

Design, findings and implications of the RECORD study program

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Rivaroxaban is a direct factor Xa inhibitor that can be administered orally for thromboprophylaxis in orthopedic patients undergoing hip or knee arthroplasty. The new drug is well tolerated with a relatively short half-life and a high bioavailability. Rivaroxaban has undergone an extensive clinical evaluation program in elective orthopedic surgery compared with one of the most commonly used antithrombotic drugs on the market – enoxaparin, which is a low-molecular-weight heparin. The results of the Phase III Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE (RECORD) studies was that rivaroxaban was more effective and equally safe relative to enoxaparin. This article is dedicated to these findings and the clinical implications.

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Rivaroxaban is an orally administered, antithrombotic drug for thromboprophylaxis in orthopedic surgery. In 2008, with the brand name Xarelto®, it was marketed in the EU and Canada for thromboprophylaxis in patients undergoing total hip and knee arthroplasty (THA and TKA, respectively) and is now approved in more than 100 countries around the world. Rivaroxaban has a rapid onset of action after intake with a high bioavailability and a half-life of 7–11 h [1]. The recommended dosage of rivaroxaban for thromboprophylaxis is 10 mg once-daily, started 6–10 h after surgery and continued for a total of 5 weeks after THA and 2 weeks after TKA [101].

Rivaroxaban differs in action from the commonly used indirect factor Xa (FXa) inhibitors such as low molecular weight heparins because it does not need anti-thrombin to inhibit FXa. Rivaroxaban is able to directly inhibit both free FXa and FXa bound in the prothrombinase complex resulting in reduced thrombin generation [2]. The effect of direct inhibition of FXa compared with indirect inhibition on the *ex vivo* thrombin generation (using thrombelastography) and the *in vivo* thrombin generation measured by prothrombin fragment 1+2 and thrombin–antithrombin complexes in plasma, was exemplified in a recent clinical study in patients undergoing THA or TKA who had thromboprophylaxis with rivaroxaban or dalteparin, a commonly used low molecular weight heparins, started 6–8 h postoperatively. The result was that patients treated with rivaroxaban showed a greater decrease of thrombin generation, with less interindividual variation, than those on dalteparin measured approximately 24 h after the operation [3].

The clinical evaluation of rivaroxaban

Rivaroxaban has undergone an extensive clinical evaluation program before market introduction. A number of these studies were carried out in healthy subjects to assess the elimination characteristics and the pharmacodynamic and pharmacokinetic

features of the drug [1,4,5]. In the Phase II program, a number of dose-escalation studies in THA and TKA patients evaluated the clinical efficacy and safety of different dose regimens of the drug [6–8]. The main outcome of this program was to use a once-daily dosage of rivaroxaban 10 mg for thromboprophylaxis in the Phase III program [9].

Design of the RECORD program

The clinical Phase III program of rivaroxaban in orthopedic surgery was named the Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE (RECORD) study. The basic design of the RECORD studies is shown in Figure 1. The studies were prospective, randomized and double-blind. Randomization took place before operation and all patients were followed up for approximately 1 month after the last dose of the study drug. All RECORD studies used the same efficacy and safety criteria and the same diagnostic methodology: contrast ascending venography of both lower extremities after the operation in order to visualize deep vein thrombosis (DVT) formation. In case of clinical symptoms of DVT or pulmonary embolism (PE), relevant objective diagnostic methods were used (venography/compression ultrasound scanning or CT angiography). In case of death, an autopsy was planned whenever possible. The primary and secondary efficacy and safety end points were the same in all RECORD studies and the same adjudication committees evaluated all observed efficacy and safety events in a blinded manner. The statistical evaluation of the studies was identical, enabling a number of prespecified pooled analyses to be performed after finalization of the studies.

