (no reports); and all-cause death (no reports).

†Components of major VTE (a secondary efficacy end point): proximal DVT; nonfatal, symptomatic, objectively confirmed PE (no reports); and death associated with VTE (no reports).



**Figure 2.** Dose-response relationships between rivaroxaban and the primary efficacy end point (DVT, non-fatal PE, all-cause death; PP population) and the primary safety end point (major postoperative bleeding events; safety population). The solid lines are the dose-response curves for rivaroxaban, estimated by logistic regression including total daily dose as a covariate. The dotted lines represent the 95% CIs for safety. The hatched lines represent the 95% CIs for efficacy.

respectively, compared with 1.9% of patients receiving enoxaparin (Table 3). There was a significant dose trend for major postoperative bleeding ( $P=0.0391$ ; Figure 2). There were no significant differences in the incidences of major postoperative bleeding between any rivaroxaban dose and enoxaparin; however, this study was not powered to detect differences between individual rivaroxaban doses and enoxaparin.

No bleeding into a critical organ was reported, and all major postoperative bleeding events were confined to the surgical site. The majority of major bleeding events were due to clinically overt bleeding associated with a fall in hemoglobin  $\geq 2$  g/dL within 24 hours and/or leading to transfusion of at least 2 units of blood. The incidences of the secondary

bleeding end points are also shown in Table 3. In general, proportions of patients requiring blood transfusions were similar across all rivaroxaban dose groups and for enoxaparin, and the volume of blood transfused was also similar (Table 4). No dose arm was stopped because of safety concerns.

Treatment-emergent increases (up to 7 days after the last dose of study drug) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels  $>3\times$  the upper limit of normal (ULN) occurred in 3.0% to 5.4% and 3.4% to 6.2% of patients, respectively, in the rivaroxaban groups, compared with 7.1% of patients in the enoxaparin group (10/140 and 10/141 patients, respectively; Table 5). There did not seem to be dose dependency between rivaroxaban and increased liver enzymes.

One patient in the 30-mg rivaroxaban OD group had a combination of ALT  $>3\times$  ULN and bilirubin  $>2\times$  ULN 3 hours after receiving his first dose of study medication. Bilirubin returned to within normal limits the next day. ALT levels decreased despite continued study drug administration: They were  $<3\times$  ULN on the last day of administration and within normal limits at the follow-up visit (34 days after receiving the last dose of study drug).

In addition, 1 patient in the 10-mg rivaroxaban OD group who had normal ALT and AST levels at baseline had raised ALT and AST 3 days after surgery (approximately  $2\times$  ULN; bilirubin was within normal limits). The patient received study medication for 7 days after surgery, according to the protocol. Liver enzymes continued to rise during the follow-up period, with ALT and AST  $>3\times$  ULN 59 days after receiving the last dose of study drug, and 14 days later. An ultrasound examination 99 days after surgery revealed cholecystolithiasis.

## Discussion

The ODIXa-OD-HIP study demonstrated that oral rivaroxaban given once daily postoperatively was equally efficacious

**TABLE 3. Bleeding End Points (Safety Population; n=845)**

Bleeding Classification	Rivaroxaban					Enoxaparin
	5 mg OD (n=128)	10 mg OD (n=142)	20 mg OD (n=139)	30 mg OD (n=142)	40 mg OD (n=137)	40 mg OD (n=157)
Major postoperative bleeding*, n (%)	3 (2.3)	1 (0.7)	6 (4.3)	7 (4.9)	7 (5.1)	3 (1.9)
95% CI	0.5, 6.7	0.0, 3.9	1.6, 9.2	2.0, 9.9	2.1, 10.2	0.4, 5.5
Components of major bleeding†						
Fatal/critical bleeding, n (%)	0	0	0	0	0	0
Bleeding leading to reoperation, n (%)	0	0	1 (0.7)	1 (0.7)	0	0
Clinically overt bleeding leading to treatment cessation, n (%)	0	0	1 (0.7)	0	1 (0.7)	0
Clinically overt bleeding with a fall in hemoglobin, n (%)	2 (1.6)	0	4 (2.9)	6 (4.2)	5 (3.6)	1 (0.6)
Clinically overt bleeding leading to blood transfusion, n (%)	3 (2.3)	1 (0.7)	5 (3.6)	6 (4.2)	6 (4.4)	3 (1.9)
Clinically relevant non-major bleeding, n (%)	2 (1.6)	3 (2.1)	1 (0.7)	3 (2.1)	4 (2.9)	5 (3.2)
Minor bleeding, n (%)	5 (3.9)	5 (3.5)	6 (4.3)	8 (5.6)	14 (10.2)	6 (3.8)

