

Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial



Ajay K Kakkar, Benjamin Brenner, Ola E Dahl, Bengt I Eriksson, Patrick Mouret, Jim Muntz, Andrea G Soglian, Ákos F Pap, Frank Misselwitz, Sylvia Haas, for the RECORD2 Investigators*

Summary

Background The risk of venous thromboembolism is high after total hip arthroplasty and could persist after hospital discharge. Our aim was to compare the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis with enoxaparin.

Methods 2509 patients scheduled to undergo elective total hip arthroplasty were randomly assigned, stratified according to centre, with a computer-generated randomisation code, to receive oral rivaroxaban 10 mg once daily for 31–39 days (with placebo injection for 10–14 days; n=1252), or enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo tablet for 31–39 days; n=1257). The primary efficacy outcome was the composite of deep-vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venography), non-fatal pulmonary embolism, and all-cause mortality up to day 30–42. Analyses were done in the modified intention-to-treat population, which consisted of all patients who had received at least one dose of study medication, had undergone planned surgery, and had adequate assessment of thromboembolism. This study is registered at ClinicalTrials.gov, number NCT00332020.

Findings The modified intention-to-treat population for the analysis of the primary efficacy outcome consisted of 864 patients in the rivaroxaban group and 869 in the enoxaparin group. The primary outcome occurred in 17 (2·0%) patients in the rivaroxaban group, compared with 81 (9·3%) in the enoxaparin group (absolute risk reduction 7·3%, 95% CI 5·2–9·4; p<0·0001). The incidence of any on-treatment bleeding was much the same in both groups (81 [6·6%] events in 1228 patients in the rivaroxaban safety population vs 68 [5·5%] of 1229 patients in the enoxaparin safety population; p=0·25).

Interpretation Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events, in patients undergoing total hip arthroplasty.

Funding Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and Development LLC.

Introduction

Heparin-based thromboprophylaxis in the perioperative period reduces fatal pulmonary embolism.¹ Its provision for the duration of hospital stay has been recommended for more than two decades,² and its use is one of the most highly rated patient safety interventions.³ For patients undergoing elective hip arthroplasty, consensus guidelines recommend pharmacological prophylaxis for a minimum of 10 days, and up to 35 days after surgery.^{4–6} Despite evidence from meta-analyses indicating that extended thromboprophylaxis after elective hip arthroplasty reduces the frequency of venous thromboembolic disease,^{7,8} its use out of hospital is infrequent, with less than 50% of patients receiving prophylaxis for 28 days in a large prospective registry.⁹ Alternative pharmacological methods include acetylsalicylic acid which, when used as extended thromboprophylaxis in a large trial,¹⁰ reduced the risk of

pulmonary embolism and deep-vein thrombosis compared with placebo, although its use remains controversial in this setting.^{4,5} Physicians have remained sceptical about the clinical relevance of extended prophylaxis, and are concerned about the potential risk for adverse outcomes, in particular bleeding.¹¹

Trials of sufficient magnitude to show a consistent benefit for extending the duration of thromboprophylaxis, in terms of asymptomatic and symptomatic venous thromboembolism, with rigorous assessment of potential adverse events, are still required if the potential benefits of such interventions are to be more widely realised.^{12–14} Furthermore, the duration of short-term prophylaxis in existing trials has been suggested to be too short (7–10 days), and that trials comparing 10–14 days' prophylaxis with 28–35 days' prophylaxis and assessing symptomatic events would provide more valuable information.¹⁵ The aim of RECORD2 (Regulation of

Lancet 2008; 372: 31–39

Published Online

June 25, 2008

DOI:10.1016/S0140-

6736(08)60880-6

See [Comment](#) page 6

*Listed at end of paper

Barts and the London School of Medicine and Dentistry, London, UK

(Prof A K Kakkar MD);

Thrombosis Research Institute, London, UK (Prof A K Kakkar,

O E Dahl MD); Rambam Medical Center, Haifa, Israel

(Prof B Brenner MD);

Sahlgrenska University Hospital/Östra, Gothenburg,

Sweden (B I Eriksson MD);

Frankfurt-Höchst Clinic, Frankfurt, Germany

(P Mouret MD); Methodist and St Luke's Hospitals, Houston,

TX, USA (J Muntz MD); Bayer HealthCare, Milan, Italy

(A G Soglian MD); Bayer HealthCare AG, Wuppertal,

Germany (F Misselwitz MD,

Á F Pap); and Institute for Experimental Oncology and Therapy Research, TU, Munich,

Germany (Prof S Haas MD)

Correspondence to:

Prof Ajay K Kakkar, Barts and the London School of Medicine and Dentistry, Turner Street, London

E1 2AD, UK

akkakkar@tri-london.ac.uk

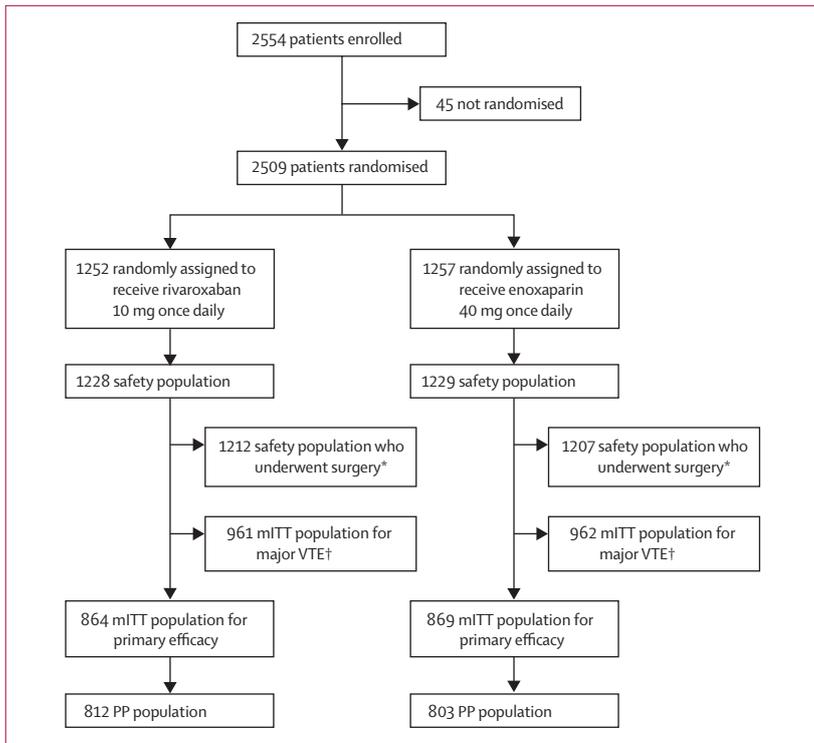


Figure 1: Trial profile

mITT=modified intention-to-treat. PP=per-protocol. VTE=venous thromboembolism. *Analysis of symptomatic venous thromboembolism done in patients valid for the safety analysis who had undergone surgery, because the incidence of symptomatic venous thromboembolism is not affected by the validity of venograms. †Patients could be valid for the assessment of major venous thromboembolism if proximal veins were evaluable on the venogram, irrespective of whether distal veins were.