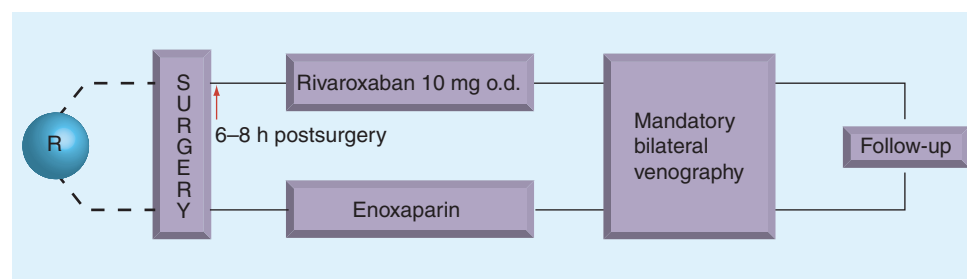


Figure 1. Basic design of the RECORD studies. In RECORD 1, 2 and 3, the European enoxaparin regimen was used (40 mg once-daily started the evening before surgery). In the RECORD 4 study, the north American enoxaparin regimen was used (30 mg twice-daily started 12–24 h following operation). Day 1 was the day of surgery. The mandatory venography was performed at day 36 ± 6 in RECORD 1, day 36 ± 4 in RECORD 2 and day 13 ± 2 in RECORD 3 and 4. Follow-up was day 60 ± 5 in RECORD 1 and 2, and day 42 ± 5 in RECORD 3 and 4. DVT: Deep vein thrombosis; o.d.: Once-daily; PE: Pulmonary embolism; R: Randomization; RECORD: Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE.

The RECORD studies in detail

The RECORD program consists of four clinical prophylaxis studies, which are presented in Table 1. All studies compared the antithrombotic efficacy and safety of rivaroxaban 10 mg given orally once-daily and enoxaparin 40 mg once-daily or 30 mg twice-daily in patients undergoing THA or TKA [10–13]. RECORD 1 and 2 were performed in THA patients and 40 mg once-daily of enoxaparin was used for comparison in both studies. In RECORD 1, both prophylactic regimens were given for a total duration of 35 ± 4 days (long-term), whereas in RECORD 2 only rivaroxaban was given long-term compared with enoxaparin, which was given for 10–14 days (short-term) (Table 1) since it is not universally accepted to use long-term prophylaxis after THA. Another reason for the design was to demonstrate the benefits of extended prophylaxis with rivaroxaban over a short-term prophylactic regimen. RECORD 3 and 4 were performed in TKA patients, thus, short-term duration (10–14 days) was used for both regimens. In RECORD 3, rivaroxaban 10 mg once-daily started 6–8 h after surgery was compared with enoxaparin 40 mg started in the evening before surgery, whereas in RECORD 4, enoxaparin 30 mg twice-daily started 12–24 h after surgery was used in the comparator arm (Table 1).

Efficacy end points in the individual RECORD studies

The primary efficacy end point was the composite of the incidence of any DVT (proximal and/or distal), nonfatal symptomatic, objectively confirmed PE and all-cause deaths. The main secondary efficacy outcome – major venous thromboembolism (VTE) – was defined as the composite of proximal DVT, nonfatal PE or death from VTE. Other efficacy end points were frequency of any DVT, including both proximal and distal DVT, symptomatic VTE during treatment and follow-up, and death during the follow-up period.

Safety end points in the RECORD studies

The primary safety outcome was major bleeding, beginning after the first dose of study drug and up to 2 days after the last dose, defined as follows: fatal bleeding; bleeding into a critical organ (e.g. retroperitoneal, intracranial, intraocular or intraspinal); bleeding requiring reoperation; and clinically overt extrasurgical-site bleeding associated with a fall in hemoglobin ≥ 2 g/dl or requiring

Table 1. Specific design of the RECORD studies.

