

Rivaroxaban, a new option for thromboprophylaxis after knee or hip replacement



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Rivaroxaban, an orally active direct Factor Xa inhibitor, offers an effective alternative to traditional methods of thromboprophylaxis following elective hip and knee replacement surgery.

Patients undergoing major orthopaedic surgery are at particularly high risk of venous thromboembolism (VTE) [1], a condition associated with significant mortality and morbidity rates, reduced quality of life and a substantial burden on healthcare resources. Thromboprophylaxis is recommended in all patients undergoing elective hip and knee replacement surgery [1]. Current guidelines from the American College of Chest Physicians recommend that patients undergoing hip replacement surgery receive thromboprophylaxis for at least 10 days and up to 35 days [1]. For patients undergoing knee replacement surgery thromboprophylaxis is recommended for 10 days, and it is suggested that this is extended to 35 days [1].

Current therapeutic options for thromboprophylaxis have various limitations, highlighting the need for new anticoagulants with improved efficacy and safety profiles, see the paper from Dr Hoppe-Tichy, pages 20–23 in this issue of *EJHP Practice*. This review focuses on the new agent rivaroxaban, an orally active direct inhibitor of Factor Xa, approved in more than 70 countries worldwide (including Canada, China, Mexico and those in the EU) for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery.

Phase I and II studies

Pharmacokinetics and pharmacodynamics

Rivaroxaban is an orally active direct inhibitor of Factor Xa that binds to the active site. Factor Xa catalyses the con-

version of prothrombin to thrombin (Factor II to IIa), which is the rate-limiting step in thrombin formation [2]. In phase I studies with healthy volunteers rivaroxaban inhibited Factor Xa in a dose-dependent manner [3]. Rivaroxaban is rapidly absorbed following oral administration, with peak plasma concentrations reached after 2.5–4 hours, 80% bioavailability, and a short half-life (5–9 hours) in healthy volunteers after multiple dosing [3]. Pharmacokinetic studies showed that no dose adjustment is required for body weight or gender [4]. Rivaroxaban demonstrates a low potential for drug–drug interactions, with no clinically significant interactions observed with a range of drugs, including aspirin, naproxen and digoxin [3].

Phase II studies

A series of phase II studies in patients undergoing either elective knee (one study) or hip replacement (three studies) were conducted to assess the safety and efficacy of rivaroxaban in preventing VTE, and to determine the optimum dosing regimen for investigation in phase III studies. All studies compared a range of rivaroxaban doses (administered once daily or twice daily) with enoxaparin (40 mg once daily, hip study; 30 mg twice daily, knee study) [5–8]. Overall, the phase II studies showed an incidence of major bleeding with rivaroxaban (total daily dose, 5–20 mg) that was low and similar to that observed with enoxaparin, with similar efficacy. On the basis of these studies, rivaroxaban 10 mg once daily was selected for investigation in the phase III clinical study programme.

The phase III RECORD programme

The 10 mg once-daily regimen of rivaroxaban has been evaluated for prevention of VTE in patients undergoing elective hip or knee replacement surgery in four phase III clinical trials – the RECORD (**R**egulation of **C**oagulation in **O**ртопаedic **S**urgery to **P**revent **D**eep **V**ein **T**hrombosis and **P**ulmonary **E**mbolism) studies [9–12]. The RECORD programme involved more than 12,500 patients.

Study design and assessments

All four RECORD trials were randomised, double-blind, double-dummy, active-comparator studies comparing oral rivaroxaban 10 mg once daily with enoxaparin regimens for VTE prevention following elective hip (RECORD1 and 2) [9, 10] or knee (RECORD3 and 4) [11, 12] replacement surgery (see Table 1). In all studies, rivaroxaban was initiated 6–8 hours after surgery and then administered once daily. In RECORD1, 2 and 3, enoxaparin 40 mg was administered subcutaneously once daily, initiated 12 hours before surgery and restarted 6–8 hours post-operatively. In RECORD4, enoxaparin 30 mg was administered subcutaneously twice daily (at 12 hour intervals), initiated 12–24 hours after surgery.

