

A pooled analysis of four pivotal studies of rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty

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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 major orthopaedic surgery. 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). In RECORD1 and 2, patients undergoing total hip arthroplasty received rivaroxaban for 31–39 days. Enoxaparin was given for 31–39 days in RECORD1, 10–14 days followed by placebo in RECORD2. In RECORD3 and 4, patients undergoing total knee arthroplasty received prophylaxis for 10–14 days. After prophylaxis, all patients were followed up for a further 30–35 days. Rivaroxaban significantly reduced the incidence of the primary efficacy outcome for the individual studies (total VTE; composite of any deep vein thrombosis, non-fatal pulmonary embolism [PE] and all-cause mortality) compared with the enoxaparin regimens, with similar rates of major bleeding.

Methods: A pre-specified pooled analysis of all four trials was performed on all randomized patients who received at least one dose of double-blind study medication to evaluate the effect of rivaroxaban on the composite of symptomatic VTE and all-cause mortality (primary outcome for pooled analysis), and bleeding. This outcome was analysed at day 12±2 in the active treatment pool (enoxaparin-controlled in all studies) and in the total study duration pool (including follow-up after treatment).

Results: Rivaroxaban significantly reduced the incidence vs enoxaparin of the composite of symptomatic VTE and death (day 12±2: 0.47% vs 0.97%,

respectively, $p=0.001$; total study duration: 0.81% vs 1.6%, respectively, $p<0.001$) and the composite of PE and death (day 12 \pm 2: 0.19% vs 0.39%, respectively, $p=0.049$; total study duration: 0.47% vs 0.76%, respectively, $p=0.039$). The rates of major bleeding with the rivaroxaban and enoxaparin regimens were 0.34% and 0.21%, respectively, $p=0.175$ at day 12 \pm 2 and at total study duration were 0.44% and 0.27%, respectively, $p=0.135$. Rivaroxaban also reduced the composite of death, infarction, stroke, symptomatic VTE and major bleeding vs enoxaparin (total study duration: 1.6% vs 2.2%, respectively, $p=0.006$).

Conclusion: Rivaroxaban reduced the composites of major clinical outcomes compared with enoxaparin regimens, with similar rates of major bleeding, in patients undergoing major orthopaedic surgery.