

Effects of Age, Weight, Gender, and Renal Function in a Pooled Analysis of Four Rivaroxaban Studies

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Introduction

- Rivaroxaban – an oral, direct Factor Xa inhibitor – was investigated in a large, multinational phase III clinical program, consisting of four randomized studies (RECORD1–4)
- The RECORD program investigated rivaroxaban for the prevention of venous thromboembolism (VTE) in patients ≥18 years undergoing total hip or knee replacement (THR or TKR) surgery
- In all four trials, rivaroxaban regimens demonstrated superior efficacy for the primary endpoint of prevention of total VTE compared with enoxaparin regimens, with no significant difference in major bleeding^{1–4}
- In a pooled analysis of the RECORD1–4 studies, rivaroxaban demonstrated superiority to enoxaparin for the prevention of symptomatic VTE and death (the prespecified composite primary endpoint), and major bleeding was not significantly increased with rivaroxaban compared with enoxaparin⁵

Objective

- To assess the influence of age, weight, gender, and mild to moderate renal impairment on the efficacy and safety of rivaroxaban, from the RECORD1–4 pooled data

Methods

- Patients scheduled to undergo elective THR or TKR were randomized to receive either oral rivaroxaban 10 mg once daily (od) or subcutaneous enoxaparin 40 mg od (RECORD1–3) or enoxaparin 30 mg every 12 hours (RECORD4) (Figure 1)
 - Patients received prophylaxis for 31–39 days in RECORD1 (THR), and for 10–14 days in RECORD3 and 4 (TKR). In RECORD2 (THR), patients received either rivaroxaban for 31–39 days or enoxaparin for 10–14 days followed by placebo
- RECORD1–4 pooled subgroup analyses were performed to assess efficacy and safety in important subgroups of patients
- Patients were stratified by age (<65, 65–75, >75 years), weight (≤70, >70–90, >90 kg), gender, and renal function (creatinine clearance <50, 50–80, >80 mL/min)
- Separate analyses were performed for each subgroup
- Interaction testing was performed using logistic regression models

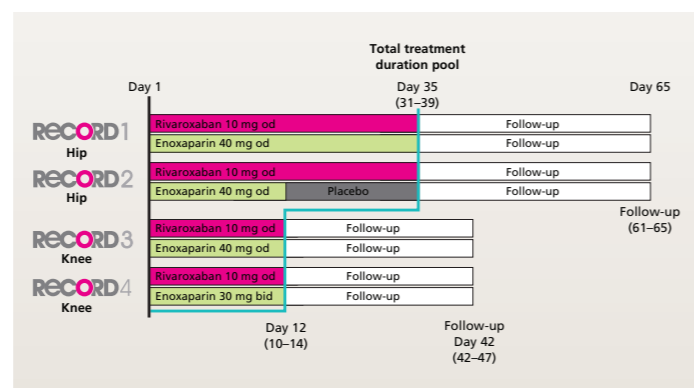


Figure 1. RECORD1–4 study design. bid, twice daily; od, once daily.

Efficacy endpoints

- The following venography-dependent endpoints were evaluated at the end of the total treatment duration pool, which comprised the treatment phase of each study and included the placebo arm of RECORD2 (Figure 1)
 - Total VTE: the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality
 - Major VTE: the composite of proximal DVT, non-fatal PE, and VTE-related death

- Pooled results for efficacy endpoints were expressed as odds ratios

Safety endpoints

- The following treatment-emergent bleeding events were measured from the first intake of blinded study medication up to 2 days after the last dose of study medication
 - The composite of major and clinically relevant non-major bleeding (major bleeding was too infrequent to be included as a separate endpoint)
 - Any bleeding

- Pooled results for safety endpoints were expressed as hazard ratios

Results

- Subgroup analyses showed that rivaroxaban had consistently superior efficacy to enoxaparin, irrespective of age, weight, gender, mild to moderate renal impairment (Figure 2A and B)
- The rate of any treatment-emergent bleeding with rivaroxaban was similar to enoxaparin regimens within and between subgroups (Figure 3A)

