

Prothrombin Time and Bleeding Events in Patients Undergoing Total Hip or Knee Replacement Surgery Receiving 10 mg Rivaroxaban

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Introduction

- Rivaroxaban is an oral, direct Factor Xa inhibitor and is in advanced clinical development for several thromboembolic indications
- The phase III clinical RECORD (REgulation of Coagulation in ORThopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) program consisted of four double-blind, randomized studies that compared the efficacy and safety of oral rivaroxaban 10 mg once daily (qd) with subcutaneous enoxaparin 40 mg qd (the regimen most commonly used in Europe and some other countries; RECORD1–3) or enoxaparin 30 mg every 12 hours (most commonly used in North America; RECORD4) for the prevention of venous thromboembolism (VTE) in patients undergoing total hip or total knee replacement (THR or TKR) surgery^{1–4}
- The pooled analysis from these four studies demonstrated that rivaroxaban significantly reduced the incidence of symptomatic VTE and death with no significant increase in major bleeding compared with enoxaparin regimens⁵
- Prothrombin time (PT) is a global clotting test that is commonly used to assess the activity of clotting factors involved in the extrinsic coagulation pathway and to monitor appropriate dosing of vitamin K antagonists such as warfarin
- Although rivaroxaban exhibits a linear dose relationship between plasma concentration and prolongation of PT,^{6,7} interindividual variabilities do not allow precise quantitation of rivaroxaban concentration from an individual's PT measurement⁸

Objective

- This was a post hoc, explorative analysis to evaluate any potential relationship between PT and the occurrence of adjudicated bleeding events in the pooled RECORD1–4 studies

Methods

- Patients (N=6,040) included in this analysis were part of the safety population, had undergone appropriate surgery, and had taken at least one active dose of rivaroxaban
- PT was measured in a central laboratory from frozen plasma samples using the reagent Neoplastin® (Diagnostica Stago, Asnières-sur-Seine, France) at day 0 (baseline), predose at day 6 (trough), and at 2–4 hours postdose on day 6 (peak), and grouped according to quartiles (the value of the boundary at the 25th, 50th, or 75th percentiles of a frequency distribution divided into four parts, each containing a quarter of the population); day 1 was defined as the day of surgery
- Post-baseline measurements of PT were taken only at one time point (day 6), as it was assumed that the trough and peak value on this day represented the course of coagulation time at each treatment day
- Therefore, all adjudicated bleeding events that occurred before, or at, or after day 6 were analyzed with respect to the values taken at this single day
- The analysis focused on treatment-emergent bleeding events up to 12±2 days after the initiation of active rivaroxaban administration
- Adjudicated bleeding events were grouped into 'any bleeding' and 'clinically relevant bleeding', which was the composite of 'major and clinically relevant non-major bleeding'

Results

- A total of 5,912 patients had PT measurements at baseline; 345 patients experienced any bleeding event, of which 149 patients experienced clinically relevant bleeding events. Only a small proportion of the patients with a bleeding event discontinued the study drug before or after day 6
- Cumulative distribution function of baseline PT was similar in patients with and without bleeding events (Figure 1)
- Mean PT (in seconds) at baseline, day 6 trough, and day 6 peak/baseline ratios of rivaroxaban-treated patients with and without bleeding events are presented in Table 1
- The box and whisker plot shows a similar distribution of PT at baseline, day 6 trough, and day 6 peak in rivaroxaban-treated patients with and without bleeding events (Figure 2)

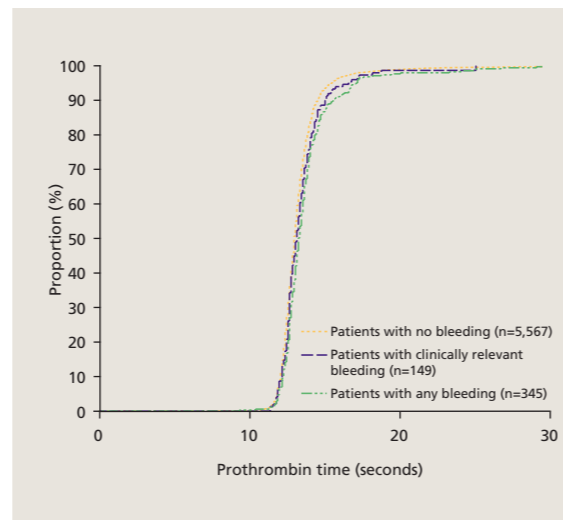


Figure 1. Cumulative distribution of baseline prothrombin time (using Neoplastin) in rivaroxaban-treated patients with and without bleeding events from the RECORD1–4 studies. Clinically relevant bleeding was the composite of major and clinically relevant non-major bleeding.

