Real-world data confirm clinical trial outcomes for rivaroxaban in orthopaedic patients

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ABSTRACT

Venous thromboembolism (VTE) is a potential cause of morbidity and mortality in patients after major orthopaedic surgery. Based on the results of the international phase III RECORD (Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) program, the oral, direct Factor Xa inhibitor rivaroxaban has been approved in many countries for the prevention of VTE after elective hip arthroplasty or knee arthroplasty. However, study results of randomized controlled trials may have limited generalizability to routine clinical practice in unselected patients. The phase IV XAMOS (Xarelto® in the Prophylaxis of Postsurgical Venous Throboembolism after Elective Major Orthopaedic Surgery of the Hip or Knee) study and the ORTHO-TEP (large single-center registry) collected real-world data to assess the effectiveness and safety of rivaroxaban compared with standard of care in large cohorts of patients undergoing major orthopaedic surgery. This review evaluates real-world data from XAMOS and ORTHO-TEP, confirming the favorable benefit–risk profile of rivaroxaban for the prevention of VTE in patients after major orthopaedic surgery that was demonstrated by the phase III RECORD studies in patients after elective hip or knee arthroplasty.

Key Words

Arthroplasty, real-life data, rivaroxaban, thromboprophylaxis, venous thromboembolism

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INTRODUCTION

Patients undergoing major orthopaedic surgery are at a high risk of developing postoperative venous thromboembolism (VTE).[1] Traditionally, low molecular weight heparins (LMWHs), fondaparinux, or vitamin K antagonists (VKAs) have been used for VTE prophylaxis in these patients. However, although effective, these established agents each have limitations. LMWHs are administered subcutaneously and are associated with a risk of heparin-induced thrombocytopenia.[2] The indirect Factor Xa inhibitor fondaparinux also requires subcutaneous administration.[2,3] VKAs are oral drugs that target multiple sites in the coagulation cascade. VKAs have a slow onset of action, are subject to multiple drug–drug and drug–food interactions, show substantial inter-individual variability in patient response, and require regular coagulation monitoring and dose adjustment to achieve a target international normalized ratio (INR) value.[4,5] To address these limitations, oral anticoagulants that target specific factors (e.g. Factor Xa or thrombin) in the coagulation cascade have been developed.

The Factor Xa inhibitor rivaroxaban is a direct, oral anticoagulant that has been approved in many countries for the prevention of VTE in adult patients after elective hip arthroplasty or elective knee arthroplasty. Approvals granted in the European Union (EU; 2008) and the US (2011) were based on the results of the international phase III RECORD (REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) clinical trial program, which consisted of four studies.[6–9] The results from the RECORD program, which randomized 12,729 patients, demonstrated superior efficacy of rivaroxaban for VTE prevention and a similar safety profile compared with both the North American and the European regimens of the LMWH enoxaparin.

After a drug has been approved and reaches the market, daily clinical experience in unselected patients can sometimes identify issues that were not apparent at the time of approval. Potential reasons are that real-world patients do not always fit the profile of those included in phase III clinical trials, which

TABLE 1. Patient demographics in RECORD1–4 pooled,[15] XAMOS,[10] and ORTHO-TEP[8,9]

Category	RECORD1–4 pooled		XAMOS		ORTHO-TEP		
	Rivaroxaban (n = 6183)	Enoxaparin (n = 6200)	Rivaroxaban (n = 8778)	SOC (n = 8635)	Rivaroxaban (n = 1043)	LMWH (n = 1495)	Fondaparinux (n = 1994)
Age, mean (SD) (year)	64.0 (11.3)	64.2 (11.2)	65 (11.0)	66 (11.0)	64.9 (12.5)	62.3 (13.1)	66.8 (11.9)
Sex, female (%)	60.7	59.4	62.7	63.0	59.1	55.4	63.8
Weight, mean (SD) (kg)	79.4 (17.3)	79.8 (17.5)	–	–	81.9 (17.6)	79.4 (16.5)	80.9 (18.4)
Body mass index, mean (SD) (kg/m²)	28.7 (5.4)	28.8 (5.4)	28.1 (5.9)	28.2 (5.7)	28.9 (6.0)	27.9 (5.2)	29 (5.8)
History of VTE (%)	2.3	2.3	3.3[a]	4.1[a]	4.0	0.9	1.0

