

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

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Rivaroxaban is a new, oral, direct Factor Xa inhibitor with a linear dose-relationship between Factor Xa inhibition and drug concentrations in plasma. It also affects global clotting tests such as prothrombin time (PT), particularly when Neoplastin<sup>®</sup> is used for testing. Rivaroxaban was investigated in four randomized, double-blind phase III studies (RECORD1, 2, 3, and 4) for the prevention of venous thromboembolism (VTE) after total hip or knee replacement surgery. This post hoc, explorative analysis evaluated the relationship between PT and bleeding events from pooled RECORD1–4 data. Patients were randomized to receive oral rivaroxaban 10 mg once daily (od) starting 6–8 hours after surgery, or subcutaneous enoxaparin 40 mg od starting the evening before surgery (RECORD1–3), or 30 mg twice daily starting 12–24 hours after wound closure (RECORD4). RECORD1, 3, and 4 were head-to-head comparisons of rivaroxaban and enoxaparin; RECORD2 compared extended-duration rivaroxaban with short-duration enoxaparin. Pooled analysis of the results of these studies showed that rivaroxaban significantly reduced the incidence of

symptomatic VTE and death compared with enoxaparin regimens. The relationship between PT (measured by Neoplastin reagent) and adjudicated bleeding events was evaluated in 6,040 subjects valid for the safety analysis who underwent surgery and had taken at least one dose of rivaroxaban. The day of the surgery was defined as day 1. PT was measured on day 0 (baseline) and day 6 (trough and peak, and grouped according to quartiles). All adjudicated bleeding events were analyzed with respect to the day 6 measurements. The analysis focused on treatment-emergent adjudicated bleeding events up to 12±2 days after the initiation of active rivaroxaban administration. Bleeding events were grouped as major and clinically relevant non-major bleeding (composite) or any bleeding. A total of 5,912 patients had PT measurements at baseline; 345 experienced any bleeding event, of which 149 events were major or clinically relevant non-major bleeding events. Baseline mean PT ranged from 13.5 (with no bleeding) to 14.0 seconds (with any bleeding). Mean trough values on day 6 ranged from 14.3 (no bleeding) to 15.3 seconds (any bleeding). Mean peak values for PT on day 6 (measured at 2–4 hours after dosing) ranged from 18.9 (no bleeding) to 20.5 seconds (any bleeding). The peak/baseline PT ratios were 1.42 (no bleeding events), 1.46 (with major and clinically relevant non-major bleeding events), and 1.49 (any bleeding events). Of the patients with bleeding events, most events occurred in those with PT values in the extreme (Q4) peak and trough quartiles (Table). This explorative analysis indicated that PT values (seconds) in patients with no bleeding or with different types of bleeding were similar for each time point (baseline, day 6 trough and peak). The reproducible effects of rivaroxaban on PT are consistent with its known pharmacokinetics in plasma. Although extreme PT trough and peak values were associated with an increased risk of bleeding, this analysis suggests that PT over a wide range is not an accurate predictor of bleeding events in individual patients undergoing total hip or knee replacement surgery receiving 10 mg rivaroxaban. Refinement of PT testing methods has focused specifically on vitamin K antagonist (VKA) monitoring; therefore PT testing may be of greater utility for monitoring VKAs than Factor Xa inhibitors.

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

	<b>Prothrombin time range (seconds)</b>	<b>Patients with bleeding events (%)</b>	<b>95% confidence interval</b>
<b>Any bleeding</b>			
Prothrombin time 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
Prothrombin time 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
<b>Major and clinically relevant non-major bleeding</b>			
Prothrombin time 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
Prothrombin time 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

Day 6 trough: value at pre-dose on day 6. Day 6 peak: value at 2–4 hours post-dose on day 6. Q, quartile.

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