Introduction

Rivaroxaban is an oral, direct Factor Xa inhibitor that has received a positive CHMP recommendation for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement surgery.

Three phase III trials (RECORD1-3) studied rivaroxaban for the prevention of VTE after total hip replacement (THR) or total knee replacement (TKR).

In individual studies, rivaroxaban regimens significantly reduced the incidence of total VTE (the composite of any deep vein thrombosis [DVT], any pulmonary embolism [PE] and all-cause mortality) and major VTE (the composite of proximal DVT, non-fatal PE and VTE-related death), compared with enoxaparin regimens, with no significant increase in the risk of major bleeding.

Objective

To assess the incidence of symptomatic VTE, all-cause mortality and bleeding through a pre-specified analysis of pooled data from the RECORD1–3 trials.

Methods

Patients and study medication

Patients (N=9,310) were randomised to receive oral rivaroxaban 10 mg once daily (oral) or enoxaparin 40 mg od at 2 weeks after surgery; or subcutaneous enoxaparin 40 mg od (oral) started operatively:

– Patients undergoing THR received rivaroxaban or enoxaparin for 35 days in RECORD1, and rivaroxaban for 35 days or enoxaparin for 10–14 days, followed by placebo up to 35 days, in RECORD2. In RECORD3 (THI), prophylaxis was for 10–14 days with either rivaroxaban or enoxaparin.

Endpoints

Primary efficacy outcome: composite of symptomatic VTE (i.e. symptomatic DVT and symptomatic PE and non-fatal PE) and all-cause mortality up to 2 weeks after surgery (day 12/14) (Figure 1), i.e. the enoxaparin-controlled period in all three trials.

Secondary efficacy outcome: composite of symptomatic VTE and all-cause mortality at the end of the planned medication period (Figure 1) Up to 2 weeks (range, 13–17 days) in RECORD3.

Results

Efficacy

Primary efficacy outcome: rivaroxaban 10 mg significantly reduced the composite of symptomatic VTE and all-cause mortality compared with enoxaparin 40 mg od at 2 weeks:

– The outcome occurred in 0.8% (39/4,692) of patients in the enoxaparin group, compared with 0.5% (23/4,657) of those who received rivaroxaban, compared with 0.5% (23/4,657) of those who received enoxaparin, compared with 0.5% (23/4,657) of those who received enoxaparin (p = 0.005) (Figure 2B).

– A Kaplan-Meier plot of the occurrence of the composite of symptomatic VTE and death over the entire study period showed an early favor of rivaroxaban, that increased over time and persisted at the end of follow-up (Figure 2).

Secondary efficacy outcome: rivaroxaban also significantly reduced the composite of symptomatic VTE and all-cause mortality compared with enoxaparin at the end of the planned medication period:

– This outcome occurred in 1.3% (61/4,692) of patients who received enoxaparin, compared with 0.5% (23/4,657) of those who received rivaroxaban (relative risk reduction of 62%; p<0.001) (Figure 2B).

Safety

– The rates of major bleeding were low and similar for the enoxaparin and rivaroxaban regimens 2 weeks after surgery: 0.2% (9/4,692) and 0.2% (14/4,657) with the enoxaparin and rivaroxaban regimens, respectively (Figure 3).

– Rates of non-major bleeding were also similar: 0.3% (14/4,692) and 0.3% (13/4,657) with the enoxaparin and rivaroxaban regimens, respectively (Figure 4).

Summary

In patients who underwent major orthopaedic surgery, rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality at 2 weeks after surgery compared with enoxaparin (p<0.001).

The incidence of major bleeding and all on-treatment bleeding events was low and similar in the rivaroxaban and enoxaparin groups.

Rivaroxaban regimens were associated with a low and similar incidence of cardiovascular adverse events to enoxaparin.

Conclusions

– Rivaroxaban is the first novel, oral anticoagulant to significantly reduce the composite outcome of symptomatic VTE and all-cause mortality after major orthopaedic surgery.

– Rivaroxaban shows superior safety to enoxaparin for this clinical outcome with a similar safety profile.

– Bleeding rates where low with no significant increase in major bleeding between the studied drug regimens.

References


Disclosure of Conflict of Interest

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Rivaroxaban is in clinical development and not yet licensed.

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