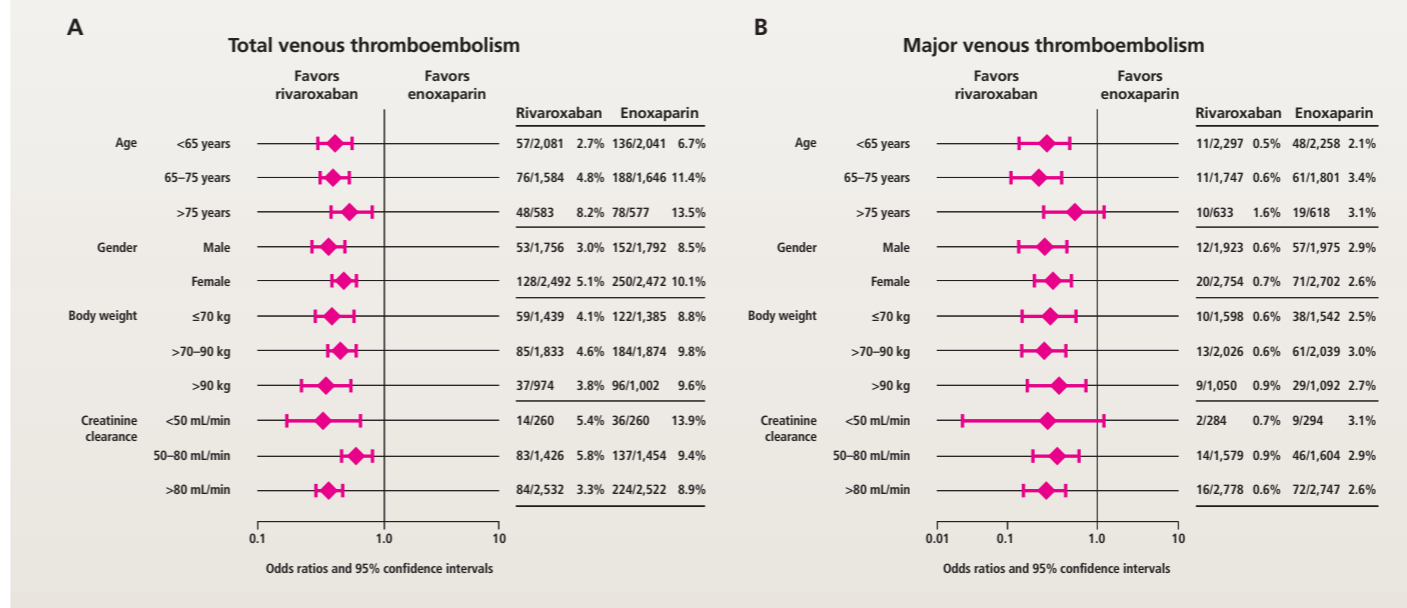


Figure 2. Efficacy endpoint odds ratios for (A) total venous thromboembolism and (B) major venous thromboembolism. Odds ratios and two-sided 95% confidence intervals are from exact study stratified analysis. The creatinine clearance <50 mL/min subgroup contained mainly patients with creatinine clearance 30–50 mL/min, as creatinine clearance <30 mL/min was one of the exclusion criteria of the RECORD studies.