[a]Numbers account for events within 12 mo before enrollment.
Abbreviations: LMWH, low molecular weight heparin; SD, standard deviation; SOC, standard of care; VTE, venous thromboembolism.

have strict inclusion and exclusion criteria, a specified active comparator, and a well-defined treatment approach, including duration, intervention, and outcome measures. In everyday clinical practice, the treating physician decides on the type, dose, and duration of pharmacologic thromboprophylaxis on a patient-by-patient basis.

In clinical practice, the safety of anticoagulants, in particular the risk of bleeding and related complications and how these events are managed, is of particular concern to surgeons.[10] Since its approval in 2008, rivaroxaban has been widely used in routine clinical practice for VTE prevention after orthopaedic surgery, and real-life data have become available regarding the effectiveness and safety of rivaroxaban in this setting.[11–14] Recently, the results of the large, phase IV XAMOS study (XArelto in the prophylaxis of post-surgical venous thromboembolism after elective Major Orthopaedic Surgery of hip or knee) and the ORTHO-TEP (large single-center) registry have been published.[12–14] Both studies were designed to assess the effectiveness and safety of rivaroxaban compared with standard of care (SOC) in daily clinical practice in patients after major orthopaedic surgery. The aim of this review is to discuss the results of the RECORD phase III clinical studies in light of the real-world data from XAMOS and ORTHO-TEP.

THE PHASE III RECORD PROGRAM

The multinational RECORD clinical trial program consisted of four phase III studies in patients undergoing elective total hip arthroplasty (THA; RECORD1 and RECORD2)[6,7] or total knee arthroplasty (TKA; RECORD3 and RECORD4)[8,9] to assess the efficacy and safety of oral rivaroxaban compared with subcutaneous enoxaparin for the prevention of VTE. The four RECORD studies had a randomized, double-blind, active comparator-controlled design. In RECORD1, RECORD2, and RECORD3, patients were randomized to receive either rivaroxaban 10 mg once daily (administered 6–8 h after surgery) or enoxaparin 40 mg once daily (initiated 12 h before surgery and restarted 6–8 h after wound closure).[6–9] RECORD4 compared rivaroxaban 10 mg once daily (administered 6–8 h after surgery) with enoxaparin 30 mg twice daily (initiated 12–24 h after wound closure and every

10–14 h thereafter),[9] the US-approved enoxaparin regimen. Study drugs were given for 35 ± 5 days in RECORD1 and for 12 ± 2 days in RECORD3 and RECORD4. In RECORD2, rivaroxaban was given for 35 ± 5 days and enoxaparin for 10 ± 5 days followed by placebo. The follow-up period was 30–35 days in all four studies.

Patients older than 18 yr of age who were scheduled to undergo elective THA or TKA were eligible for inclusion in the RECORD trials.[15] Ineligibility criteria included active or high risk of bleeding, pregnancy or breastfeeding, significant liver disease, severe renal impairment (calculated creatinine clearance < 30 mL/minute), planned intermittent pneumatic compression, an ongoing condition for which anticoagulant therapy could not be stopped, or concomitant use of human immunodeficiency virus (HIV) protease inhibitors or fibrinolytic agents.

A total of 12,729 patients were randomized across 617 centers in 41 countries between February 7, 2006 and January 31, 2008.[15] The demographic and surgical characteristics of patients included in the RECORD studies are summarized in Table 1. On average, patients were 64 yr of age (range 18–93 yr), 60% of patients were women, and most patients were Caucasian (∼79%).

Efficacy

The primary efficacy endpoint was total VTE (defined as the composite of symptomatic or asymptomatic deep vein thrombosis, nonfatal pulmonary embolism, and all-cause mortality) in all four RECORD trials. Each RECORD study demonstrated superior efficacy of rivaroxaban for the prevention of total VTE compared with the EU or US enoxaparin regimens. Superiority of rivaroxaban was shown to be statistically significant in all four RECORD trials (RECORD1: $P < 0.001$; RECORD2: $P < 0.0001$; RECORD3: $P < 0.001$; RECORD4: $P = 0.0118$).

