

A pooled analysis of three pivotal studies of rivaroxaban for thromboprophylaxis after orthopaedic surgery: effect on symptomatic venous thromboembolism, all-cause mortality and bleeding

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Introduction

- Rivaroxaban is an oral, direct Factor Xa inhibitor that has received a positive CHMP recommendation for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement surgery
- Three phase III trials (RECORD1–3) studied rivaroxaban for the prevention of VTE after total hip replacement (THR) or total knee replacement (TKR)
- In individual studies, rivaroxaban regimens significantly reduced the incidence of total VTE (the composite of any deep vein thrombosis [DVT], non-fatal pulmonary embolism [PE] and all-cause mortality) and major VTE (the composite of proximal DVT, non-fatal PE and VTE-related death), compared with enoxaparin regimens, with no significant increase in the risk of major bleeding^{1–3}

Objective

- To assess the incidence of symptomatic VTE, all-cause mortality and bleeding through a pre-specified analysis of pooled data from the RECORD1–3 trials

Methods

Patients and study medication

- Patients (N=9,581) were randomized to receive oral rivaroxaban 10 mg once daily (od) (n=4,772) 6–8 hours after surgery, or subcutaneous enoxaparin 40 mg od (n=4,809) started pre-operatively
- Patients undergoing THR received rivaroxaban or enoxaparin for 35 days in RECORD1, and rivaroxaban for 35 days or enoxaparin for 10–14 days, followed by placebo up to 35 days, in RECORD2. In RECORD3 (TKR), prophylaxis was for 10–14 days with either rivaroxaban or enoxaparin

Endpoints

- Primary efficacy outcome: composite of symptomatic VTE (i.e. symptomatic DVT and symptomatic non-fatal PE) and all-cause mortality up to 2 weeks after surgery (day 12±2) (Figure 1), i.e. the enoxaparin-controlled period in all three trials
- Secondary efficacy outcome: composite of symptomatic VTE and all-cause mortality at the end of the planned medication period (Figure 1)
 - Up to 5 weeks (range, 30–42 days) in RECORD1 and RECORD2 (including the placebo-controlled period in the enoxaparin group in RECORD2)
 - Up to 2 weeks (range, 13–17 days) in RECORD3

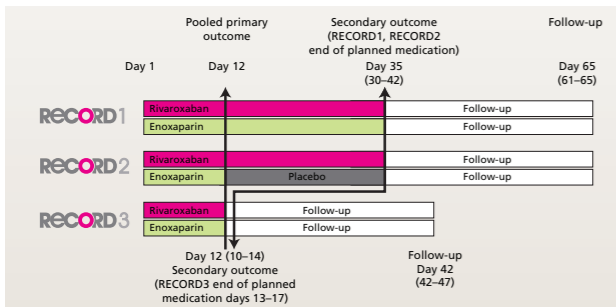


Figure 1. Definition of endpoints in the pooled analysis of data from the RECORD1, RECORD2 and RECORD3 studies.

Safety outcomes

- Primary safety outcomes were major bleeding (fatal bleeding; bleeding into a critical organ; bleeding requiring re-operation; clinically overt extra-surgical-site bleeding associated with a drop in haemoglobin of ≥ 2 g/dl or requiring the infusion of ≥ 2 units of blood or packed cells) up to 2 weeks after surgery (i.e. the enoxaparin-controlled period in all three trials; predefined) and up to the end of the planned medication period
- Other safety outcomes included any on-treatment bleeding, wound infections or adverse events (up to 2 days after the last dose of study medication), as well as all-cause mortality over the entire study period (planned medication plus follow-up)

Rationale for pooled analysis

- A pre-specified integrated analysis strategy for the primary efficacy and safety outcome analyses was prepared before the first RECORD study was unblinded
- Pooling was performed because the number of events in the individual studies was expected to be low
- Pooling across the studies would increase statistical precision and allow for a better assessment of the efficacy and safety of prophylaxis in regard to clinically important outcomes

Statistical analysis

- All outcomes were analysed in patients who had received at least one dose of study medication (including placebo injection)
- Although the primary efficacy and main safety analyses were pre-specified, they were considered exploratory with no α -adjustments made for the number of outcomes and comparisons (nominal p -values)
- Efficacy outcomes between the two groups were compared with odds ratios. Exact methods for a study-stratified pooled estimate (series of three 2x2 tables) and two-sided 95% confidence intervals (CIs) were used
- All safety data were analysed descriptively using two-sided p -values based on Fisher's exact test