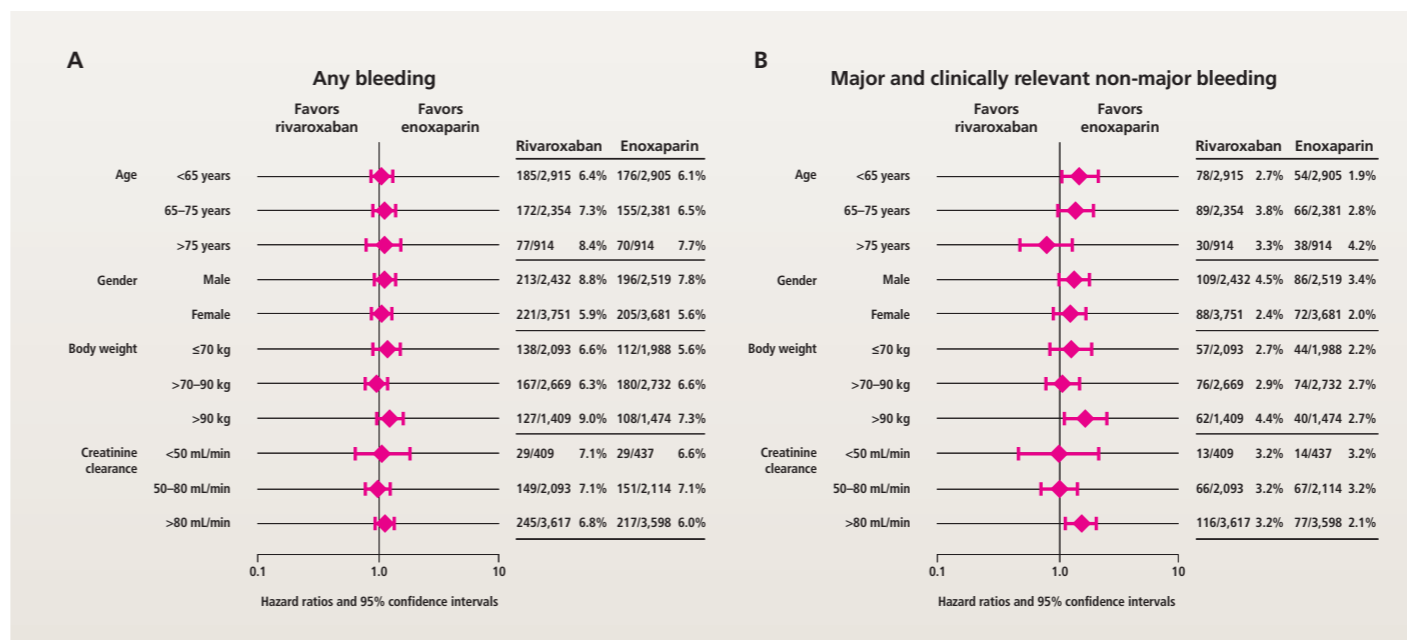


Figure 3. Safety endpoint hazard ratios for (A) any bleeding and (B) major plus clinically relevant non-major bleeding. Hazard ratios and 95% confidence intervals are from the Cox regression model. The creatinine clearance <50 mL/min subgroup contained mainly patients with creatinine clearance 30–50 mL/min, as creatinine clearance <30 mL/min was one of the exclusion criteria of the RECORD studies.

Conclusions

- These results suggest that age, weight, gender, and mild to moderate renal impairment have no clinically relevant effect on the efficacy of rivaroxaban after total hip or knee replacement surgery
- There were no statistically or clinically significant differences between subgroups for any treatment-emergent bleeding events
- These findings are consistent with the use of rivaroxaban 10 mg once daily for the prevention of venous thromboembolism after total hip or knee replacement surgery without routine coagulation monitoring or dose adjustment for age, weight, gender, or mild to moderate renal impairment

- There were significant differences in the composite of major plus clinically relevant non-major bleeding between rivaroxaban and enoxaparin groups in the subgroup categories of age <65 years, body weight >90 kg, and creatinine clearance >80 mL/min, but not for the other subgroups (Figure 3B)

- Interaction testing in logistic regression models indicated no treatment effect differences for total VTE, major VTE, any treatment-emergent bleeding or major plus clinically relevant non-major bleeding within the subgroups for all efficacy and safety endpoints, except for total VTE in the creatinine clearance subgroup

- The treatment effect with rivaroxaban appeared to be greater for the creatinine clearance >80 and <50 mL/min subgroups compared with the 50–80 mL/min subgroup ($p=0.012$) (Figure 2A)

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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