A pooled analysis of the four RECORD studies confirmed that rivaroxaban significantly reduced the incidence of the composite of symptomatic VTE and all-cause mortality compared with enoxaparin in the "Day 12 ± 2 active treatment" pool (0.5% vs. 1.0%; relative risk reduction 52%) and in the "total treatment duration" pool, defined as the planned treatment period for double-blind study medication for each RECORD study (0.6% vs. 1.3%; relative risk reduction 58%).[15] Rivarox-

TABLE 2. Efficacy and safety outcomes in RECORD1–4 pooled,[15] XAMOS,[10] and ORTHO-TEP[8,9]

Category	RECORD1–4 pooled[a]			XAMOS[b]			ORTHO-TEP[c]				
	Rivaroxaban (n=6183)	Enoxaparin (n=6200)	OR (95% CI)	Rivaroxaban (n=8778)	SOC (n=8635)	OR (95% CI)	Rivaroxaban (n=1043)	LMWH (n=1495)	Fondaparinux (n=1994)	P value LMWH vs. rivaroxaban	P value fondaparinux vs. rivaroxaban
Symptomatic VTE (%)	0.45	1.10	0.41[d] (0.26–0.64)	0.65	1.02	0.63 (0.45–0.89)	2.11	4.15	5.62	0.005	<0.001
Major bleeding (%)											
RECORD definition	0.4	0.2	1.84 (0.94–3.62)	0.4	0.3	1.19 (0.73–1.95)	—	—	—	—	—
EMA definition	2.2	1.8	1.24 (0.96–1.59)	1.7	1.4	1.19 (0.93–1.51)	—	—	—	—	—
ISTH definition	1.8	1.4	1.31 (0.99–1.74)				2.9[e]	7.0[e]	4.9[e]	<0.001	0.010
Major bleeding leading to reoperation (%)	0.2	0.1		0.3	0.2		0.38	1.34	1.10	0.020	0.041
Fatal bleeding, n	2	0		0	1		—	—	—	—	—
All-cause mortality, n	8	16	0.50[d] (0.21–1.16)	7	8	0.86 (0.31–2.37)	2	1	3	—	—
Wound complications, n (%)											
Postoperative wound infection	27 (0.4)	28 (0.5)		13 (0.1)	7 (0.1)	1.83 (0.68–5.41)	—	—	—	—	—
Postoperative wound drainage/discharge	6 (0.1)	3 (<0.1)		37 (0.4)	10 (0.1)	3.65 (1.78–8.24)	—	—	—	—	—
Hemorrhagic wound complications[f]	100 (1.6)[a]	105 (1.7)[a]		41 (0.5)	36 (0.4)	1.12 (0.71–1.76)	—	—	—	—	—