RECORD1 compared extended prophylaxis (35 days) with rivaroxaban (10 mg once daily) with extended prophylaxis with enoxaparin (40 mg once daily) in patients undergoing elective hip replacement surgery [9]. RECORD2 compared extended prophylaxis with rivaroxaban (35 ± 4 days) with short-duration pro-

phylaxis of enoxaparin (12 ± 2 days) in patients undergoing elective hip replacement surgery [10]. RECORD3 compared rivaroxaban (10 mg once daily) with enoxaparin (40 mg once daily), both administered for 12 ± 2 days, in patients undergoing elective knee replacement surgery [11]. RECORD4 compared 12 ± 2 days of rivaroxaban with enoxaparin (30 mg twice daily) in patients undergoing elective knee replacement surgery [12]. In the RECORD1, 2 and 3 studies enoxaparin (40 mg once daily) was started pre-operatively, compared with the RECORD4 study where enoxaparin (30 mg twice daily) was started 12–24 hours after surgery.

All four studies used the same efficacy and safety outcome measures, and outcomes were assessed blindly by the same independent, central adjudication committees (see Table 1). Patients underwent mandatory bilateral venography to assess deep vein thrombosis (DVT) the day after the last dose of

study medication. The primary efficacy measure was the incidence of total VTE (defined as the composite of any DVT as detected by bilateral venography, non-fatal pulmonary embolism [PE] and death from any cause). Secondary efficacy measures included major VTE (defined as the composite of proximal DVT, non-fatal PE and death from VTE) and symptomatic VTE. The main safety endpoint was major bleeding occurring during the period between initiation of blinded treatment and two days after the last dose. Major bleeding was defined as bleeding that was fatal, occurred in a critical organ, e.g. retroperitoneal, intracranial, intra-ocular and intraspinal bleeding, or required re-operation, or clinically overt extra-surgical-site bleeding associated with a drop in haemoglobin of ≥2 g/dL or requiring the infusion of ≥2 units of blood or packed cells.

Owing to the low number of events expected, a pooled analysis of RECORD1-3 [13] was pre-specified to determine

whether rivaroxaban 10 mg once daily was more effective than the 40 mg once-daily regimen of enoxaparin in reducing the incidence of the composite endpoint of symptomatic VTE and death from all causes, both at two weeks and at the end of the planned medication period.

Clinical efficacy

In the RECORD1 study rivaroxaban significantly reduced the incidence of total VTE compared with the enoxaparin regimen (1.1% vs. 3.7%; absolute risk reduction, -2.6% [95% CI, -3.7, -1.5]; p < 0.001) (see Figure 1). Major VTE events were also significantly less frequent with rivaroxaban than enoxaparin therapy (0.2% vs. 2.0%; an absolute risk reduction of -1.7% [95% CI, -2.5, -1.0]; p < 0.001). Rates of symptomatic VTE events were similar in the two groups (rivaroxaban, 0.3%; enoxaparin, 0.5%) [9].

In RECORD2 the incidence of total VTE was significantly lower with the extended rivaroxaban regimen than with the short-term enoxaparin regimen (2.0% versus 9.3%; absolute risk reduction of 7.3% [95% CI, 2.0–9.4]; p < 0.0001) (see Figure 1). Both major VTE events and symptomatic VTE events were significantly reduced with rivaroxaban therapy compared with enoxaparin therapy. Major VTE occurred in 0.6% of patients in the rivaroxaban group compared with 5.1% of patients in the enoxaparin group (absolute risk reduction with rivaroxaban, 4.5% [95% CI, 3.0–6.0]; p < 0.0001). Symptomatic VTE occurred in 0.2% of patients in the rivaroxaban group and 1.2% of patients in the enoxaparin group (absolute risk reduction with rivaroxaban, 1.0% [95% CI, 0.3–1.8]; p = 0.004) [10].