Coagulation in ORthopaedic surgery to prevent Deep-vein thrombosis and pulmonary embolism 2) was to assess extended thromboprophylaxis with an oral factor Xa inhibitor, rivaroxaban, for 31–39 days,^{16–18} compared with a short-term enoxaparin regimen for 10–14 days followed by placebo in patients undergoing total hip arthroplasty.

Methods

Patients

Patients were enrolled between February, 2006, and April, 2007, in this randomised, multinational, double-blind, double-dummy trial, involving 123 centres across 21 countries worldwide. Patients, aged 18 years or over, who were scheduled to undergo elective total hip arthroplasty were eligible for inclusion. Patients were ineligible if they were scheduled to undergo staged bilateral hip arthroplasty, had active bleeding or a high risk of bleeding, or had any condition contraindicating the use of enoxaparin or that might require enoxaparin dose adjustment, including severe renal impairment. Other ineligibility criteria included: significant liver disease, pregnancy or breastfeeding, concomitant use of HIV protease inhibitors, use of fibrinolytic therapy or planned intermittent pneumatic compression during the

study period, conditions preventing bilateral venography, or the requirement for an anticoagulant that could not be discontinued.

The trial was done in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by the institutional ethics review board of each centre and written, informed consent was obtained from patients before randomisation.

Procedures

Patients were randomly assigned to study medication before surgery, using permuted blocks (size four) with stratification according to centre, via a central telephone system using a computer-generated randomisation code. Patients were randomly assigned to receive double-blind, oral rivaroxaban 10 mg tablets once daily (Xarelto, Bayer HealthCare AG, Wuppertal, Germany) or subcutaneous injections of enoxaparin sodium 40 mg once daily (Clexane/Lovenox, Sanofi-Aventis, Frankfurt am Main, Germany). Rivaroxaban was started 6–8 h after wound closure and continued for 31–39 days; patients also received placebo injections for 10–14 days, starting 12 h before surgery. Enoxaparin was initiated 12 h before surgery and restarted 6–8 h after wound closure and continued for 10–14 days; patients also received placebo tablets for 31–39 days starting 6–8 h after wound closure. Rivaroxaban 10 mg once daily was selected on the basis of the results of a phase IIb study.¹⁶

The day of surgery was defined as day 1. Patients underwent mandatory, bilateral venography the day after the last dose of study medication—ie, day 32–40. After venography, no further study medication was given, and further thromboprophylaxis was at the investigator's discretion. Patients were followed up 30–35 days after the last dose of study medication.

All outcomes were assessed by independent, central adjudication committees blinded to treatment allocation. The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality up to day 30–42. The major secondary efficacy outcome was major venous thromboembolism—the composite of proximal deep-vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death. Other efficacy outcomes included the incidence of deep-vein thrombosis (any, proximal, distal), the incidence of symptomatic venous thromboembolism in the treatment and follow-up period, and death during the follow-up period.

Deep-vein thrombosis was assessed on day 32–40, or earlier if symptomatic, by ascending, bilateral venography using the Rabinov and Paulin technique.¹⁹ All suspected deep-vein thromboses had to be confirmed by venography (positive ultrasound had to be confirmed). In cases of suspected pulmonary embolism, pulmonary angiography, perfusion/ventilation lung scintigraphy with chest radiography, or spiral computed tomography

was done. If death occurred, all relevant documentation was collected, including autopsy reports, if available.

The main safety outcome was the incidence of major bleeding events beginning after the first intake, and up to 2 days after the last intake, of study medication (on-treatment). Major bleeding was defined as bleeding that was fatal, was into a critical organ (eg, retroperitoneal, intracranial, intraocular, intraspinal), required re-operation, or clinically overt extra-surgical-site bleeding associated with a fall in haemoglobin of 20 g/L or more, calculated from the day 1 post-operative baseline value, or requiring infusion of two or more units of whole blood or packed cells. Other

safety outcomes included: any on-treatment bleeding; any on-treatment non-major bleeding (any on-treatment bleeding event not adjudicated as major bleeding); haemorrhagic wound complications (the composite of excessive wound haematoma and surgical-site bleeding); any post-operative bleeding (ie, bleeding starting after the first tablet intake and ending up to 2 days after last intake of study medication); adverse events; and death. Liver biochemistry and cardiovascular adverse events were monitored throughout the treatment and follow-up periods, and each event was independently and blindly adjudicated.

Statistical analysis

The sample size calculation was based on an assumed event rate of 11% in the enoxaparin group and a risk reduction of 40% with rivaroxaban. If these assumptions were correct, 914 patients per group would be sufficient to detect such a reduction in relative risk with a power of 90% and a two-sided type 1 error rate of 5% (corresponding to an absolute risk reduction of 4.4% and an event rate of 6.6% in the rivaroxaban group). An invalidity rate of 25% was assumed, resulting in a target sample size of 2500 patients.

