

A Pooled Analysis of Four Pivotal Studies of Rivaroxaban for the Prevention of Venous Thromboembolism after Orthopaedic Surgery: Effects of Specified Co-medications

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Introduction

- ◆ RECORD is a pivotal clinical trial program investigating rivaroxaban – an oral, direct Factor Xa inhibitor – for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement (THR and TKR) surgery
- ◆ It comprised four multinational, randomized, double-blind, double-dummy phase III studies (RECORD1, 2, 3, and 4) in patients undergoing THR or TKR surgery, and compared rivaroxaban 10 mg once daily (od) with enoxaparin 40 mg od or 30 mg twice daily (bid)¹⁻⁴
- ◆ Patients (N=12,729) were randomized to receive oral rivaroxaban 10 mg od starting 6–8 hours after surgery, or subcutaneous enoxaparin 40 mg od starting the evening before surgery (RECORD1–3), or 30 mg bid starting 12–24 hours after wound closure or adequate hemostasis (RECORD4)
- ◆ Those patients undergoing THR received rivaroxaban or enoxaparin for 31–39 days in RECORD1, and rivaroxaban for 31–39 days or enoxaparin for 10–14 days followed by placebo in RECORD2
- ◆ In RECORD3 and 4 (TKR), prophylaxis was 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 bleeding

Objectives

- ◆ The aim of the present subgroup analysis was to investigate potential drug–drug interactions with specified co-medications, by describing the risk of bleeding after first tablet intake in the total study duration pool of all four RECORD studies (Figure 1)
- ◆ The co-medications investigated were non-steroidal anti-inflammatory drugs (NSAIDs) and platelet aggregation inhibitors or acetylsalicylic acid (ASA) – frequently used medications known to have a pharmacodynamic effect on bleeding

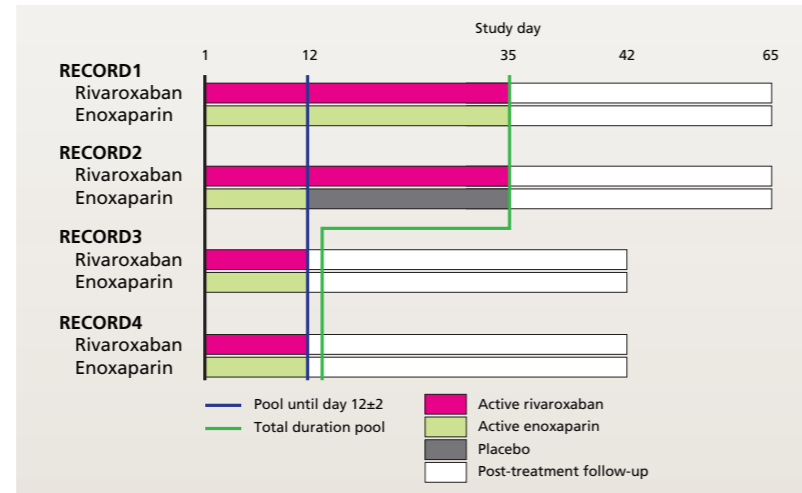


Figure 1. Illustration of RECORD1–4 study pools.

Methods

- ◆ The prespecified analyses focused on adjudicated bleeding events – the composite of major bleeding and non-major bleeding, as well as the composite of major bleeding and clinically relevant non-major bleeding – after the first postoperative tablet intake (rivaroxaban or matching placebo) and up to 2 days after the last dose of study medication
- ◆ Co-medication use was evaluated over time and relative bleeding rates with and without the co-medication were calculated for the rivaroxaban and enoxaparin/placebo groups separately
- ◆ Days between co-medication start and stop and the 2 days following the co-medication stop date (if stopped) were analyzed as being with co-medication use
- ◆ The time relative to surgery (day of surgery was day 1) was stratified into three time periods (days 1–3, days 4–7, and day 7 onwards), 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
- ◆ Analyses were conducted in all subjects who underwent surgery and had a tablet (rivaroxaban or matching placebo) administered. Bleeding rates were recorded for each time period and rate ratios (relative rates) were derived using stratified Mantel–Haenszel methods for person–time data
- ◆ Bleeding events starting post-tablet intake and during the at-risk period, which extended from the day of surgery until the last day of study medication intake +2 days or until event onset (recurrent bleedings were not included in the analyses), were considered
- ◆ Co-medications were defined via the WHO-Drug Dictionary: NSAIDs (Anatomical Therapeutic Chemical [ATC] code M01A) and platelet aggregation inhibitors or ASA (ATC code B01AC or multiple-ingredient drugs containing ASA)