aPeriod of data collection was the total treatment duration pool, defined as the planned treatment period for the double-blind study medication for each RECORD study.
bSafety population; for symptomatic arterial and venous thromboembolic events, period of data collection was up to 3 mo after surgery; bleeding events and any other adverse events were included when treatment-emergent, i.e. started after the day of the first dose and within 48 h after the last dose.
cOnly in-hospital symptomatic VTE events were included; all safety outcomes were evaluated until hospital discharge.
dHazard ratio.
eORTHO-TEP used a modified ISTH definition for major bleeding events excluding transfusions of more than two units of red blood cells or for drop of hemoglobin in the absence of overt bleeding.
fTreatment-emergent hemorrhagic wound complications were defined as the composite of nonmajor clinically relevant excessive wound and surgical-site bleeding.
Abbreviations: CI, confidence interval; EMA, European Medicines Agency; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; OR, odds ratio; SOC, standard of care; VTE, venous thromboembolism.
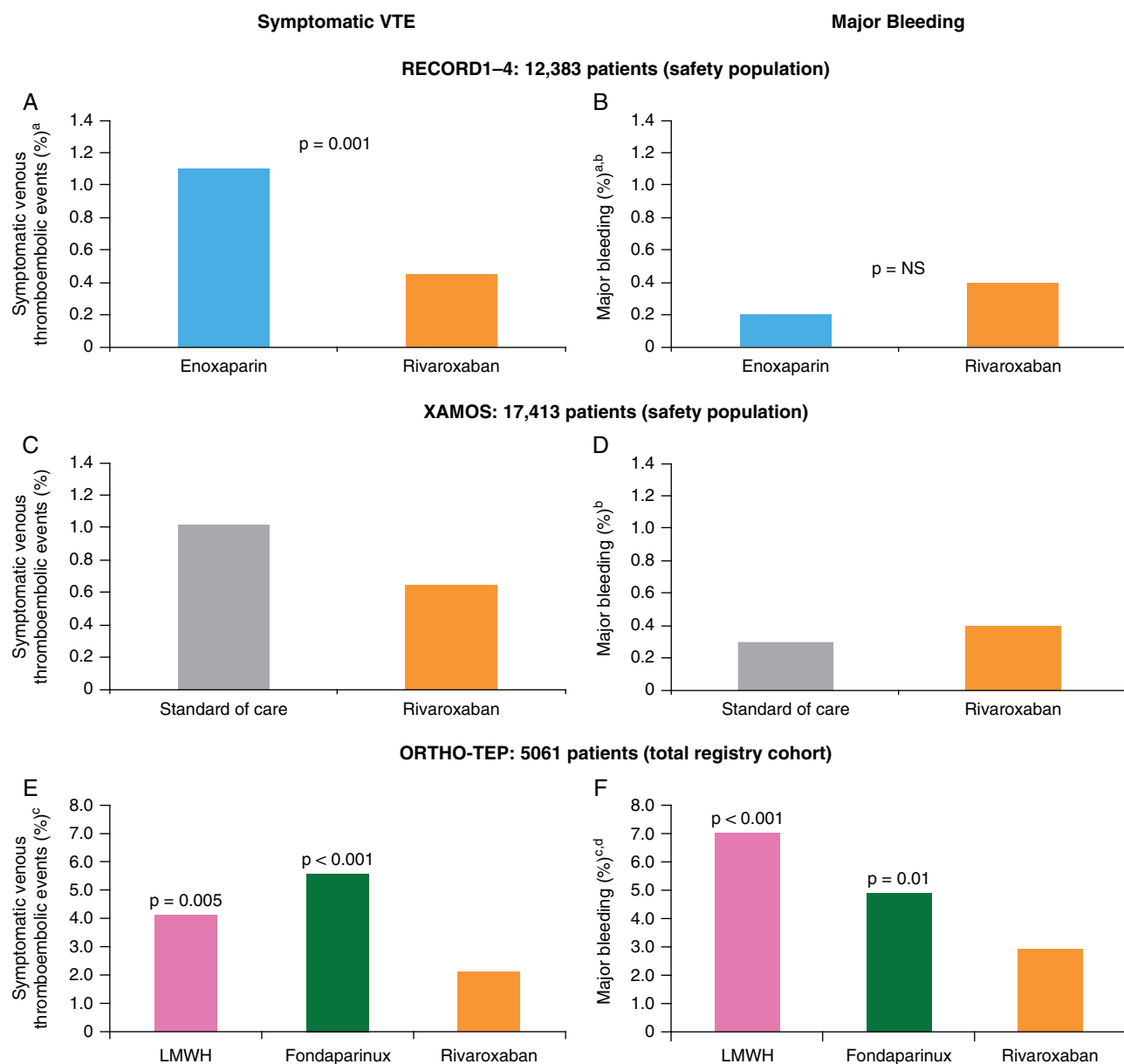
Symptomatic VTE

Major Bleeding

RECORD1–4: 12,383 patients (safety population)

XAMOS: 17,413 patients (safety population)

ORTHO-TEP: 5061 patients (total registry cohort)

FIGURE 1. A–F. Outcomes of rivaroxaban compared with standard of care for the prevention of venous thromboembolism in patients after major orthopaedic surgery in the pooled RECORD1–4 analysis (A, B), the XAMOS study (C, D), and the ORTHO-TEP Registry (E, F).[8–10,15] [a]During the total treatment duration. [b]According to the RECORD definition. [c]Until hospital discharge. [d]According to a modification of the ISTH definition. Abbreviations: ISTH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; NS, not significant; VTE, venous thromboembolism.

aban also significantly reduced the incidence of symptomatic VTE in the "total treatment duration" pool (Table 2, Figure 1A).