The aim of the trial was to determine whether 5 weeks' prophylaxis with rivaroxaban was better than 2 weeks'

	Extended thromboprophylaxis with rivaroxaban	Short-term thromboprophylaxis with enoxaparin
Randomised	1252 (100%)	1257 (100%)
Safety population	1228 (98.1%)	1229 (97.8%)
No intake of study medication	24 (1.9%)	28 (2.2%)
Symptomatic venous thromboembolism population (safety population who underwent surgery)	1212 (96.8%)	1207 (96.0%)
Major venous thromboembolism population (modified intention to treat)*	961 (76.8%)	962 (76.5%)
Major venous thromboembolism population (per protocol)	898 (71.7%)	884 (70.3%)
Primary efficacy population (modified intention to treat)	864 (69.0%)	869 (69.1%)
No planned surgery	16 (1.3%)	22 (1.8%)
Inadequate assessment of thromboembolism	348 (27.8%)	338 (26.9%)
Venography not done	155 (12.4%)	159 (12.6%)
Unilateral venography	57 (4.6%)	57 (4.5%)
Indeterminate/unevaluable venography	127 (10.1%)	111 (8.8%)
Not in time window	9 (0.7%)	11 (0.9%)
Per-protocol population	812 (64.9%)	803 (63.9%)
Incorrect time interval between end of surgery and first post-operative dose	18 (1.4%)	18 (1.4%)
Incorrect time interval between last dose and assessment of venous thromboembolism	15 (1.2%)	23 (1.8%)
Inadequate assessment of thromboembolism	0 (0.0%)	2 (0.2%)
Inadequate compliance†	17 (1.4%)	13 (1.0%)
Intake of prohibited anticoagulant	0 (0.0%)	8 (0.6%)
Intermittent pneumatic compression	1 (0.1%)	2 (0.2%)
Wrong intake of study medication	1 (0.1%)	0 (0.0%)

Data are n (%). *Patients could be valid for major venous thromboembolism assessment if proximal veins were evaluable on the venogram, irrespective of whether distal veins were. †Based on documented administration of drug and counting of unused study medication.

Table 1: Patients included and excluded from analyses, and reasons for exclusion

	Extended thromboprophylaxis with rivaroxaban (N=1228)	Short-term thromboprophylaxis with enoxaparin (N=1229)
Sex (female)	667 (54.3%)	651 (53.0%)
Age (years)	61.4 (13.2, 18–93, 53.0–71.0)	61.6 (13.7, 19–93, 54.0–72.0)
Weight (kg)	74.3 (15.8, 41–149, 62.0–84.0)	75.2 (17.5, 33–151, 63.0–85.0)
Body-mass index (kg/m ²)	26.8 (4.8, 15.6–54.7, 23.5–29.4)	27.1 (5.2, 15.5–59.0, 23.6–30.0)
Ethnic origin		
White	799 (65.1%)	798 (64.9%)
Asian	247 (20.1%)	244 (19.9%)
Hispanic	134 (10.9%)	142 (11.6%)
Black	35 (2.9%)	29 (2.4%)
American Indian	1 (0.1%)	1 (0.1%)
Other/missing	12 (1.0%)	15 (1.2%)
History of venous thromboembolism	10 (0.8%)	20 (1.6%)
Previous orthopaedic surgery	225 (18.3%)	232 (18.9%)
Type of surgery		
Primary	1160 (94.5%)	1157 (94.1%)
Revision	52 (4.2%)	50 (4.1%)
Missing/no surgery	16 (1.3%)	22 (1.8%)
Use of cement	621 (50.6%)	608 (49.5%)
Type of anaesthesia		
General only	341 (27.8%)	333 (27.1%)
General and regional	77 (6.3%)	91 (7.4%)
Regional only	794 (64.7%)	783 (63.7%)
Missing	16 (1.3%)	22 (1.8%)
Duration of surgery (min)	95.0 (30–475, 72–125)	93.0 (28–595, 73–126)

Data are mean (SD, range, IQR), median (range, IQR), or n (%).

Table 2: Baseline characteristics and surgical characteristics of patients in safety population (N=2457)

	Extended thromboprophylaxis with rivaroxaban	Short-term thromboprophylaxis with enoxaparin	Absolute risk reduction (95% CI)*	p value†
Primary efficacy outcome‡	17/864 (2.0%, 1.2–3.1)	81/869 (9.3%, 7.5–11.5)	7.3% (5.2–9.4)	<0.0001
Death	2/864 (0.2%, <0.1–0.8)	6/869 (0.7%, 0.3–1.5)	0.5% (–0.2 to 1.1)	0.29
Non-fatal pulmonary embolism	1/864 (0.1%, <0.1–0.6)	4/869 (0.5%, 0.1–1.2)	0.3% (–0.2 to 1.1)	0.37
Deep-vein thrombosis	14/864 (1.6%, 0.9–2.7)	71/869 (8.2%, 6.4–10.2)	6.5% (4.5–8.5)	<0.0001
Proximal	5/864 (0.6%, 0.2–1.3)	44/869 (5.1%, 3.7–6.7)	4.5% (2.9–6.0)	<0.0001
Distal only	9/864 (1.0%, 0.5–2.0)	27/869 (3.1%, 2.1–4.5)	2.0% (0.7–3.3)	0.0025
Major venous thromboembolism§	6/961 (0.6%, 0.2–1.4)	49/962 (5.1%, 3.8–6.7)	4.5% (3.0–6.0)	<0.0001
Symptomatic venous thromboembolism¶	3/1212 (0.2%, <0.1–0.7)	15/1207 (1.2%, 0.7–2.0)	1.0% (0.3–1.8)	0.0040
Symptomatic venous thromboembolism in follow-up period¶	1/1212 (0.1%, <0.1–0.5)	2/1207 (0.2%, <0.1–0.6)	0.1% (–0.2 to 0.4)	0.62
Death in follow-up period	0/1228 (0.0%, 0.0–0.3)	2/1229 (0.2%, <0.1–0.6)	0.2% (–0.1 to 0.6)	0.50

Data are n/N (% , 95% CI) unless otherwise specified. *Mantel-Haenszel weighted absolute risk reduction in patients receiving extended thromboprophylaxis with rivaroxaban compared with short-term enoxaparin. For endpoints that occurred infrequently (less than ten events in total—ie, death [within the time window and during follow-up], non-fatal pulmonary embolism, symptomatic venous thromboembolism in the follow-up), unweighted risk reductions and exact CIs are given. Calculation and rounding of absolute risk reduction is based on the difference in unrounded incidences. †Values calculated based on the Mantel-Haenszel weighted estimate. For endpoints that occurred infrequently (less than ten events in total—ie, death [within the time window and during follow-up], non-fatal pulmonary embolism, symptomatic venous thromboembolism in the follow-up), p values according to Fisher's exact test are given. ‡Composite of any deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality. §Composite of proximal deep-vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death. ¶Any symptomatic deep-vein thrombosis (proximal or distal) or symptomatic non-fatal or fatal pulmonary embolism in patients valid for the safety population who underwent surgery. ||Follow-up started the day after adequate assessment of thromboembolism (venography or symptomatic event up to day 41 after surgery) for each patient.

