

Pooled analysis of four clinical studies of rivaroxaban after hip and knee arthroplasty: effects of NSAIDs and ASA

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Introduction: Four randomized, double-blind phase III studies (RECORD1–4) investigated the oral, direct Factor Xa inhibitor rivaroxaban for the prevention of venous thromboembolism (VTE) after elective total hip and total knee arthroplasty (THA and TKA). Patients (N=12,729) were randomized to receive oral rivaroxaban 10 mg once daily, or subcutaneous enoxaparin 40 mg once daily (RECORD1–3), or 30 mg twice daily (RECORD4). Those undergoing THA 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 (TKA), prophylaxis was for 10–14 days.

Methods: A prespecified pooled analysis of all four studies evaluated the effect of rivaroxaban on the composite of symptomatic VTE and all-cause mortality, and bleeding, relative to enoxaparin. The present subgroup analysis investigated potential drug–drug interactions with concomitant non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) – commonly used pain medications known to affect bleeding risk. The risk of on-treatment bleeding in the total study duration pool of all four RECORD studies was investigated. These prespecified analyses focused on on-treatment, adjudicated bleeding events, any bleeding, and the composite of major bleeding and clinically relevant non-major bleeding – after the first tablet intake (rivaroxaban or matching placebo). Co-medication use was evaluated over time. Relative bleeding rates with and without co-medication were calculated separately for the rivaroxaban and enoxaparin/placebo groups. Time after surgery (day of surgery was day 1) was stratified into three periods (days 1–3, days 4–7 and day 7 up to 2 days after the last dose), based on the decreasing risk with time of a first bleeding event after surgery and because

prevalence of co-medication use can vary over time. Bleeding rates were recorded for each time period over the at-risk period (the day of surgery until the last day of double-blind study medication intake +2 days or until initial event onset). The ratio of the bleeding rate for co-medication exposed vs unexposed patient-days in the rivaroxaban group was compared with the corresponding rate ratio for the enoxaparin/placebo group for bleeding events (Mantel–Haenszel methods).

Results: Concomitant use of ASA in the rivaroxaban groups showed rate ratios similar to those in the enoxaparin/placebo group (1.32 and 1.40, respectively, for any bleeding). Rate ratios were also similar with concomitant use of NSAIDs (1.22 in both groups, for any bleeding).

Conclusion: In the RECORD1–4 subanalysis, there was no indication of increased bleeding associated with the use of these co-medications in patients taking rivaroxaban, compared with enoxaparin.