

Pooled Analysis of Four Rivaroxaban Studies: NSAIDs, ASA and Platelet Inhibitors

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Introduction

- Rivaroxaban – an oral, direct Factor Xa inhibitor – was investigated for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement (THR or TKR) surgery in four phase III clinical trials (RECORD1–4)
- Randomized patients (N=12,729) received rivaroxaban 10 mg once daily (od), or subcutaneous enoxaparin 40 mg od (RECORD1–3) or 30 mg every 12 hours (RECORD4) (Figure 1)^{1–4}
 - In RECORD1 and 2 (THR), rivaroxaban was given for 31–39 days
 - Enoxaparin was given for 31–39 days in RECORD1 or 10–14 days followed by placebo in RECORD2
 - In RECORD3 and 4 (TKR), prophylaxis was given for 10–14 days
- A pooled analysis of the results of all four RECORD studies evaluated the effect of rivaroxaban on the composite of symptomatic VTE and all-cause mortality, and bleeding⁵

Objective

- To investigate potential drug–drug interactions by comparing the risk of bleeding between rivaroxaban-treated and enoxaparin-treated subjects with and without the use of specified co-medications in the total treatment duration pool of all four RECORD studies (Figure 1)

Methods

- The co-medications investigated were non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) or platelet aggregation inhibitors – frequently used medications known to have a pharmacodynamic effect on bleeding
- Prespecified analyses focused on on-treatment adjudicated bleeding events – any bleeding and the composite of major and clinically relevant non-major bleeding; definitions of bleeding endpoints were as defined in the RECORD studies^{1–4}

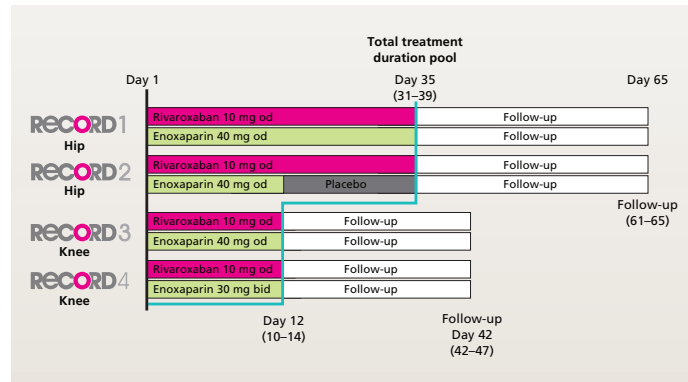


Figure 1. RECORD1–4 study pools. od, once daily; bid, twice daily.

- Analyses were conducted for all subjects who underwent surgery and had medication administered
- Bleeding rates were recorded from the day of surgery until the last day of study medication intake +2 days or until event onset
- Co-medication use was evaluated over time, and relative bleeding rates with and without co-medication were calculated for the rivaroxaban and enoxaparin/placebo groups separately. The days between co-medication start and stop, and the 2 days after the co-medication stop date (if stopped) were analyzed as being under co-medication use
- Time relative to surgery was stratified into three time periods (days 1–3, 4–7, and day 7 onwards [the day of surgery was day 1]), based on the consideration that the risk of a first bleeding event decreases over time after surgery, and the prevalence of co-medication can vary over time
- Bleeding rates were recorded for each time period, and rate ratios (relative rates) were derived using Mantel–Haenszel methods
- There was no restriction on the choice of a specific drug or on the dose of NSAIDs and platelet aggregation inhibitors or ASA in the study protocols

Results

- Approximately 70% of patients were co-medicated (at least once) with NSAIDs and approximately 9% of patients were co-medicated with ASA or platelet aggregation inhibitors in both groups