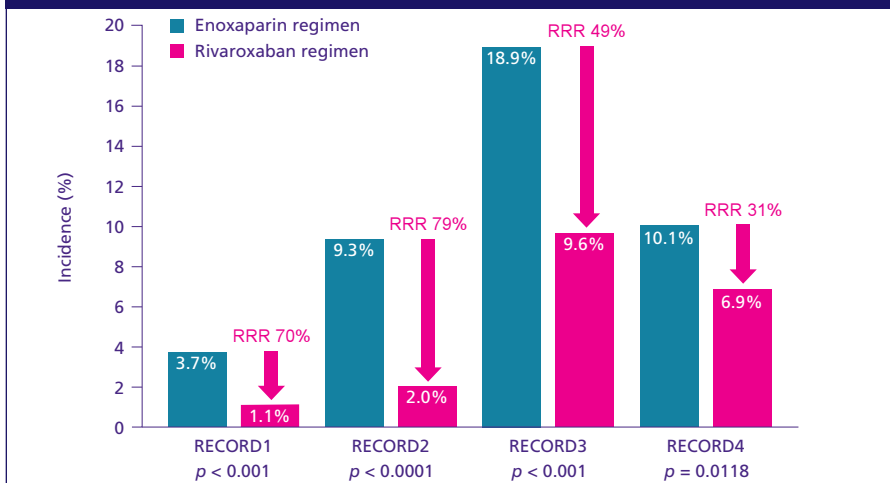
In RECORD3 rivaroxaban significantly reduced the incidence of total VTE compared with enoxaparin (9.6% vs. 18.9%; absolute risk difference of -9.2% [95% CI, -12.4, -5.9]; p < 0.001) (see Figure 1). Major VTE events were significantly less frequent in patients receiving rivaroxaban than those receiving enoxaparin (1.0% vs.

Table 1: RECORD clinical trials: study design and outcome measures [9-12]

Clinical Trials	RECORD1	RECORD2	RECORD3	RECORD4
Surgery	Hip replacement	Hip replacement	Knee replacement	Knee replacement
Randomised patients	4,541	2,509	2,531	3,148
Treatment regimens				
Rivaroxaban	10 mg o.d. for 35 ± 4 days	10 mg o.d. for 35 ± 4 days	10 mg o.d. for 12 ± 2 days	10 mg o.d. for 12 ± 2 days
Enoxaparin	40 mg o.d. for 35 ± 4 days	40 mg o.d. for 12 ± 2 days followed by placebo	40 mg o.d. for 12 ± 2 days	30 mg b.i.d. for 12 ± 2 days
Efficacy outcomes				
Primary	Total VTE (any DVT, non-fatal PE and death from any cause)			
Secondary	Major VTE (proximal DVT, non-fatal PE and death from VTE), symptomatic VTE, DVT (any, proximal or distal)			
Safety outcomes				
Main	Major bleeding starting after the first blinded dose and up to 2 days after last dose*			
Secondary	Any bleeding on treatment,† non-major bleeding, † haemorrhagic wound complications, † cardiovascular adverse events, liver enzyme levels			

*Major bleeding was defined as bleeding that was fatal, occurred in a critical organ or required re-operation, or clinically overt extra-surgical-site bleeding associated with a drop in haemoglobin of ≥2 g/dL or requiring the infusion of ≥2 units of blood or packed cells.
 †Up to 2 days after last dose.
 b.i.d.: twice daily; DVT: deep vein thrombosis; o.d.: once daily; PE: pulmonary embolism; VTE: venous thromboembolism

Figure 1: Primary efficacy outcome in the RECORD trials: incidence of total VTE



Composite of any deep vein thrombosis as detected by bilateral venography, non-fatal pulmonary embolism and death from any cause. Data from [9-12].

RRR: relative risk reduction; VTE: venous thromboembolism.

of total VTE compared with enoxaparin, 30 mg twice daily, started post-operatively (6.9% vs. 10.1%; absolute risk difference of -3.2% [95% CI, -5.7, -0.7]; p = 0.0118) (see Figure 1). The incidence of major VTE events was lower in the rivaroxaban group than the enoxaparin group (1.2% vs. 2.0%), as was the incidence of symptomatic VTE (rivaroxaban, 0.7%; enoxaparin, 1.2%), although both of these differences were not statistically significant [12].

Overall, the RECORD trials showed that a once-daily oral rivaroxaban regimen was significantly more effective than subcutaneous enoxaparin regimens in reducing the risk of VTE in patients undergoing elective hip or knee replacement surgery.