Table 3: Incidence of events (efficacy)

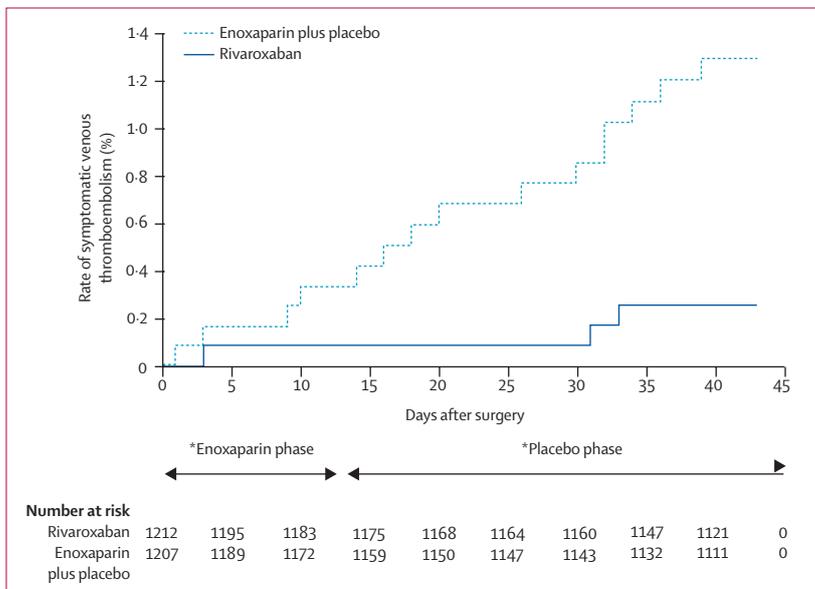


Figure 2: Cumulative event rate of symptomatic venous thromboembolism
 *Patients who received at least one dose of study medication (ie, safety population) and underwent surgery. In the case of multiple events per patient, the event that occurred first was considered. All symptomatic venous thromboembolic events were considered up to day 42 after surgery. Patients without symptomatic venous thromboembolism were deemed to be censored at day 42 after surgery or at the last contact, whichever was earlier. p=0.0043 for difference between groups; log-rank test (post-hoc analysis).

prophylaxis with enoxaparin followed by placebo, assessed in a modified intention-to-treat population. The modified intention-to-treat population consisted of all patients who were valid for the safety analysis (ie, who had received at least one dose of study medication), had undergone planned surgery, and had adequate assessment of thromboembolism. Patients valid for the

assessment of major venous thromboembolism were those who were valid for the safety analysis who had undergone surgery and in whom the venograms were evaluable for the proximal veins, irrespective of whether they were valid for distal veins.

Differences between the incidences of the primary and major secondary efficacy outcomes with extended thromboprophylaxis with rivaroxaban and short-term enoxaparin plus placebo were estimated with Mantel-Haenszel weighting (stratified by country), with a corresponding asymptotic two-sided 95% CI and two-sided p value. Superiority was demonstrated if the upper limit of the 95% CI for the treatment difference (rivaroxaban–enoxaparin) was below 0. The two-sided 95% CI and the p value for the unweighted relative risk reduction were calculated with an asymptotic method. If the incidence of the secondary outcomes was low, exact unweighted two-sided 95% CI were calculated and Fisher's exact test was used to test for superiority.

The incidence of symptomatic venous thromboembolism was assessed in patients valid for the safety analysis who had undergone surgery—this outcome was not dependent on obtaining evaluable venograms.

Differences in the incidence of major bleeding between the groups were analysed as for efficacy; other safety outcomes were analysed by appropriate descriptive methods. The time-to-onset of clinically relevant bleeding and time-to-onset of symptomatic venous thromboembolic events were compared between treatment groups with a log-rank test.

We did two sensitivity analyses for the primary efficacy outcome. The first analysis included all randomised patients who had an evaluable bilateral venography

(adjudicated), irrespective of whether it was in the time window, or a confirmed symptomatic/asymptomatic event/death, irrespective of whether it was in the time window. Events in the follow-up period were also considered. The second analysis included all randomised participants included in the first sensitivity analysis plus those who had an evaluable bilateral venography/ultrasonography as done by the investigator, irrespective of whether it was in the time window, or a symptomatic/asymptomatic event/death, irrespective of whether it was in the time window, provided the symptomatic event was not adjudicated to be a non-event by the VTE committee. Events in the follow-up period were also considered.

All statistical analyses were done with SAS version 8.2, StatXact version 7, and Stata version 10. This trial is registered with ClinicalTrials.gov, number NCT00332020.

Role of the funding source

The study sponsors were involved in the design and conduct of the trial. The data were collected and analysed by the sponsors of the study. All authors had full access to all of the data and analyses and vouch for the accuracy and completeness of the data reported. All authors were involved in the final decision to submit the manuscript.

Results

The trial profile is shown in figure 1. 776 patients were excluded from the modified intention-to-treat population for the primary efficacy analysis, and 52 patients were excluded from the safety population. Reasons for exclusion from the various study populations are shown in table 1. Baseline and surgical characteristics were much the same in the two groups (table 2). Mean duration of rivaroxaban therapy was 33.5 (SD 6.9) days, and 12.4 (3.0) days with enoxaparin (safety population).

The primary efficacy outcome occurred in significantly fewer patients receiving extended thromboprophylaxis with rivaroxaban than in those receiving short-term enoxaparin plus placebo in the modified intention-to-treat population (table 3). Likewise, major venous thromboembolism occurred in significantly fewer patients receiving extended thromboprophylaxis with rivaroxaban than in those receiving short-term enoxaparin plus placebo (table 3).