Safety

In all four RECORD studies the incidence of major bleeding events was low and similar between the study arms. Rates of nonmajor clinically relevant bleeding events in each of the RECORD studies were not statistically different between the two treatment arms.[6–9]

A pooled analysis of all four RECORD studies showed that rivaroxaban was associated with a small increase in major plus nonmajor clinically relevant bleeding events (3.2% compared with 2.5% in the enoxaparin group; odds ratio,

1.25; 95% confidence interval, 1.01–1.54) up to Day 12 ± 2.[15] This analysis also compared major bleeding outcomes according to three contemporary definitions of major bleeding (Table 3) by RECORD,[6–9] the International Society on Thrombosis and Haemostasis (ISTH),[16] and the European Medicines Agency (EMA).[15] Rates of major bleeding were not statistically different for rivaroxaban and enoxaparin in any of the pools when analyzed according to each definition (Table 3, Figure 1B). The pooled analysis also showed that the rates of patients who had postoperative wound drainage or postoperative wound infection, or who had clinically overt hemorrhagic wound complications were similar in both treatment arms (Table 2).[15] Rates of major bleeding

leading to reoperation were also similar between rivarobaxin and enoxaparin (Table 2).[15]

XAMOS: A NONINTERVENTIONAL STUDY

XAMOS was an international, noninterventional, observational, open-label, real-world study designed to assess the safety and effectiveness of oral rivaroxaban compared with any other pharmacologic VTE prophylaxis (referred to as SOC) in everyday clinical practice in patients after major orthopaedic surgery (including fracture surgery in those countries in which rivaroxaban is approved for this indication).[14]

Patients were included if they were older than 18 yr of age, if the treating physician prescribed pharmacologic VTE prophylaxis, and if the patient provided written informed consent. There were no additional exclusion criteria other than those specified by the approved local product information.[14] These criteria ensured that XAMOS included a broad range of patients treated in everyday clinical practice.

This study was conducted between February 2009 and August 2011 and included 252 centers in 37 countries. Decisions regarding type, duration, and dose of pharmacologic VTE prophylaxis for each patient were made by the attending physician before enrollment. Of the 17,701 patients enrolled, 17,413 took at least one dose of prophylactic drug (safety population). Of these patients, 8778 received rivaroxaban (50.4%) and 8635 received SOC (49.6%): SOC included LMWHs (81.7% of patients), unfractionated heparin, fondaparinux, VKAs, and dabigatran, among other types of pharmacologic thromboprophylaxis.[14]

The demographic characteristics of patients in XAMOS were similar to those of the RECORD program (Table 1). Approximately 80% of patients were 75 yr of age or older, and there were approximately twice as many women (63%) as men (37%). Hypertension, hypercholesterolemia, and diabetes mellitus were the three most frequent comorbidities observed. In total, 3.3% of patients in the rivaroxaban group and 4.1% of patients in the SOC group (safety population) had a thrombotic event within the 12 mo before enrollment (Table 1).[14]

Data on all adverse events were reported, including symptomatic venous and arterial thromboembolic events, bleeding events, uncommon adverse events, and all-cause mortality. Major bleeding events were analyzed according to the RECORD and EMA definitions of major bleeding (Table 3). Follow-up assessments were conducted 1 wk after completion of prophylaxis and 3 mo after surgery. Treatment-emergent adverse events were defined as events that started on or after the day of the first dose and within 48 h after the last dose of VTE prophylaxis.[14]

Outcomes

The incidence of symptomatic thromboembolic events was significantly lower in the rivaroxaban group (0.9%) compared with the SOC group (1.4%; odds ratio, 0.65; 95% confidence interval, 0.49–0.87) (data for symptomatic VTE only are included in Table 2; Figure 1C).[14]