\*Bleeding starting after the first postoperative dose of study drug, but not  $>2$  days after the last administration of study drug.

†Patients may have events that fall into  $>1$  category.

**TABLE 4. Blood Transfusions and Volume of Postoperative Blood Loss (Safety Population; n=845)**

	Rivaroxaban					Enoxaparin
	5 mg OD (n=128)	10 mg OD (n=142)	20 mg OD (n=139)	30 mg OD (n=142)	40 mg OD (n=137)	40 mg OD (n=157)
Patients receiving blood transfusions, n (%)	72 (56.3)	85 (59.9)	85 (61.2)	82 (57.7)	81 (59.1)	93 (59.2)
Volume, mean±SD, mL	317±400	342±356	404±422	391±456	416±460	409±455
Patients with volume in drain (postoperative), n (%)	107 (83.6)	115 (81.0)	114 (82.0)	119 (83.8)	112 (81.8)	126 (80.3)
Volume, mean±SD, mL	582±438	491±442	538±592	469±514	470±364	454±441

across an 8-fold dose range (5 to 40 mg OD), with efficacy similar to enoxaparin (40 mg OD) for the prevention of VTE after elective hip replacement surgery. The rate of major bleeding was similar to enoxaparin in the 5- and 10-mg OD dose groups.

The observed incidence of the primary efficacy end point (the composite of DVT, PE, and all-cause death) was slightly lower than observed in a similar phase II dose-finding study investigating rivaroxaban given twice daily in patients undergoing hip replacement surgery<sup>7</sup>: 14.9%, 10.6%, and 8.5% with total daily doses of 5, 10, and 20 mg rivaroxaban OD, respectively (present study), compared with 15.4%, 13.8%, and 11.9%, respectively (twice-daily study). The incidence with enoxaparin (25.2%; 95% confidence interval [CI] 17.3, 34.6) was higher than observed in the twice-daily rivaroxaban phase II study (17.0%; 95% CI 10.4, 25.5),<sup>7</sup> despite the use of the same rigorous assessment technique and the same central adjudication committee.

There was a flat dose–response relationship between rivaroxaban and the primary efficacy end point ( $P=0.0852$ ). This could be explained by the higher-than-expected efficacy achieved in the lower dose groups (higher than assumed for sample size calculations).

A total of 71% of randomized patients received study drugs and were eligible for the primary efficacy analysis (PP population). This validity rate is similar to those reported in other clinical trials investigating anticoagulants in patients undergoing orthopedic surgery: 70% and 79% of patients were valid for the primary analysis in the PENTATHLON<sup>15</sup> and European Pentasaccharide Hip Elective SURgery Study (EPHESUS)<sup>16</sup> studies with fondaparinux, respectively; 72% and 74% in the Boehringer Ingelheim Study in ThROMbosis (BISTRO) I<sup>17</sup> and II<sup>18</sup> studies with dabigatran, respectively; and 77% and 79% in the MELagatran for THRombin inhibition in Orthopaedic surgery (METHRO) II<sup>19</sup> and III<sup>20</sup> studies with ximelagatran, respectively.