Study title	Operation	Doses (mg)		Duration of prophylaxis (days)		Ref.
		Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin	
RECORD 1	THA	10 o.d. [†]	40 o.d. [‡]	35 ± 4	35 ± 4	[10]
RECORD 2	THA	10 o.d. [†]	40 o.d. [‡]	35 ± 4	10–14	[11]
RECORD 3	TKA	10 o.d. [†]	40 o.d. [‡]	10–14	10–14	[12]
RECORD 4	TKA	10 o.d. [†]	30 b.i.d. [§]	10–14	10–14	[13]

[†]Started 6–8 h after surgery (tablets). [‡]Started on the evening before surgery (injected subcutaneously). [§]Started 12–24 h after surgery (injected subcutaneously).
b.i.d.: Twice-daily; DVT: Deep vein thrombosis; o.d.: Once-daily; PE: Pulmonary embolism; RECORD: Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

an infusion of ≥ 2 units of blood or packed cells. Other safety outcomes were: clinically relevant non-major bleeding, hemorrhagic wound complications, any other bleeding events started after the first oral dose of rivaroxaban or placebo and ended up to 2 days after the last dose was administered, and any adverse events and deaths. In addition, liver enzymes and cardiovascular events were monitored in all RECORD studies.

Results of the RECORD studies

■ Efficacy results

The main efficacy results of the RECORD studies are presented in Table 2. In all four studies, rivaroxaban was significantly more effective in reducing the primary efficacy end point. In RECORD 1, 2 and 3, major VTE was also significantly reduced compared with enoxaparin and, in addition, rivaroxaban also significantly reduced the incidence of symptomatic VTE events in the RECORD 2 and 3 studies, which are important clinical outcomes.

■ Safety results

The main safety end point, major bleeding, showed no statistically significant differences between rivaroxaban and enoxaparin in any of the studies (Table 3). The RECORD 4 study was the only study with a trend towards higher bleeding incidences in the rivaroxaban

group compared with patients in the enoxaparin group for major bleeding and nonmajor clinically relevant bleeding. An explanation for this could be that the mean time from the end of surgery to the first dose of rivaroxaban was 7 h and 35 min compared with 17 h and 7 min to the first administration of enoxaparin.

■ Other results

The liver safety parameters showed no important differences between rivaroxaban and enoxaparin and there was no observed different impact on the liver function when rivaroxaban was used for long-term prophylaxis in the RECORD 1 and 2 studies compared with short-term prophylaxis with rivaroxaban in RECORD 3 and 4.

Results of prespecified pooled analyses

A pooled analysis was performed on the RECORD 1, 2 and 3 trials ($n = 9581$), which used the same comparator regimen: enoxaparin 40 mg once-daily started the evening before surgery. The aim of the prespecified analysis was to investigate whether rivaroxaban was more effective than enoxaparin to reduce the composite incidence of symptomatic VTE and all-cause mortality (the main efficacy outcome) without increasing major bleeding (the main safety outcome) or other bleeding events [14]. The analysis focused on two time periods: the active treatment period

Table 2. Main efficacy results of the RECORD studies.

Study title	Randomized (n)	Primary efficacy end point [†] (%)		Relative risk reduction (%)	p-value for difference	Ref.
		Rivaroxaban	Enoxaparin			
RECORD 1	4541	1.1	3.7	70	<0.001	[10]
RECORD 2	2509	2.0	9.3	79	<0.001	[11]
RECORD 3	2531	9.6	18.9	49	<0.001	[12]
RECORD 4	3148	6.9	10.1	31	0.012	[13]

[†]Primary efficacy end point was the composite of the incidence of any DVT (proximal and/or distal), nonfatal symptomatic, objectively confirmed pulmonary embolism and all-cause deaths.
DVT: Deep vein thrombosis; PE: Pulmonary embolism; RECORD: Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE.

of 2 weeks in which treatment with enoxaparin took place across all three studies and the total treatment period of up to 5 weeks, which included a placebo-controlled period in the enoxaparin arm in RECORD 2 and 2 weeks of treatment in RECORD 3. During both treatment periods the main efficacy outcome was significantly reduced in the rivaroxaban group, compared with the enoxaparin group with an increasing reduction over time without a statistically significant increase in major bleeding or hemorrhagic wound complications. In addition, the incidence of cardiovascular events (myocardial infarction, stroke, cardiovascular death) and unexplained death was similar in both groups. A pooled analysis of all four RECORD studies (n = 12,729) has been published recently [15]. The analysis operated with the same active treatment period of 2 weeks, which has been presented previously, and a total study period of up to day 65 (61–65), which was the total active treatment period in all studies, and 30–35 days follow-up including the placebo phase in the RECORD 2 study. The analysis included all randomized patients who received at least one dose of double-blind study medication and the main end point was the composite of major clinical outcomes such as symptomatic VTE, myocardial infarction, ischemic stroke, death and major bleeding – a composite of important clinical outcomes – in relation to treatment with rivaroxaban or enoxaparin. It has to be emphasized here that this was not the primary end point in the studies and the analysis was done *post hoc*. The result of the analysis was that rivaroxaban reduced the main end point significantly in both time periods studied and no increased risk of major bleeding with rivaroxaban was reported.