The incidence of symptomatic venous thromboembolism during the active study period (day 1–42) in patients valid for the safety analysis and who underwent surgery was also lower in patients receiving extended thromboprophylaxis with rivaroxaban than in those receiving short-term enoxaparin plus placebo (table 3 and figure 2). The symptomatic venous thromboembolic events in the rivaroxaban group occurred on days 3, 31, and 33; in the enoxaparin group they occurred on days 1, 3, 9, 10, 14, 16, 18, 20, 26, 30, 32 (two events), 34, 36, and 39. During the follow-up period, symptomatic venous thromboembolism occurred in one patient in the rivaroxaban group (non-fatal pulmonary embolism) and two in the enoxaparin plus

	Extended thromboprophylaxis with rivaroxaban (N=1228)	Short-term thromboprophylaxis with enoxaparin (N=1229)
Any on-treatment bleeding*†	81 (6.6%)	68 (5.5%)
Major bleeding†‡	1 (<0.1%, <0.1-0.5)	1 (<0.1%, <0.1-0.5)
Fatal bleeding	0 (0.0%)	0 (0.0%)
Bleeding into a critical organ	0 (0.0%)	1 (<0.1%)
Bleeding leading to re-operation	0 (0.0%)	0 (0.0%)
Clinically overt extra-surgical-site bleeding leading to a fall in haemoglobin	1 (<0.1%)	0 (0.0%)
Clinically overt extra-surgical-site bleeding leading to transfusion of ≥2 units of blood	1 (<0.1%)	0 (0.0%)
Non-major bleeding†‡	80 (6.5%)	67 (5.5%)
Clinically relevant non-major bleeding§	40 (3.3%)	33 (2.7%)
Haemorrhagic wound complications¶	20 (1.6%)	21 (1.7%)
Other non-major bleeding	43 (3.5%)	36 (2.9%)
Post-operative wound infections	8 (0.7%)	6 (0.5%)
Any bleeding beginning after initiation of rivaroxaban or placebo tablet**	56/1197 (4.7%)	49/1193 (4.1%)
Patients receiving blood transfusions	485 (39.5%)	514 (41.8%)
Volume of blood transfusion (mL)	600 (91–4900)	600 (81–8900)
Number of patients with post-operative volume in drain	791 (64.4%)	789 (64.2%)
Volume in drain (mL)	470 (2–2700)	441 (20–2680)
Any on-treatment adverse event††	768 (62.5%)	807 (65.7)
Drug-related adverse events	245 (20.0%)	249 (20.3)
Cardiovascular adverse events	8 (0.7%)	4 (0.3)‡‡
Cardiovascular death	2 (0.2%)	0 (0)
Ischaemic stroke	2 (0.2%)	1 (<0.1)
Myocardial infarction§§	4 (0.3%)	3 (0.2)
Serious on-treatment adverse events	90 (7.3%)	131 (10.7)
Drug-related serious on-treatment adverse events	13 (1.1%)	17 (1.4)
Adverse events leading to discontinuations	46 (3.8%)	64 (5.2)

Data are n (%), n (%), 95% CI, n/number of patients with particular symptom (%), or median (range). *p=0.25 for difference. †Adjudicated on-treatment bleeding events beginning after initiation of double-blind study medication and up to 2 days after the last intake of double-blind study medication. ‡Patients may have events that fall into more than one category. §Clinically relevant non-major bleeding events included events such as multiple source bleeding, spontaneous haematoma >25 cm² and excessive wound haematoma. ¶Composite of excessive wound haematoma and surgical-site bleeding. ||Events coded as post-operative wound infection according to the MedDRA classification are shown. **Adjudicated on-treatment bleeding events beginning after initiation of rivaroxaban or placebo tablet and up to 2 days after the last intake of double-blind study medication. The denominator includes patients who took at least one tablet (rivaroxaban or placebo—ie, the safety population). ††MedDRA term after coding for all events. ‡‡All events occurred when patients were receiving active enoxaparin. §§One event occurred in a patient who had received one placebo injection only and had a myocardial infarction 2 days later.

Table 4: Safety outcomes

placebo group (one fatal pulmonary embolism and one non-fatal pulmonary embolism).

There were eight deaths during the active study period (table 3). Both deaths in the rivaroxaban group were judged to have been of cardiovascular cause; one occurred in a patient who had received one dose of rivaroxaban; the second patient died on day 39 having received a full course of rivaroxaban. In the enoxaparin group, the deaths were adjudicated as follows: one death related to pulmonary embolism, four unrelated to venous thromboembolism, and one unexplained. There was a further death in a patient randomised to receive rivaroxaban who did not undergo surgery or receive study

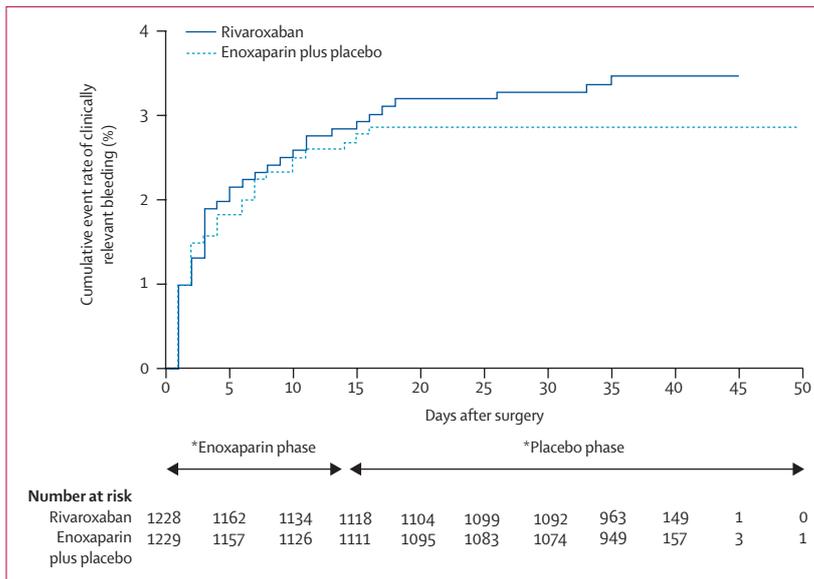


Figure 3: Cumulative event rate of clinically relevant bleeding events

*Patients who received at least one dose of study medication (ie, safety population). Clinically relevant bleeding events that occurred up to 2 days after last intake of study medication are included. Patients without clinically relevant bleeding were deemed to be censored 2 days after last study medication intake. $p=0.43$ for difference between groups; log-rank test (post-hoc analysis).

drug; this death was deemed to be unrelated to venous thromboembolism. During the follow-up period, two patients in the enoxaparin plus placebo group died (one was adjudicated as related to pulmonary embolism and the other was unexplained).