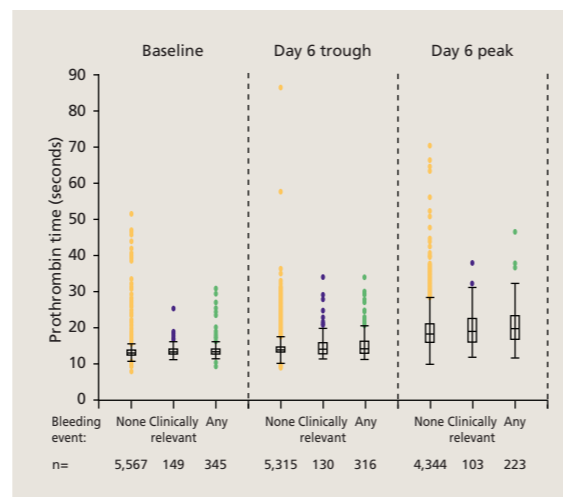


Figure 2. Box and whisker plot to show distribution of prothrombin time (using Neoplastin) at baseline and day 6 in rivaroxaban-treated patients with and without bleeding events from the RECORD1–4 studies. Clinically relevant bleeding was the composite of major and clinically relevant non-major bleeding.

- Of the patients with bleeding events, most events occurred in those with PT values in the extreme (Q4) peak and trough quartiles (Table 2)

Table 1. Prothrombin time (using Neoplastin) in rivaroxaban-treated patients with or without bleeding events from the RECORD1–4 studies

| Bleeding events | Baseline (day 0) (seconds) | Day 6 trough (seconds) | Day 6 peak (seconds) | Peak/baseline ratios |
|--------------------------------------|----------------------------|------------------------|----------------------|----------------------|
| No bleeding (n=5,567) | 13.5±2.0 | 14.3±2.6 | 18.9±4.4 | 1.42±0.3 |
| Any bleeding (n=345) | 14.0±2.3 | 15.3±3.4 | 20.5±5.5 | 1.49±0.4 |
| Clinically relevant bleeding (n=149) | 13.7±1.9 | 15.2±3.5 | 19.8±4.7 | 1.46±0.3 |

Results are mean ± standard deviation. n = patients with baseline, day 6 trough, and day 6 peak measurements of prothrombin time. Day 6 trough: value at predose on day 6. Day 6 peak: value at 2–4 hours postdose on day 6. Clinically relevant bleeding was the composite of major and clinically relevant non-major bleeding.

Table 2. Percentage of patients with bleeding events grouped by day 6 prothrombin time (PT) peaks and troughs according to quartiles in rivaroxaban-treated patients from the RECORD1–4 studies