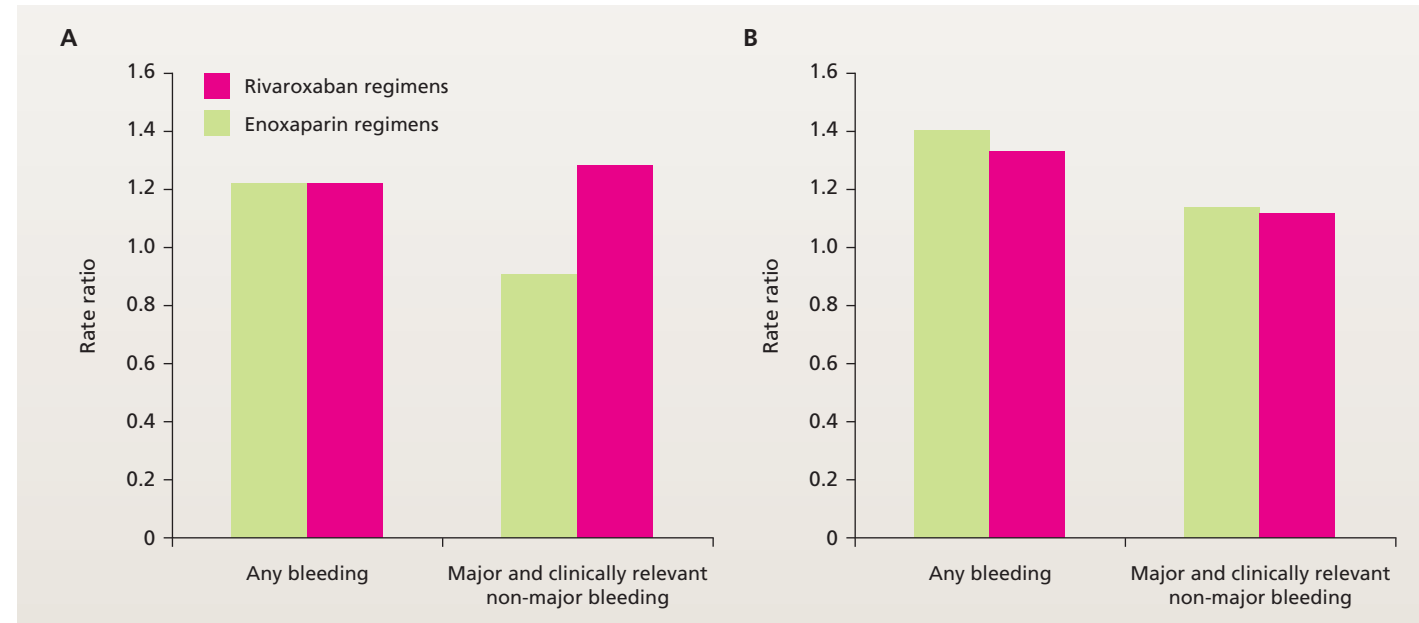


Figure 2. Bleeding rate ratios for enoxaparin and rivaroxaban regimens with concomitant use versus non-use of (A) non-steroidal anti-inflammatory drugs and (B) acetylsalicylic acid or platelet aggregation inhibitors in the RECORD1–4 pool.

Table 1. Relative bleeding rates for co-medication use versus non-use in the RECORD1–4 pool. Rate ratio calculated from the date of surgery to final medication date +2 days or until bleeding onset

Bleeding endpoint	Enoxaparin regimens (n=6,107)	Rivaroxaban regimens (n=6,093)
Non-steroidal anti-inflammatory drugs		
Number of patients with co-medication use	4,432	4,396
Any bleeding	Rate per 100 patient-weeks	
	With co-medication	2.51
	Without co-medication	1.17
	Rate ratio for use versus non-use (95% CI)	1.22 (0.98–1.51)
Major and clinically relevant non-major bleeding	Rate per 100 patient-weeks	
	With co-medication	0.81
	Without co-medication	0.47
	Rate ratio for use versus non-use (95% CI)	0.90 (0.63–1.28)
Acetylsalicylic acid/platelet aggregation inhibitors		
Number of patients with acetylsalicylic acid use	468	516
Any bleeding	Rate per 100 patient-weeks	
	With co-medication	2.06
	Without co-medication	1.63
	Rate ratio for use versus non-use (95% CI)	1.40 (0.87–2.25)
Major and clinically relevant non-major bleeding	Rate per 100 patient-weeks	
	With co-medication	0.59
	Without co-medication	0.59
	Rate ratio for use versus non-use (95% CI)	1.13 (0.47–2.75)

Twenty-eight of the enoxaparin-treated patients and 25 of the rivaroxaban-treated patients were co-medicated with clopidogrel. CI, confidence interval.

Conclusions

- This RECORD1–4 explorative pooled analysis shows that concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid/platelet aggregation inhibitors with rivaroxaban 10 mg once daily was associated with an increase in bleeding risk, but this increase was not statistically different from the enoxaparin regimens
- Very few patients used platelet aggregation inhibitors (except acetylsalicylic acid), hence our experience with platelet aggregation inhibitors is limited
- In both treatment groups there was a slight increase in bleeding with concomitant use of NSAIDs and ASA, although this was not statistically significant
- Rivaroxaban-treated patients co-medicated with NSAIDs showed similar rate ratios to the enoxaparin/placebo groups for any bleeding (rivaroxaban: 1.22 [95% confidence interval {CI} 0.99–1.50]; enoxaparin 1.22 [95% CI 0.98–1.51]), and rate ratios for major and clinically relevant non-major bleeding (1.28 [95% CI 0.94–1.73] versus 0.90 [95% CI 0.63–1.28]) were not significantly different between rivaroxaban and enoxaparin/placebo groups (Table 1; Figure 2A)
- Rivaroxaban-treated patients co-medicated with ASA or platelet aggregation inhibitors showed similar rate ratios to the enoxaparin/placebo groups for any bleeding (1.32 [95% CI 0.85–2.05] versus 1.40 [95% CI 0.87–2.25]) and major and clinically relevant non-major bleeding (1.11 [95% CI 0.55–2.25] versus 1.13 [95% CI 0.47–2.75]) (Table 1; Figure 2B)

References

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Disclosure of conflict of interest

This study was supported by Bayer Schering Pharma AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The data contained within this poster do not support or recommend the use of rivaroxaban in indications or countries in which it is not licensed.

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