Major bleeding occurred in one patient in each group (table 4). The patient who received rivaroxaban had a suspected gastrointestinal bleeding event (haemorrhagic diarrhoea and haematemesis), and was given two units of whole blood because of low haemoglobin levels (8.9 g/L). Her haemoglobin levels fell to 12.3 g/L, which led to hospitalisation and discontinuation of rivaroxaban. The patient received acetylsalicylic acid without gastric protection before surgery. The patient who received enoxaparin had blood in the cerebrospinal fluid during spinal anaesthesia, which was deemed by the adjudication committee to be a major bleeding event not related to study drug; enoxaparin was discontinued. There were no reports of major surgical-site bleeding in either group.

Haemorrhagic wound complications, the composite of excessive wound haematoma and reported surgical-site bleeding, occurred in similar numbers of patients in both groups (table 4).

In a post-hoc analysis, the combination of major bleeding and clinically relevant non-major bleeding occurred in 41 (3.4%) patients receiving extended thromboprophylaxis with rivaroxaban and in 34 (2.8%) patients receiving short-term enoxaparin plus placebo (table 4). The temporal relationship between active thromboprophylaxis and bleeding events is shown in figure 3.

The requirements for blood transfusions, and the amounts of blood transfused were similar in each

group, as were drain volumes and the number of patients who had blood in their drain (table 4). The incidence of adverse events was similar in patients receiving extended thromboprophylaxis with rivaroxaban and short-term enoxaparin plus placebo (table 4 and table 5).

On-treatment, post-operative increases in plasma alanine aminotransferase concentrations greater than three times the upper limit of normal occurred in 19 (1.6%) of 1167 patients receiving extended thromboprophylaxis with rivaroxaban (all resolved by the end of the follow-up period) and 55 (4.7%) of 1164 patients receiving short-term enoxaparin (all resolved by the end of the follow-up period, except in two patients, both in the enoxaparin group, who withdrew from the trial prematurely and for whom no follow-up data were available). During the follow-up period, plasma alanine aminotransferase concentrations greater than three times the upper limit of normal occurred in six (0.5%) of 1101 patients receiving extended thromboprophylaxis with rivaroxaban and seven (0.6%) of 1097 patients receiving short-term enoxaparin. Two patients receiving extended thromboprophylaxis with rivaroxaban and three receiving short-term enoxaparin plus placebo had alanine aminotransferase concentrations greater than three times the upper limit of normal coupled with total bilirubin concentrations greater than twice the upper limit of normal; all cases resolved except for one patient who received enoxaparin plus placebo who had cholecystitis and in whom no follow-up data were available.

The incidence of cardiovascular events was low (table 4). Three patients had a cardiovascular event while receiving rivaroxaban (one had an ischaemic stroke, two had a myocardial infarction), and four had an event while receiving active enoxaparin (one had an ischaemic stroke, and three had a myocardial infarction). Five patients (0.4%) had a cardiovascular event more than one day after their last dose of rivaroxaban, four of which were an acute coronary event (0.3%; two events were cardiovascular deaths, and one event occurred in a patient who had received one placebo injection only and had a myocardial infarction 2 days later). There were no post-prophylaxis cardiovascular events in patients receiving enoxaparin.

A sample size of 2500 patients was planned to allow for a venography invalidity rate of 25%. We failed to obtain valid venograms for 348 (28%) rivaroxaban recipients and 338 (27%) enoxaparin plus placebo recipients, therefore sensitivity analyses were done. The first analysis included all events and all venograms that had been done. The weighted absolute risk reduction for the primary efficacy endpoint with extended thromboprophylaxis with rivaroxaban over short-term enoxaparin plus placebo was 7.1% (95% CI 4.9–9.2). The second analysis included all investigator assessments of venous thromboembolism; the weighted abso-

lute risk reduction with extended thromboprophylaxis with rivaroxaban was 6·4% (95% CI 4·3–8·5), similar to that seen for venographically detected deep-vein thrombosis.

Discussion

This trial indicates that extended thromboprophylaxis with rivaroxaban is significantly more effective than short-term thromboprophylaxis with enoxaparin followed by placebo for the prevention of venous thromboembolism—a composite of deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality—in patients undergoing total hip arthroplasty.

Current guidelines for extended prophylaxis after total hip arthroplasty are based on individual trials^{8,20–26} that show reductions in the incidence of asymptomatic deep-vein thrombosis, and on meta-analyses that show reductions in the incidence of symptomatic venous thromboembolism.^{7,8} Early trials that assessed extended prophylaxis included venographic assessment at discharge and at the end of the extended thromboprophylaxis period,^{25,26} which could potentially alter the natural history of thromboembolic disease. Our trial was powered to show that extended prophylaxis was better than short-term prophylaxis using the composite outcome of deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality, and included an a-priori analysis of symptomatic events, without any systematic intervention to alter the natural history of venous thromboembolism during therapy.

A potential limitation of our trial is the higher than anticipated invalidity rate for venograms. A sample size of 2500 patients was planned to allow for an invalid venography rate of 25%. We failed to obtain valid venograms for 28% of rivaroxaban recipients and 27% of enoxaparin recipients. However, sensitivity analyses showed that the missing data did not affect the power of the trial or bias the outcomes.

Although this study was not powered to assess differences in bleeding risk, rates of bleeding were low and much the same in both groups. The low rate of major bleeding could be due, at least in part, to the definition used—major bleeding did not include surgical-site bleeding events unless they required re-operation or were fatal. Although the definition of major bleeding differs from that used in other similar trials, and thus cannot be compared across studies, the classification of such events was agreed in advance of analysis with the relevant regulatory authorities and is consistent across the RECORD programme.^{27,28} Further research into the risk of bleeding is warranted.

The use of transfusion in post-operative patients is a subjective clinical judgment, and intra-operative blood loss before the administration of study medication could affect post-operative transfusion. In general, almost half of the patient population undergoing this type of surgical procedure require a transfusion of two or more units of