The observed incidence of major VTE (which comprised proximal DVT because there were no reports of death or PE

during the study) was lower with all doses of rivaroxaban, except the 5-mg OD dose, compared with enoxaparin. Furthermore, there was a significant dose–response relationship between rivaroxaban and major VTE ( $P=0.0072$ ). Except for the 5-mg OD dose, there was a similar incidence of major VTE in this study (8.5%, 2.7%, 0.9%, 1.9%, and 1.1% for the 5-, 10-, 20-, 30-, and 40-mg rivaroxaban groups, respectively) compared with the phase II twice-daily dosing study with rivaroxaban (2.9%, 0.9%, 1.0%, and 3.0% for total daily doses of 5, 10, 20, and 40 mg rivaroxaban, respectively).<sup>7</sup> Because of its limited efficacy for the prevention of major VTE, and despite its efficacy for the prevention of the primary end point, 5 mg rivaroxaban OD was defined as the lowest effective dose.

The incidence of proximal DVT observed with enoxaparin (2.8%) was lower than that observed in previous studies that used 40 mg enoxaparin OD (5.2%),<sup>18</sup> which was similar to that observed in the rivaroxaban phase II twice-daily dosing study (4.7%).<sup>7</sup> The incidence of symptomatic VTE events was low during treatment and follow-up after short-term rivaroxaban (6 to 10 days).

There was a significant dose trend for major postoperative bleeding across the rivaroxaban treatment groups ( $P=0.0391$ ). The observed incidences were similar in the 5- and 10-mg rivaroxaban OD dose groups and the enoxaparin group (2.3% and 0.7% versus 1.9%, respectively). The observed incidences in the 20-, 30-, and 40-mg rivaroxaban OD dose groups were higher than with enoxaparin, but no dose group was discontinued because of excessive bleeding. Importantly, there were no fatal bleeding events or bleeding into a critical organ, all major bleeding events were confined to the surgical site, and only 2 patients (1 in each of the 20- and 30-mg rivaroxaban OD groups) required reoperation.

The incidence of major postoperative bleeding was similar in this study, after once-daily dosing (2.3%, 0.7%, 4.3%, 4.9%, and 5.1% for rivaroxaban doses of 5, 10, 20, 30, and 40 mg OD), to that seen with twice-daily dosing in the previous phase II study (0.8%, 2.2%, 2.3%, and 4.5% for total daily

**TABLE 5. Patients With Liver Aminotransferase Levels >3× ULN (Safety Population; n=845)**

Laboratory Parameter	Rivaroxaban					Enoxaparin
	5 mg OD (n=128)	10 mg OD (n=142)	20 mg OD (n=139)	30 mg OD (n=142)	40 mg OD (n=137)	40 mg OD (n=157)
ALT >3× ULN, n/N* (%)	5/119 (4.2)	5/133 (3.8)	4/133 (3.0)	7/129 (5.4)	5/127 (3.9)	10/140 (7.1)
AST >3× ULN, n/N* (%)	4/119 (3.4)	5/134 (3.7)	6/133 (4.5)	8/129 (6.2)	5/127 (3.9)	10/141 (7.1)

\*Number of patients with specified laboratory abnormality/total number of patients who had laboratory tests.

rivaroxaban doses of 5, 10, 20, and 40 mg).<sup>7</sup> This suggests that once-daily administration of rivaroxaban does not increase bleeding risk compared with twice-daily dosing.

The observed incidence of clinically relevant, non-major bleeding was lower in all rivaroxaban dose groups than that observed with enoxaparin, and minor bleeding followed the same pattern as major bleeding, with a similar incidence compared with enoxaparin in the lower rivaroxaban dose groups. The proportion of patients requiring transfusion was similar in all rivaroxaban dose groups and the enoxaparin group, and similar to that reported in other clinical trials investigating anticoagulants in patients undergoing hip replacement surgery<sup>16,20,21</sup>; the volume of blood transfused was also similar in all rivaroxaban dose groups and the enoxaparin group.