Expert commentary

The results of the individual RECORD studies, but also of the pooled analyses, are very promising and there is no doubt that the drug will be a popular prophylactic modality in the near future among orthopedic surgeons.

However, there have, not surprisingly, been diverging opinions on the RECORD program, which I will shortly address here. First of all, a general scepticism has been raised towards any new antithrombotic drug because of uncertainty about the benefit:risk ratio. This scepticism has been expressed among anesthesiologists because of the risk of hemorrhagic complications in relation to spinal anesthesia, which is still much used in orthopedic surgery. I consider this risk low with rivaroxaban because the drug is administered postoperatively after the spinal puncture has been performed and there was no report of such complications during the entire RECORD program. Concerning indwelling epidural catheters, they should not be removed until at least two half-lives after the last dose of anticoagulant and it may be necessary to wait even longer in cases with reduced renal function [16]. Bleeding is also feared by surgeons among whom different views are dominating, ranging from disbelief in results of clinical studies to a general fear of new potent antithrombotics [17]. It has been emphasized by some authors that it should be possible to compare the various safety criteria between different clinical studies in order to be able to compare the safety profile of different drugs [18,19]. Some authors have claimed that the definition of major bleeding used in the RECORD studies did not include surgical site bleedings [18,19]; however, this is only partially correct because the clinically most important surgical site bleedings – bleeding leading to death or reoperation – were covered by the definition of major bleeding used. Hemorrhagic wound complications and wound infections were reported separately and this has led to speculations about underestimation of the major bleeding rates in the RECORD studies. However, when major bleedings, nonmajor clinically relevant bleedings and surgical-site bleedings were combined across all RECORD studies, only a nonsignificant trend towards a lower bleeding rate with enoxaparin compared with rivaroxaban was seen [20].

In addition to the above-mentioned studies, in orthopedic surgery, rivaroxaban has recently completed Phase III trials for VTE prevention in medically ill patients, for the prevention of stroke or systemic embolism in patients with atrial fibrillation, for the treatment of VTE and for the prevention of recurrent ischemia in patients with acute coronary syndrome.

Future perspective

In the next 5 years, I expect rivaroxaban to be among the most widely antithrombotic regimens in elective orthopedic indications such as THA and TKA, especially in countries where postdischarge prophylaxis is much used. Other prophylactic regimens, such as dabigatran, an oral direct thrombin inhibitor, which is already approved on the indication, and possibly apixaban, another oral direct FXa inhibitor, will also be available.

Table 3. Main safety results of the RECORD studies.

Study title	Major bleeding [*] (%)		p-value for difference	Ref.
	Rivaroxaban	Enoxaparin		
RECORD 1	0.3	0.1	0.18	[10]
RECORD 2	0.1	0.1	NS	[11]
RECORD 3	0.6	0.5	0.77	[12]
RECORD 4	0.7	0.3	0.11	[13]

^{*}Primary safety end point was the incidence of major bleeding (according to preset criteria) starting after the first postoperative dose of study drug, but no later than 2 days after the last dose of study drug.
DVT: Deep vein thrombosis; NS: Nonsignificant; PE: Pulmonary embolism;
RECORD: Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE.