	Extended thromboprophylaxis with rivaroxaban (N=1228)	Short-term thromboprophylaxis with enoxaparin (N=1229)
Adverse events		
Serious adverse events	90 (7·3%)	131 (10·7%)
Total with adverse events*	742 (60·4%)	758 (61·7%)
Adverse events leading to treatment discontinuation	46 (3·8%)	64 (5·2%)
Adverse events during treatment with an incidence of ≥3% or difference of 10 or more events between any treatment group†		
Any event‡	768 (62·5%)	807 (65·7%)
Blood and lymphatic system disorders	105 (8·6%)	99 (8·1%)
Anaemia	73 (5·9%)	67 (5·5%)
Cardiac disorders	51 (4·2%)	55 (4·5%)
Tachycardia	12 (1·0%)	22 (1·8%)
Gastrointestinal disorders	323 (26·3%)	302 (24·6%)
Constipation	91 (7·4%)	90 (7·3%)
Diarrhoea	25 (2·0%)	39 (3·2%)
Nausea	165 (13·4%)	151 (12·3%)
Vomiting	94 (7·7%)	100 (8·1%)
General disorders and administration-site conditions	164 (13·4%)	164 (13·3%)
Oedema peripheral	55 (4·5%)	48 (3·9%)
Pyrexia	70 (5·7%)	58 (4·7%)
Infections and infestations	88 (7·2%)	87 (7·1%)
Injury, poisoning, and procedural complications	178 (14·5%)	177 (14·4%)
Wound secretion	33 (2·7%)	20 (1·6%)
Investigations	219 (17·8%)	249 (20·3%)
Alanine aminotransferase increased	40 (3·3%)	60 (4·9%)
Aspartate aminotransferase increased	36 (2·9%)	56 (4·6%)
Blood amylase increased	24 (2·0%)	13 (1·1%)
Gamma-glutamyltransferase increased	37 (3·0%)	56 (4·6%)
Haemoglobin decreased	54 (4·4%)	58 (4·7%)
Musculoskeletal and connective tissue disorders	83 (6·8%)	71 (5·8%)
Arthralgia	15 (1·2%)	26 (2·1%)
Pain in extremity	24 (2·0%)	12 (1·0%)
Nervous system disorders	134 (10·9%)	119 (9·7%)
Dizziness	54 (4·4%)	51 (4·2%)
Headache	37 (3·0%)	32 (2·6%)
Psychiatric disorders	46 (3·8%)	44 (3·6%)
Renal and urinary disorders	64 (5·2%)	54 (4·4%)
Skin and subcutaneous tissue disorders	130 (10·6%)	94 (7·7%)
Blister	23 (1·9%)	10 (0·8%)
Pruritus	37 (3·0%)	27 (2·2%)
Vascular disorders	153 (12·5%)	192 (15·6%)
Deep-vein thrombosis	37 (3·0%)	86 (7·0%)
Hypotension	79 (6·4%)	70 (5·7%)

Data are n (%). *Excluding bleeding, acute deep-vein thrombosis, and pulmonary embolic events (as assessed by the investigator). †According to MedDRA System Organ Class and Preferred Term, descending total frequency. ‡Including bleeding, acute deep-vein thrombosis and pulmonary embolic events (as assessed by the investigator).

Table 5: Adverse events during treatment

blood;²⁹ and peri-operative bleeding of 1500–2000 mL (greater than three units) is considered acceptable by most surgeons undertaking this procedure.³⁰ The assessment of clinically relevant non-major bleeding allowed these surgical-site bleeding events to be captured

(as part of haemorrhagic wound complications); extended thromboprophylaxis with rivaroxaban was not associated with any increase in such wound events, or any increase in wound infections. These findings may have important practical implications, because such events have been identified as potential clinical concerns contributing to the current underuse of extended pharmacological prophylaxis.³¹ The rate of symptomatic venous thromboembolic events in the short-term enoxaparin plus placebo group in this study is consistent with that reported in administrative datasets of 19 586 primary hip arthroplasties (2.8% within 90 days of surgery),¹⁴ indicating the relevance of our trial results in the context of contemporary orthopaedic clinical practice.

Although there seems to have been an increase in skin and subcutaneous tissue disorders, and in blistering in the rivaroxaban group compared with the enoxaparin group, no discernible trend can be seen if all three RECORD trials are considered together.^{27,28} Likewise, there exists an apparent excess of cardiovascular adverse events after discontinuation of rivaroxaban in this trial. This difference could be due to chance, and no trend is apparent when viewed across all three RECORD trials. We believe that the number of events is too low to allow us to draw any meaningful conclusions at this point; however, further research into the safety of rivaroxaban is warranted. Indeed, it is likely that further adoption of extended thromboprophylaxis will be aided by an emphasis on the evaluation of bleeding and other adverse events that might affect surgical outcome in these high-risk populations.

In summary, extended thromboprophylaxis with rivaroxaban—an orally active factor Xa inhibitor—substantially reduced the burden of venous thromboembolism, including major and symptomatic events in patients undergoing total hip arthroplasty, compared with short-duration prophylaxis with enoxaparin followed by placebo.

Contributors

All authors are members of the steering committee and contributed to the study concept, design and implementation, and to content and development of this manuscript.

RECORD2 Study Group

Steering committee—A K Kakkar, B Brenner, O E Dahl, B I Eriksson, P Mouret, J Muntz, A G Soglian, F Misselwitz, S Haas.

Independent central adjudication committee—M Levine.

Venous thromboembolic event adjudication committee—H Eriksson, G Sandgren, J Wallin.

Cardiovascular adverse event adjudication committee—J P Bassand, C Bode, T Lüscher.

Bleeding event adjudication committee—U Angeras, A Falk, M Prins.

Data safety and monitoring board—H Bounameaux, S Dittmar (sponsor contact), D Larray, W Lehmacher (independent statistician), A Leizorovicz.

Sponsor (Bayer HealthCare AG)—H Beckmann, A Benson, J Curram, M Fletcher, Á F Pap, T Westermeyer (statistical analysis); C Povesi (study management); A G Soglian (medical expert); C Fritze, M Hunke, K Müller (data management)

Investigators—(number of patients randomised and number of sites in each country is included in parenthesis). *Australia* (22 patients, six sites)—T Brighton, P Coughlin, A Curtin, I Prosser, B Richards,