Results

Efficacy

- Primary efficacy outcome: rivaroxaban 10 mg od significantly reduced the composite of symptomatic VTE and all-cause mortality compared with enoxaparin 40 mg od at 2 weeks
- The outcome occurred in 0.8% (39/4,692) of patients in the enoxaparin group compared with 0.4% (17/4,657) of patients in the rivaroxaban group – a relative risk reduction of 56% ($p=0.005$) (Figure 2A)

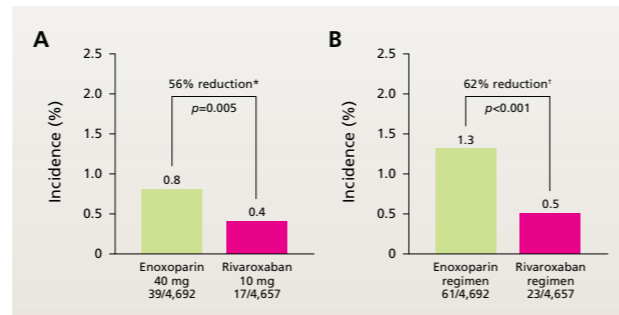


Figure 2. (A) Pooled primary efficacy outcome (symptomatic venous thromboembolism [VTE] plus all-cause mortality at 2 weeks) and (B) pooled secondary efficacy outcome (symptomatic VTE plus all-cause mortality at the end of the planned medication period) among patients undergoing major orthopaedic surgery given enoxaparin 40 mg once daily (od) or rivaroxaban 10 mg od for the prevention of VTE. *Based on an odds ratio of 0.44; two-sided 95% confidence interval 0.23–0.79. †Based on an odds ratio of 0.38; two-sided 95% confidence interval 0.22–0.62.

- Secondary efficacy outcome: rivaroxaban also significantly reduced the composite of symptomatic VTE and all-cause mortality compared with enoxaparin at the end of the planned medication period
- This outcome occurred in 1.3% (61/4,692) of patients who received enoxaparin, compared with 0.5% (23/4,657) of those who received rivaroxaban – a relative risk reduction of 62% ($p<0.001$) (Figure 2B)
- A Kaplan–Meier plot of the occurrence of the composite of symptomatic VTE and death over the entire study period showed an early separation, in favour of rivaroxaban, that increased over time and persisted at the end of follow-up (Figure 3)

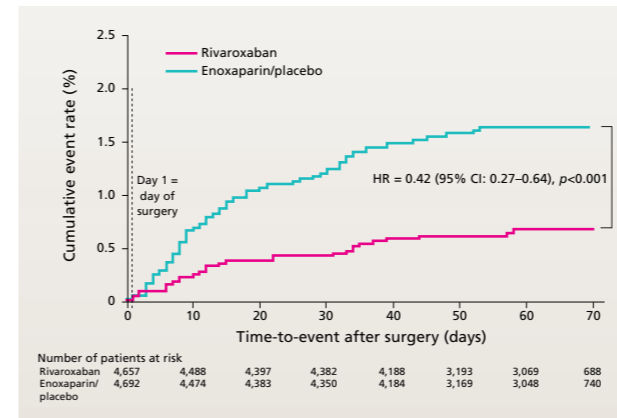


Figure 3. Kaplan–Meier estimate of cumulative incidence of symptomatic venous thromboembolism and all-cause mortality in patients (valid for safety population) receiving the rivaroxaban or the enoxaparin regimens in the RECORD1–3 studies. HR, hazard ratio.