Treatment-emergent major bleeding events according to both the RECORD and EMA definitions occurred at low and similar rates in the rivaroxaban and SOC groups in the safety population (Table 2; Figure 1D). There were no fatal bleeding events in the rivaroxaban group and one fatal bleeding event in the SOC group. There was a higher incidence of any treatment-emergent bleeding event in the rivaroxaban group compared with the SOC group (4.7% vs. 3.2%). The incidences of all serious treatment-emergent adverse events and the rates of mortality were similar in both treatment groups (Table 2). Furthermore, the incidence of thrombocytopenia (a limitation that is associated with LMWHs) was significantly lower with rivaroxaban compared with SOC.[14]

Data after propensity score adjustment (safety population adjusted to balance covariates of patients between treatment groups including patient demographics, risk factors, and other relevant factors that may influence the outcomes) were similar to the incidences in the safety population. The rates of major bleeding according to the EMA definition were greater in the rivaroxaban group.[14]

The results of the XAMOS study showed that results from the RECORD trials were reflected in routine clinical practice and confirmed the favorable benefit–risk profile of rivaroxaban compared with SOC in patients after major orthopaedic surgery of the hip or knee (Figure 1).

THE ORTHO-TEP REGISTRY

ORTHO-TEP was a single-center, retrospective registry of consecutive patients that compared the efficacy and safety of different types of VTE prophylaxis (including LMWH, fondaparinux, and rivaroxaban) in unselected patients undergoing major orthopaedic surgery in daily practice.[12,13] A total of 5061 patients were evaluated: 1495 had received LMWH according to hospital standard (January 2006–December 2007), 1994 had received fondaparinux (January 2008–December 2009), and 1043 had received rivaroxaban (January 2010–June 2011).

The patient demographics of the three cohorts (rivaroxaban, LMWH, and fondaparinux) were similar compared with those of RECORD and XAMOS (Table 1). The rivaroxaban cohort of ORTHO-TEP had a higher percentage of patients with a history of VTE (4.0% with rivaroxaban compared with 0.9% and 1.0% with LMWH and fondaparinux, respectively; both comparisons $P < 0.001$; Table 1)

Endpoints were evaluated retrospectively based on patient charts, complication and transfusion databases, and autopsy reports. Therefore, only symptomatic VTE that occurred in hospital were used as efficacy endpoints.[12,13] The primary safety endpoint was major bleeding complications defined according to the modified ISTH definition for major bleeding.[16]

Outcomes

The rate of symptomatic VTE was lowest in the rivaroxaban group (2.1%) compared with LMWH (4.2%; $P = 0.005$) or fondaparinux (5.6%; $P < 0.001$) (Table 2; Figure 1E), mainly driven by lower rates of distal VTE in the rivaroxaban group (1.1% compared with 2.5% and 3.9% in the LMWH [$P = 0.011$] and fondaparinux [$P < 0.001$] groups, respectively). These retrospective registry data suggest that

TABLE 3. Major bleeding according to three contemporary definitions of major bleeding

	Definition
RECORD[11–14]	Fatal bleeding, bleeding into a critical organ; bleeding leading to reoperation; clinically overt bleeding (extrasurgical site bleeding) associated with a fall in hemoglobin of $\geq 2\,g/dL$, or transfusion of ≥ 2 units of whole blood or packed cells; importantly, this definition excludes clinically overt surgical-site bleeding events
European Medicines Agency (EMA)[15]	As per the RECORD definition but including clinically overt surgical-site bleeding events and bleeding warranting treatment cessation
International Society on Thrombosis and Haemostasis (ISTH)[16]	As per the RECORD definition but including clinically overt surgical-site bleeding events

rivaroxaban was significantly more effective for VTE prevention compared with LMWH or fondaparinux.[12,13]

The rate of major bleeding events was lowest in the rivaroxaban group (2.9%) compared with LMWH (7.0%; $P < 0.001$) or fondaparinux (4.9%; $P = 0.010$) (Figure 1F).[12,13] The mean length of hospital stay was significantly shorter in the rivaroxaban group compared with the fondaparinux group (8.3 and 9.3 days, respectively; $P < 0.001$) and also compared with the LMWH group (8.3 days and 11.1 days, respectively; $P < 0.001$).