C Ward, S Williams; Brazil (187 patients, 11 sites)—G Duarte, L Gomes, E Guydes, R Ikemoto, F Maldorado, K Mesquita, R Moreira, N Ono, M Roos, E Takata; *Canada* (127 patients, 11 sites)—P Ali, L Bredo, V DeKorompay, E Dessouki, S Dolan, J Guerra, G Jasey, P Kim, K McKenzie, J Naude, D Puskas, E Wai; *China* (325 patients, 12 sites)—T Chen, W He, H Lv, K Wang, Y Wang, Y Wang, W Xu, Q Yang, B Zeng, H Zhang, M Zhang; *Colombia* (172 patients, six sites)—R Botero, S Escandon, C Palacios, A Reyes, M Urina; *Denmark* (174 patients, six sites)—J Bagger, A Borgwardt, P Gebhur, N Krarup, G Lausten, P Mikkelsen, S Mikkelsen, A Phillipsen, B Roennow Duus; *Estonia* (93 patients, two sites)—A Koop, A Martson; *India* (42 patients, six sites)—S K Becera, M Desai, S J Mahajan, B Prasad, K Puttakemparaju, N Rajagopalan; *Indonesia* (14 patients, two sites)—D Roeshadi, F Tandjung; *Latvia* (43 patients, three sites)—U Argalis, J Dobelnieks, J Keselis; *Lithuania* (204 patients, four sites)—J Belickas, R Mazutaviene, V Smilgiene, R Tarasevicius; *Mexico* (35 patients, six sites)—E Nafarrete, E Sanchez; *New Zealand* (six patients, two sites)—S Chunilal, P Harper; *Norway* (113 patients, five sites)—K Griegel, B Haakan, O Hovik, H Hovind, P Stahl; *Peru* (137 patients, six sites)—L Arrieta, R Cotrina, C Diaz, Z Moncada, E Pastor, C Ruiz, M Salas, C Tochio; *Portugal* (35 patients, seven sites)—L Amaral, C Moniz, J Mousinho, P Oliveira, A Rodriguez; *South Africa* (132 patients, 13 sites)—U Dhanjee, J Diedericks, F Greeff, B Jacobson, S Moodley, R Routier, O Van der Spuy, J Viljoen, G J Vlok; *South Korea* (117 patients, four sites)—S Y Kim, Y H Kim, S H Lee, Y S Park; *Sweden* (234 patients, seven sites)—L Ahnfelt, L Bengtson, B Edshage, M Flondell, H C Hylidahl, J Johansson, H Laestander, B Pålsson, L Rytberg; *UK* (218 patients, 12 sites)—I Brenkel, E Crawford, A Cohen, R Field, S Frostick, D Meek, A Ratnam, S Sadullah, P Williams; *USA* (79 patients, five sites)—P Comp, A Corces, S Hakki, J Papilion, J Ward.

Conflict of interest statement

AFP and FM are employees of Bayer HealthCare AG. AGS is a former employee of Bayer HealthCare AG. All other authors received honoraria as members of the steering committee and have served as consultants to Bayer HealthCare AG.

Acknowledgments

This trial was supported by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research and Development LLC. The authors would like to thank Clare Ryles for editorial assistance in the preparation of the manuscript, with funding from Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research and Development LLC.

References

- 1 Kakkar VV, Corrigan TP, Fossard DP, et al. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *Lancet* 1975; 2: 45–51.
- 2 NIH. Prevention of venous thrombosis and pulmonary embolism. NIH consensus statement. 1986; 6: 1–8.
- 3 Shojania KG, Duncan BW, McDonald KM, Wachter RM. Making health care safer: a critical analysis of patient safety practices. <http://www.ahrq.gov/clinic/ptsafety/pdf/ptsafety.pdf> (accessed May 23, 2008).
- 4 Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126: 338–400S.
- 5 Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. A national clinical guideline. Edinburgh: SIGN Publication, 2002.
- 6 NICE. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. NICE clinical guidelines. www.nice.org.uk/nicemedia/pdf/VTEFullGuide.pdf (accessed May 23, 2008).
- 7 Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; 358: 9–15.
- 8 Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; 135: 858–69.

- 9 Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. *J Bone Joint Surg Br* 2007; **89**: 799–807.
- 10 Pulmonary Embolism Prevention (PEP) trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**: 1295–302.
- 11 American Academy of Orthopaedic Surgeons. American Academy of Orthopaedic Surgeons clinical guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. www.aaos.org/Research/guidelines/PE_guideline.pdf (accessed May 23, 2008).
- 12 Anderson FA Jr, Hirsh J, White K, Fitzgerald RH Jr. Temporal trends in prevention of venous thromboembolism following primary total hip or knee arthroplasty 1996–2001: findings from the Hip and Knee Registry. *Chest* 2003; **124**: 349–356S.
- 13 Callaghan JJ, Dorr LD, Engh GA, et al. Prophylaxis for thromboembolic disease: recommendations from the American College of Chest Physicians—are they appropriate for orthopaedic surgery? *J Arthroplasty* 2005; **20**: 273–74.
- 14 White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998; **158**: 1525–31.
- 15 Friedman RJ. Optimal duration of prophylaxis for venous thromboembolism following total hip arthroplasty and total knee arthroplasty. *J Am Acad Orthop Surg* 2007; **15**: 148–55.
- 16 Eriksson BI, Borris LC, Dahl OE, et al. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation* 2006; **114**: 2374–81.
- 17 Eriksson BI, Borris L, Dahl OE, et al. Oral, direct factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2006; **4**: 121–28.
- 18 Eriksson BI, Borris LC, Dahl OE, et al. Dose-escalation study of rivaroxaban (BAY 59-7939) – an oral, direct factor Xa inhibitor – for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Res* 2007; **120**: 685–93.
- 19 Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972; **104**: 134–44.
- 20 Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996; **335**: 696–700.
- 21 Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty—the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res* 1998; **89**: 281–87.
- 22 Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. *J Bone Joint Surg Am* 2001; **83-A**: 336–45.
- 23 Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002; **162**: 1966–71.
- 24 Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery—results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost* 1997; **77**: 26–31.
- 25 Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind randomized comparison. North American Fragmin Trial Investigators. *Arch Intern Med* 2000; **160**: 2208–15.
- 26 Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996; **348**: 224–28.
- 27 Eriksson BI, Borris LC, Friedman RJ, et al. Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: the RECORD1 trial. *Blood* 2007; **110**: abstract 6.
- 28 Lassen MR, Turpie AGG, Rosenthal N, et al. Rivaroxaban – an oral, direct factor Xa inhibitor – for thromboprophylaxis after total knee arthroplasty: the RECORD3 trial. *Blood* 2007; **110**: abstract 308.
- 29 Rosenthal N, Kerckamp HE, Macheras G, et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion* 2003; **43**: 459–69.
- 30 Dahl OE. Orthopaedic surgery as a model for drug development in thrombosis. *Drugs* 2004; **64** (suppl 1): 17–25.
- 31 Kakkar AK, Davidson BL, Haas SK. Compliance with recommended prophylaxis for venous thromboembolism: improving the use and rate of uptake of clinical practice guidelines. *J Thromb Haemost* 2004; **2**: 221–27.