The incidence of increased aminotransferase levels after short-term exposure to rivaroxaban (6 to 10 days) did not exceed that observed with enoxaparin. However, an undesired effect on liver functions tests was noted in 2 patients receiving rivaroxaban. One patient had an increase in ALT  $>3\times$  ULN and bilirubin  $>2\times$  ULN early during treatment, and another had an early rise in ALT that persisted during follow-up. Neither of these patients had clinical symptoms suggestive of impaired liver function. It was not possible to draw definite conclusions to elucidate the causes of these raised liver enzymes; further studies are required to determine whether there is a relationship with rivaroxaban.

In the present study, an 8-fold dose range of rivaroxaban (5 to 40 mg) given once daily postoperatively showed similar efficacy to enoxaparin (40 mg OD) for the prevention of VTE after elective total hip replacement surgery, without the need for routine coagulation monitoring. Major bleeding rates observed in the 5- and 10-mg rivaroxaban OD dose groups were similar to those with enoxaparin. When both efficacy and safety are considered, the results of this study suggest that 10 mg rivaroxaban OD should be investigated in future clinical studies. When compared with current anticoagulants, the improved pharmacological characteristics of rivaroxaban—such as oral, once-daily dosing without the need for coagulation monitoring—make it potentially attractive for long-term anticoagulation.

### Acknowledgments

We thank A. Migge and K. Müller for their valuable contributions to this study.

### Source of Funding

This study was sponsored by Bayer HealthCare.

### Disclosures

Drs Eriksson, Borris, Dahl, Haas, Kakkar, and Huisman received reimbursement as consultants in this project. Dr Kälebo was reimbursed as a member of the adjudication committee. Drs Muehlhofer, Dierig, and Misselwitz are employed by and have ownership interest in Bayer. Drs Borris, Dahl, and Huisman have served as consultants to and/or received honoraria from Bayer. Dr Eriksson has received research grants from Astellas and Boehringer Ingelheim; has received honoraria from Bayer, Astellas, and Boehringer Ingelheim; and has served as a paid consultant to Bayer, Astellas, and Boeh-

ringer Ingelheim. Dr Haas has received a research grant for the Phase IIa-study with Liery Xa-inhibitor; has served on the speakers' bureaus of sanofi-aventis and GlaxoSmithKline; has received honoraria from AstraZeneca; and has served as an expert witness in medico-legal cases settled at court in Germany. Dr Kakkar has received research funding from AstraZeneca and Sanofi-Aventis; has received honoraria from sanofi-aventis, Pfizer, Bayer, Emisphere, Merck, and Boehringer Ingelheim; and has served as a consultant to and/or on the advisory boards of Bayer, sanofi-aventis, and Emisphere.