DISCUSSION

The design of randomized controlled trials may limit the generalizability of study results to real-world clinical practice. Here we compare two large, real-world datasets with that of the phase III RECORD clinical trial program investigating the efficacy and safety of rivaroxaban. Patient demographics regarding average age, male to female ratio, weight, and body mass index were similar in the RECORD program, the XAMOS study, and the ORTHO-TEP registry. Overall, the real-world data from XAMOS and ORTHO-TEP confirmed the effectiveness and acceptable safety profile of rivaroxaban for the prevention of VTE in patients after major orthopaedic surgery that was demonstrated by the results of the RECORD program in patients after THA or TKA.

The rates of symptomatic VTE in patients included in the ORTHO-TEP registry were approximately fourfold higher in all treatment groups compared with the rates reported in XAMOS and RECORD. Potential reasons that may have contributed to this higher than expected incidence of symptomatic VTE in ORTHO-TEP include this being a single-center, retrospective registry with specific hospital practices, such as more rigorous methods used to investigate clinical suspicion of deep vein thrombosis. Differences in other clinical characteristics, for example with respect to patient co-morbidities and revision surgery, may also have

contributed to the higher rate of VTE in ORTHO-TEP compared with XAMOS and RECORD.

The rates of treatment-emergent adverse events, including bleeding, were anticipated to be generally higher in XAMOS owing to the longer median treatment duration for patients who underwent elective knee arthroplasty (median 27 days or 28 days dependent on treatment) compared with RECORD3 and RECORD4 (~ 12 days). However, similar rates of major bleeding (according to both the RECORD and EMA definitions) were observed for rivaroxaban and SOC in the XAMOS and RECORD studies. Any bleeding events occurred at similar rates in both treatment arms in RECORD. In XAMOS, any bleeding events occurred at a higher rate in the rivaroxaban group compared with the SOC group, but overall rates were approximately half of those observed in RECORD. The higher rates of any bleeding events in the rivaroxaban arm compared with the SOC arm were due at least in part to the higher rates of reporting because of the Weber effect (an increase in adverse event reporting within the first 1–2 yr of a drug being approved).[17] The principal safety endpoint in ORTHO-TEP was major bleeding (according to a modified ISTH definition).[16] Rates of major bleeding in the different treatment groups of ORTHO-TEP were much higher (2.9–7.0%) than in RECORD and XAMOS (0.2–2.2%). This may be at least partially because of the different definitions of major bleeding used in RECORD and XAMOS, compared with ORTHO-TEP. Therefore, a direct comparison of rates of bleeding between studies is not feasible. However, whereas RECORD and XAMOS showed that the rates of major bleeding were similar in patient groups treated with rivaroxaban or SOC, ORTHO-TEP showed that the incidence of major bleeding was significantly lower in the rivaroxaban group compared with the SOC or fondaparinux groups.

The XAMOS study involved over 17,000 patients from 37 countries and, therefore, is expected to provide a more robust dataset than a single-center retrospective study, such as ORTHO-TEP. As with all noninterventional studies and registries, one of the limitations of XAMOS and ORTHO-TEP is their open-label design, in which both the patients and physicians knew which drug they were receiving or prescribing, respectively. This is in contrast to the double-blind design of the RECORD phase III studies.

Although one previously published study showed that in clinical practice rivaroxaban was associated with an increased rate of return to theater because of wound complications,[11] the large datasets available from XAMOS and ORTHO-TEP did not support these findings.

Real-world data for the other direct oral anticoagulants, which are approved in many countries for the prevention of VTE after elective hip or knee arthroplasty, are more limited. To date, there have been no publications of large-scale, real-world studies with other direct oral anticoagulants. Studies that evaluated dabigatran utility in the real-world setting showed that dabigatran was an effective anticoagulant with an acceptable safety profile, but did not report comparative outcomes with SOC.[18-20] Apixaban has been associated with a trend towards a lower risk of bleeding versus enoxaparin in clinical studies,[21–24] but this has not yet been confirmed in routine practice.

It is important to note that all anticoagulants carry a risk of bleeding, owing to their mode of action. Although there

are currently no clinically approved specific antidotes for any direct oral anticoagulants, most bleeding events can generally be managed by discontinuing antithrombotic administration and using appropriate supportive measures. In XAMOS and ORTHO-TEP, fatal bleeding events were rare, and major bleeding events were managed according to routine practice.