| | PT range (seconds) | Patients with bleeding events (%) | 95% confidence interval |
|-------------------------------------|--------------------|-----------------------------------|-------------------------|
| Any bleeding | | | |
| PT day 6 trough | | | |
| Q1 | 9.1–12.9 | 3.00 | 2.11–4.10 |
| Q2 | >12.9–13.6 | 3.43 | 2.40–4.74 |
| Q3 | >13.6–14.7 | 4.89 | 3.66–6.38 |
| Q4 | >14.7–36.4 | 8.17 | 6.60–9.96 |
| PT day 6 peak | | | |
| Q1 | 10.0–16.0 | 3.70 | 2.66–4.98 |
| Q2 | >16.0–18.4 | 3.48 | 2.47–4.74 |
| Q3 | >18.4–21.1 | 4.11 | 3.01–5.45 |
| Q4 | >21.1–70.4 | 8.09 | 6.52–9.87 |
| PT day 6 peak/baseline ratio | | | |
| Q1 | 0.277–1.209 | 4.57 | 3.41–5.98 |
| Q2 | >1.209–1.396 | 3.56 | 2.54–4.83 |
| Q3 | >1.396–1.588 | 4.22 | 3.10–5.59 |
| Q4 | >1.588–6.883 | 6.94 | 5.50–8.61 |
| Clinically relevant bleeding | | | |
| PT day 6 trough | | | |
| Q1 | 9.1–12.9 | 1.54 | 0.92–2.39 |
| Q2 | >12.9–13.6 | 1.86 | 1.12–2.89 |
| Q3 | >13.6–14.7 | 1.92 | 1.17–2.94 |
| Q4 | >14.7–36.4 | 3.71 | 2.66–5.02 |
| PT day 6 peak | | | |
| Q1 | 10.0–16.0 | 1.62 | 0.96–2.55 |
| Q2 | >16.0–18.4 | 2.20 | 1.41–3.25 |
| Q3 | >18.4–21.1 | 1.73 | 1.04–2.69 |
| Q4 | >21.1–70.4 | 3.44 | 2.43–4.70 |
| PT day 6 peak/baseline ratio | | | |
| Q1 | 0.277–1.209 | 1.83 | 1.12–2.80 |
| Q2 | >1.209–1.396 | 1.92 | 1.19–2.91 |
| Q3 | >1.396–1.588 | 2.57 | 1.71–3.69 |
| Q4 | >1.588–6.883 | 2.65 | 1.78–3.78 |

Day 6 trough: value at predose on day 6. Day 6 peak: value at 2–4 hours postdose on day 6. Clinically relevant bleeding was the composite of major and clinically relevant non-major bleeding. Q, quartile.

Discussion and Conclusions

- This analysis indicated that the distribution of PT values in patients with no bleeding events or with different types of bleeding events were similar for each time point (baseline, day 6 trough, and day 6 peak)
- Extreme PT values at day 6 trough and peak were associated with an increased risk of bleeding; however, these values were mainly represented by outliers, a pattern also seen in patients who did not bleed
- PT values obtained with rivaroxaban are measured in seconds and are not converted into international normalized ratios because it has been shown that the conversion failed to correct the apparent differences in PT assay sensitivity to rivaroxaban⁹
- This analysis therefore suggests that the PT assay is not an accurate predictor of bleeding events in individual patients undergoing THR or TKR receiving a therapeutic dose of 10 mg rivaroxaban

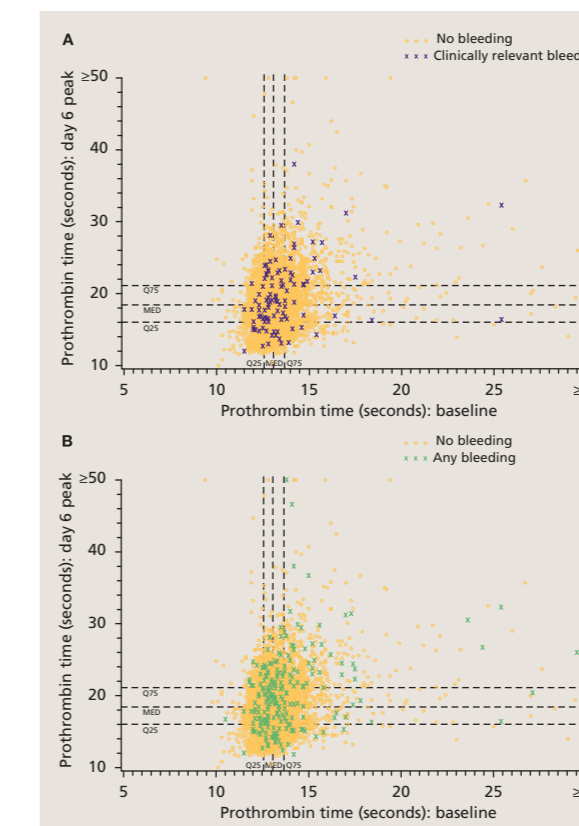


Figure 3. Scatter plots to show distribution of prothrombin time (using Neoplastin) measured at baseline versus day 6 peak in rivaroxaban-treated patients without bleeding events and with (A) clinically relevant bleeding (composite of major and clinically relevant non-major bleeding) or (B) with any bleeding from the RECORD1–4 studies.

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Disclosure of Conflict of Interest

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