Clinical safety

In all four RECORD studies, rivaroxaban was generally well tolerated, with a good safety profile and a low risk of bleeding [9-13]. On-treatment death from all causes with rivaroxaban was low (0–0.2%) and similar to that in the enoxaparin groups (0–0.7%). The incidence of major bleeding during treatment, the main safety measure, was low in patients receiving rivaroxaban (<0.1–0.7%), and did not differ significantly from the incidence with enoxaparin (<0.1–0.5%) in any of the four studies (see Table 2). In the pooled analysis of RECORD1-3, the incidence of major bleeding at two weeks was 0.2% in both treatment groups [13]. At the end of the planned medication period, the incidence of major bleeding was 0.3% in the rivaroxaban group and 0.2% in the enoxaparin group. The incidences of clinically relevant non-major bleeding and haemorrhagic wound complications were similar with rivaroxaban and enoxaparin therapies (see Table 2).

Overall adverse event profiles were similar with rivaroxaban and enoxaparin. Cardiovascular (CV) adverse events (CV death, ischaemic stroke and myocardial infarction) were infrequent with

2.6%; absolute risk difference, -1.6% [95% CI, -2.8, -0.4]; p = 0.01), as were symptomatic VTE events (0.7% vs. 2.0%; absolute risk reduction, -1.3% [95% CI, -2.2, -0.4]; p = 0.005) [11].

In the pooled analysis of RECORD1-3 rivaroxaban, 10 mg once daily, significantly reduced the incidence of the composite of symptomatic VTE and all-

cause mortality at two weeks compared with enoxaparin 40 mg once daily (0.4% vs. 0.8%; p = 0.005). The incidence at the end of the planned medication period was also significantly lower with rivaroxaban than with enoxaparin (0.5% vs. 1.3%; p < 0.001) [13].

In RECORD4 rivaroxaban 10 mg once daily significantly reduced the incidence

Table 2: Summary of safety outcome measures in the RECORD trials; data from [9-12]

	Rivaroxaban regimen	Enoxaparin regimen	p value
Major bleeding			
RECORD1	0.3%	0.1%	0.18
RECORD2	<0.1%	<0.1%	nr
RECORD3	0.6%	0.5%	0.77
RECORD4	0.7%	0.3%	0.1096
Clinically relevant non-major bleeding			
RECORD1	2.9%	2.4%	nr
RECORD2	3.3%	2.7%	nr
RECORD3	2.7%	2.3%	nr
RECORD4	2.6%	2.0%	nr
Haemorrhagic wound complications*			
RECORD1	1.5%	1.7%	nr
RECORD2	1.6%	1.7%	nr
RECORD3	2.0%	1.9%	nr
RECORD4	1.4%	1.5%	nr

*Composite of excessive wound haematoma and surgical-site bleeding.
nr: not reported.

the two agents ($\leq 0.7\%$), both during treatment and follow-up. There was no evidence of drug-induced liver toxicity with rivaroxaban in any of the RECORD trials, consistent with findings from earlier studies. Increased alanine aminotransferase levels (>3 times the upper limit of normal) were observed in some patients in both the rivaroxaban (1.3–2.0%) and enoxaparin (1.7–4.7%) groups, but levels returned to normal by the end of the study period.

Conclusion

The RECORD clinical study programme has demonstrated that rivaroxaban provides significantly lower rates of VTE compared with enoxaparin regimens in patients undergoing elective hip or knee replacement surgery. Rivaroxaban significantly reduced the incidence of total VTE compared with enoxaparin regimens in all four studies, and provided significantly greater reductions in the incidences of major and symptomatic VTE in three out of four studies. In the pooled analysis (RECORD1-3), rivaroxaban (started 6–8 hours after surgery) was more effective than enoxaparin (40 mg once daily, started before surgery) in preventing symptomatic VTE and death from all causes, without increasing major bleeding. Rivaroxaban was well tolerated, and had a good safety profile in all four studies. There were no significant differences in the risk of major or clinically relevant bleeding between the rivaroxaban and enoxaparin groups, and rivaroxaban was associated with consistently low levels of cardiovascular adverse events. In addition, there was no evidence of drug-induced liver toxicity in the RECORD programme.

Rivaroxaban, an orally active direct Factor Xa inhibitor, offers an effective new alternative for thromboprophylaxis following elective hip and knee replacement surgery, providing improved VTE prevention compared with enoxaparin regimens without a significant increase in bleeding risk or other safety measures.

Conflict of interest

The authors report receiving honoraria and acting as consultants to Bayer Healthcare AG.

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