In summary, the results of the large, real-world datasets of XAMOS and ORTHO-TEP in patients undergoing major orthopaedic surgery support the findings of the RECORD clinical trial program and confirm that rivaroxaban reduces the incidence of VTE, including symptomatic events, with a similar safety profile compared with SOC.

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REFERENCES

1. Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012; 141:e278S–e325S.
2. Garcia DA, Baglin TP, Weitz JI, *et al.* Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012; 141:e24S–e43S.
3. Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombo-cytopenia associated with fondaparinux. *N Engl J Med.* 2007; 356:2653–2655.
4. Moualla H, Garcia D. Vitamin K antagonists - current concepts and challenges. *Thromb Res.* 2011; 128:210–215.
5. Ageno W, Gallus AS, Wittkowsky A, *et al.* Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012; 141:e44S–e88S.
6. Eriksson BI, Borris LC, Friedman RJ, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med.* 2008; 358:2765–2775.
7. Kakkar AK, Brenner B, Dahl OE, *et al.* Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet.* 2008; 372:31–39.
8. Lassen MR, Ageno W, Borris LC, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthro-plasty. *N Engl J Med.* 2008; 358:2776–2786.
9. Turpie AGG, Lassen MR, Davidson BL, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet.* 2009; 373:1673–1680.
10. Bauer KA. Reversal of antithrombotic agents. *Am J Hematol.* 2012; 87(Suppl 1):S119–S126.
11. Jensen CD, Steval A, Partington PF, *et al.* Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban: a retrospective cohort study. *J Bone Joint Surg Br.* 2011; 93:91–95.
12. Beyer-Westendorf J, Lützner J, Donath L, *et al.* Efficacy and safety of rivaroxaban or fondaparinux thromboprophylaxis in major orthopedic surgery: findings from the ORTHO-TEP registry. *J Thromb Haemost.* 2012; 10:2045–2052.
13. Beyer-Westendorf J, Lützner J, Donath L, *et al.* Efficacy and safety of thromboprophylaxis with low-molecular-weight hep-arin or rivaroxaban in hip and knee replacement surgery. Findings from the ORTHO-TEP registry. *Thromb Haemost.* 2013; 109:154–163.
14. Turpie AGG, Haas S, Kreutz R, *et al.* A non-interventional comparison of rivaroxaban with standard of care for thrombo-prophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thromb Haemost.* 2014; 111:94–102.
15. Turpie AGG, Lassen MR, Eriksson BI, *et al.* Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost.* 2011; 105:444–453.
16. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005; 3:692–694.
17. Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs In: Rainsford KD, Velo GP, eds. *Advances in Inflammatory Research.* New York: Raven Press; 1984:1–7.
18. Rosencher N, Frostick S, Fuering M, *et al.* Real-world study of dabigatran etexilate for thromboprophylaxis in over 5000 hip or knee replacement patients: favourable safety profile in sub-groups with different BMI, renal function and age. *Blood (ASH Annual Meeting Abstracts).* 2012; 120:Abstract 1160.
19. Kendoff D, Perka C, Fritsche HM, *et al.* Oral thromboprophy-laxis following total hip or knee replacement: review and multicentre experience with dabigatran etexilate. *Open Orthop J.* 2011; 5:395–399.
20. Subramanian P, Kantharuban S, Shilston S, *et al.* A 12 month review of a modified protocol using low dose dabigatran etexilate in postoperative thromboembolic prophylaxis in joint replacement surgery. *Thromb J.* 2012; 10:14.
21. Lassen MR, Raskob GE, Gallus A, *et al.* Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med.* 2009; 361:594–604.
22. Lassen MR, Raskob GE, Gallus A, *et al.* Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet.* 2010; 375:807–815.
23. Lassen MR, Gallus A, Raskob GE, *et al.* Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med.* 2010; 363:2487–2498.
24. Eriksson BI, Quinlan DJ, Eikelboom JW. Novel oral Factor Xa and thrombin inhibitors in the management of thrombo-embolism. *Annu Rev Med.* 2011; 62:41–57.