Safety

- The rates of major bleeding were low and similar for the enoxaparin regimen and rivaroxaban regimen 2 weeks after surgery: 0.2% (9/4,692) and 0.2% (11/4,657) with the enoxaparin and rivaroxaban regimens, respectively (Figure 4A)
- Rates of major bleeding at the end of the planned medication period were also similar: 0.2% (9/4,692) and 0.3% (14/4,657) with the enoxaparin and rivaroxaban regimens, respectively (Figure 4B)

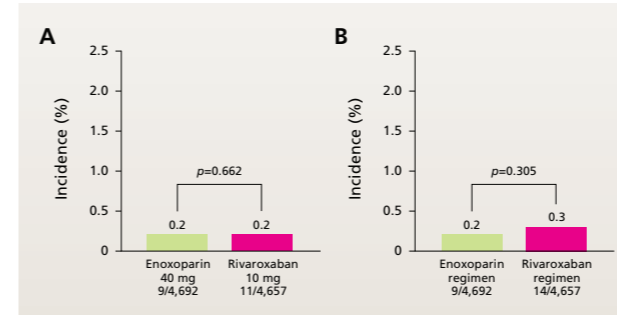


Figure 4. (A) Major bleeding at 2 weeks (primary safety outcome) and (B) major bleeding at end of planned medication period among patients undergoing major orthopaedic surgery given enoxaparin 40 mg once daily (od) or rivaroxaban 10 mg od for prevention of venous thromboembolism.

- Rates of non-major bleeding and other bleeding outcomes were also similar between the enoxaparin and rivaroxaban groups at 2 weeks and at the end of the medication period (Table 1)

Table 1. Secondary safety outcomes in patients receiving rivaroxaban 10 mg once daily (od) or enoxaparin 40 mg od across the RECORD1–3 studies: bleeding events*

	Rivaroxaban regimen n=4,657 (%)	Enoxaparin regimen n=4,692 (%)
At 2 weeks after surgery		
Any on-treatment bleeding	5.3	5.2
Non-major bleeding (on-treatment)	5.1	5.0
Clinically relevant non-major bleeding (on-treatment)	2.6	2.3
Wound infections	1.1	1.0
At the end of the planned medication period*		
Any on-treatment bleeding	5.9	5.5
Non-major bleeding (on-treatment)	5.6	5.3
Clinically relevant non-major bleeding (on-treatment)	3.0	2.5
Wound infections	1.7	1.6

*Patients may have had more than one event, or an event that falls into one or more categories.

- The incidence of cardiovascular events was low and similar for both the enoxaparin and rivaroxaban regimens during the entire study period (Table 2)
- Nineteen deaths (0.4%) occurred in the enoxaparin group and seven deaths (0.2%) in the rivaroxaban group (Table 2)

Table 2. Safety outcomes over the entire study period* in patients receiving rivaroxaban 10 mg once daily (od) or enoxaparin 40 mg od across the RECORD1–3 studies: cardiovascular events and pulmonary embolism

	Rivaroxaban regimen n=4,657 n (%)†	Enoxaparin regimen n=4,692 n (%)†
Cardiovascular events	23 (0.5)	23 (0.5)
Myocardial infarction	12 (0.3)	13 (0.3)
Ischaemic stroke	8 (0.2)	5 (0.1)
Cardiovascular death	5 (0.1)	4 (0.1)
Unexplained death	0 (0.0)	2 (<0.1)
Non-fatal pulmonary embolism	9 (0.2)	12 (0.3)
Fatal pulmonary embolism	0 (0.0)	3 (<0.1)
Death (all causes)	7 (0.2)‡	19 (0.4)

*Planned treatment period and follow-up.

†Patients may have had more than one event, or an event that falls into one or more categories.
 ‡One additional death occurred in the rivaroxaban group: a patient who did not undergo surgery and did not receive any blinded study medication was killed in a road traffic accident and, therefore, was not included in the safety population.

Summary

- In patients who underwent major orthopaedic surgery, rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality at 2 weeks after surgery compared with enoxaparin ($p=0.005$)
- The incidence of major bleeding and all on-treatment bleeding events was low and similar in both the rivaroxaban and enoxaparin groups
- Rivaroxaban regimens were associated with a low and similar incidence of cardiovascular adverse events to enoxaparin

Conclusions

- Rivaroxaban is the first novel, oral anticoagulant to significantly reduce the composite outcome of symptomatic VTE and all-cause mortality after major orthopaedic surgery
- Rivaroxaban shows superior efficacy to enoxaparin for this clinical outcome with a similar safety profile
- Bleeding rates were low with no significant increase in major bleeding between the studied drug regimens

References

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Disclosure of Conflict of Interest

This study and production of this poster was supported by Bayer HealthCare AG and J&JPRD. Rivaroxaban is in clinical development and not yet licensed.

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