### References

- Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004; 126:338S–400S.
- Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther*. 2005;78: 412–421.
- Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol*. 2005;61:873–880.
- Weinz C, Buethorn U, Daehler HP, Kohlsdorfer C, Pleiss U, Sandmann S, Schlemmer KH, Schwarz T, Steinke W. Pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—in rats and dogs. *Xenobiotica*. 2005;35:891–910.
- Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Effects of single-dose BAY 59-7939—an oral, direct Factor Xa inhibitor—in subjects with extreme body weight. *Blood*. 2005;106:Abstract 1872.
- Weinz C, Schwartz T, Pleiss U, Schmeer K, Kubitza D, Mueck W, Condol D, Atken H. Metabolism and distribution of [<sup>14</sup>C]BAY 59-7939—an oral, direct factor Xa inhibitor—in rat, dog and human. *Drug Metab Rev*. 2004;36(suppl 1):98. Abstract 196.
- Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Kalebo P. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost*. 2006;4:121–128.
- Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kalebo P, Misselwitz F, Gent M. BAY 59-7939: an oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement: a phase II dose-ranging study. *J Thromb Haemost*. 2005;3: 2479–2486.
- Harder S, Graff J, Hentig NV, Misselwitz F, Kubitza D, Zuehlsdorf M, Wensing G, Mueck W, Becka M, Breddin HK. Effects of BAY 59-7939, an oral, direct Factor Xa inhibitor, on thrombin generation in healthy volunteers. *Pathophysiol Haemost Thromb*. 2004;33(suppl 2):97. Abstract PO078.
- Kubitza D, Becka M, Voith B, Zuehlsdorf M. Effect of enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor. *J Thromb Haemost*. 2005; 3(suppl 1):P1704.
- Committee for Proprietary Medicinal Products (CPMP). *Points to Consider on Clinical Investigation of Medicinal Products for Prophylaxis of Intra- and Post-Operative Venous Thromboembolic Risk*. CPMP/EWP/ 707/98. London, UK: European Agency for the Evaluation of Medicinal Products (EMA); 2000.
- Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg*. 1972;104:134–144.
- Kalebo P, Ekman S, Lindbratt S, Eriksson BI, Pauli U, Zachrisson BE, Close P. Percentage of inadequate phlebograms and observer agreement in thromboprophylactic multicenter trials using standardized methodology and central assessment. *Thromb Haemost*. 1996;76:893–896.
- Kalebo P, Anthmyr BA, Eriksson BI, Zachrisson BE. Optimization of ascending phlebography of the leg for screening of deep vein thrombosis in thromboprophylactic trials. *Acta Radiol*. 1997;38:320–326.
- Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet*. 2002;359:1721–1726.
- Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous

- thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet*. 2002;359:1715–1720.
17. Eriksson BI, Dahl OE, Ahnfelt L, Kalebo P, Stangier J, Nehmiz G, Hermansson K, Kohlbrenner V. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J Thromb Haemost*. 2004;2:1573–1580.
  18. Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, Ahnfelt L, Piovella F, Stangier J, Kalebo P, Reilly P. 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. *J Thromb Haemost*. 2005;3:103–111.
  19. Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, Frison L, Eriksson UG, Welin L, Gustafsson D. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet*. 2002;360:1441–1447.
  20. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ogren M. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost*. 2003;89:288–296.
  21. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, Rosencher N, Kalebo P, Panfilov S, Eskilson C, Andersson M, Freij A. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. *J Thromb Haemost*. 2003;1:2490–2496.

### CLINICAL PERSPECTIVE

Anticoagulants are recommended for the management of thrombosis, including the prevention and treatment of thrombosis after major orthopedic surgery and the prevention of stroke in patients with atrial fibrillation. Currently available anticoagulants are effective but are administered parenterally (eg, low-molecular-weight heparins) or are difficult to manage because of their unpredictable pharmacological profile (eg, warfarin). Rivaroxaban is an oral, direct Factor Xa inhibitor in advanced clinical development. Rivaroxaban has been shown to be as safe and effective as enoxaparin for thromboprophylaxis after major orthopedic surgery in 2 phase II dose-finding studies that used a twice-daily regimen. The present phase II study investigated the efficacy and safety of once-daily rivaroxaban for this indication. Rivaroxaban had efficacy similar to that of enoxaparin across the dose range studied (5 to 40 mg). The rate of major bleeding (primary safety end point) was also similar to that of enoxaparin in the 5- and 10-mg once-daily dose groups. When both efficacy and safety were considered, these results suggest that rivaroxaban 10 mg once daily should be further investigated for this indication. Indeed, the ongoing phase III RECORD (REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE) study program is investigating this dosing regimen. Rivaroxaban is also in phase III development for the treatment for venous thromboembolism and the prevention of stroke in patients with atrial fibrillation. Compared with currently available anticoagulants, the predictable pharmacological profile of rivaroxaban and lack of need for coagulation monitoring make it an attractive proposition for both short- and long-term anticoagulation.