- ◆ 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 reported concomitant use (at least once) of NSAIDs and 9% reported concomitant use of platelet aggregation inhibitors or ASA in both groups (Table 1)

Table 1. Number and proportion (%) of subjects with co-medication use in the RECORD1–4 pool*

| Concomitant drugs | Rivaroxaban 10 mg od (n=6,093) | Enoxaparin/placebo (n=6,107) |
|---|--------------------------------|------------------------------|
| NSAIDs[†] | 4,396 (72%) | 4,432 (73%) |
| Aceclofenac | 80 | 95 |
| Celecoxib | 375 | 386 |
| Dexketoprofen trometamol | 123 | 125 |
| Diclofenac resinate | 113 | 123 |
| Diclofenac sodium | 893 | 900 |
| Diclofenac | 705 | 702 |
| Etoricoxib | 61 | 69 |
| Glucosamine | 80 | 83 |
| Ibuprofen | 407 | 413 |
| Indometacin | 292 | 299 |
| Ketoprofen | 900 | 911 |
| Ketorolac | 250 | 232 |
| Ketorolac tromethamine | 842 | 828 |
| Meloxicam | 251 | 246 |
| Naproxen | 122 | 111 |
| Neodolpasse (diclofenac sodium, orphenadrine citrate) | 65 | 50 |
| Nimesulide | 62 | 50 |
| Parecoxib | 91 | 88 |
| Piroxicam | 52 | 47 |
| Tenoxicam | 64 | 59 |
| Platelet aggregation inhibitors or ASA[‡] | 563 (9%) | 526 (9%) |
| Acetylsalicylate lysine | 13 | 24 |
| ASA | 450 | 403 |
| Albly-enterosolubile | 66 | 65 |
| Carbasalate calcium | 14 | 12 |
| Clopidogrel | 25 | 28 |
| Dipyridamole | 8 | 6 |

*Co-medication used at least once between the date of surgery and the last date of study medication intake +2 days. [†]Drugs/ingredients used by at least 50 rivaroxaban subjects. [‡]Drugs/ingredients used by at least five rivaroxaban subjects. ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; od, once daily.

- ◆ Co-medication prevalence (proportion of patient-days with co-medication) of NSAID use decreased over time (62% vs 62% for days 1–3, 51% vs 52% for days 4–7, and 29% vs 28% for the time period after day 7 for the rivaroxaban and enoxaparin/placebo treatment groups). Prevalence of co-medication with platelet aggregation inhibitors or ASA stayed more constant over the treatment period with small increases from approximately 3% to 5% over these time intervals in both groups

- ◆ Rate ratios for use versus non-use of concomitant NSAIDs were similar between the rivaroxaban and the enoxaparin/placebo groups for any bleeding and major or clinically relevant non-major bleeding (Table 2)
- ◆ The concomitant use of platelet aggregation inhibitors or ASA in the rivaroxaban group also showed rate ratios similar to those obtained in the enoxaparin/placebo group for both bleeding endpoints (Table 2)

Table 2. Relative bleeding rates for co-medication use versus non-use: RECORD1–4 pool

| Type of co-medication | Bleeding endpoint* | Events with use/without use of co-medication | Rivaroxaban 10 mg od (n=6,093) | Enoxaparin/placebo (n=6,107) |
|--|--|--|--------------------------------|------------------------------|
| NSAIDs | Any (major and non-major) bleeding post-tablet | 208/175 | 1.22 (0.99, 1.50) | 1.22 (0.98, 1.51) |
| | Major and clinically relevant non-major bleeding post-tablet | 92/81 | 1.28 (0.94, 1.73) | 0.90 (0.63, 1.28) |
| | Any (major and non-major) bleeding post-tablet | 20/363 | 1.32 (0.85, 2.05) | 1.40 (0.87, 2.25) |
| Platelet aggregation inhibitors or ASA | Any (major and non-major) bleeding post-tablet | 8/165 | 1.11 (0.55, 2.25) | 1.13 (0.47, 2.75) |
| | Major and clinically relevant non-major bleeding post-tablet | 5/125 | | |
| | Any (major and non-major) bleeding post-tablet | 17/338 | | |

*Post-tablet definition excludes bleeding prior to the first (blinded) postoperative tablet intake. Rate ratio (relative rates) calculated for the period from date of surgery to final medication date +2 days or until bleeding onset. ASA, acetylsalicylic acid; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; od, once daily.

Conclusion

- ◆ This RECORD1–4 analysis shows that the concomitant use of NSAIDs, or platelet aggregation inhibitors or ASA was associated with a small increase in bleeding risk. The magnitude of the increase was similar in patients treated with rivaroxaban 10 mg od and the studied enoxaparin treatment regimens

References and Disclosures

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