Executive summary

- Rivaroxaban is a new orally administered, antithrombotic drug for thromboprophylaxis in orthopedic surgery.
- Rivaroxaban is able to inhibit both free factor Xa and factor Xa bound in the prothrombinase complex directly resulting in reduced thrombin generation.
- Rivaroxaban has undergone an extensive clinical evaluation program in Phase II and III before market introduction.
- The Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT and PE (RECORD) studies in Phase III had the same basic design and each study answered a different research question.
- In all four RECORD studies, rivaroxaban was significantly more effective in reducing the primary efficacy end point compared with enoxaparin.
- The main safety end points showed that there were no statistically significant differences between rivaroxaban and enoxaparin in any of the RECORD studies.
- In the pooled analysis of the RECORD 1, 2 and 3 studies, rivaroxaban significantly reduced the main efficacy outcome compared with enoxaparin with an increasing efficacy over time, but without an increase in major bleeding.
- The influence on a composite of important clinical outcomes was higher with rivaroxaban in the pooled analysis of all RECORD studies compared with enoxaparin.
- Within the next 5 years, I expect rivaroxaban to be among the most widely used antithrombotic regimens in elective orthopedic indications.

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Bibliography

- Kubitza D, Becka M, Voith B, Zuehlendorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin. Pharmacol. Ther.* 78, 412–421 (2005).
- Borris LC. New compounds in the management of venous thromboembolism after orthopaedic surgery; focus on rivaroxaban. *Vasc. Health Risk. Manag.* 4, 855–862 (2008).
- Green L, Lawrie AS, Patel *et al.* The impact of elective knee/hip replacement surgery and thromboprophylaxis with rivaroxaban or dalteparin on thrombin generation. *Br. J. Haematol.* 151(5), 469–476 (2010).
- Perzborn E, Strassburger J, Wilmen A *et al.* *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct factor Xa inhibitor. *J. Thromb. Haemost.* 3, 514–521 (2005).
- Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr. Med. Res. Opin.* 24, 2757–2765 (2008).
- Eriksson BI, Borris L, Dahl OE *et al.* Oral, direct factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J. Thromb. Haemost.* 4, 121–128 (2006).
- Eriksson BI, Borris LC, Dahl OE *et al.* Dose-escalation study of rivaroxaban BAY 59-7939 – an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb. Res.* 120, 685–693 (2007).
- Turpie AGG, Fisher WD, Bauer KA *et al.* BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A Phase II dose-ranging study. *J. Thromb. Haemost.* 3, 2479–2486 (2005).
- Eriksson BI, Borris LC, Dahl OE *et al.* A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation* 114, 2374–2381 (2006).
- Eriksson BI, Borris LC, Friedman RJ *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N. Engl. J. Med.* 358, 2765–2775 (2008).
- Kakkar AK, Brenner B, Dahl OE *et al.* Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 372, 31–39 (2008).
- Lassen MR, Ageno W, Borris LC *et al.* Rivaroxaban – an oral, direct Factor Xa inhibitor – for the prevention of venous thromboembolism after total knee arthroplasty. *N. Engl. J. Med.* 358, 2776–2786 (2008).
- Turpie AGG, Lassen MR, Davidson BL *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. *Lancet* 373, 1673–1680 (2009).
- Eriksson BI, Kakkar AK, Turpie AGG *et al.* Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J. Bone Joint Surg.* 91B, 636–644 (2009).
- Turpie AGG, Lassen MR, Eriksson BI *et al.* Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb. Haemost.* DOI: 10.1160/TH10-09-0601 (2010) (Epub ahead of print).
- Rosencher N, Bonnet M-P, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia* 62, 1154–1160 (2007).
- Sharrock NE, Gonzalez Della Valle A, Go G, Lymann S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin. Orthop. Relat. Res.* 466, 714–721 (2008).

- 18 Hull RD, Yusen RD, Bergqvist D. Assessing the safety profiles of new anticoagulants for major orthopedic surgery thromboprophylaxis. *Clin. Appl. Thromb. Haemost.* 15(4), 377–388 (2009).
- 19 Merli G, Spyropoulos AC, Caprini JA. Use of emerging oral anticoagulants in clinical practice. Translating results from clinical trials to orthopedic and general surgical patient populations. *Ann. Surg.* 250(2), 219–228 (2009).
- 20 Van Thiel D, Kalodiki E, Wahi R, Litinas E, Haque W, Rao G. Interpretation of benefit–risk of enoxaparin as comparator in the RECORD program: rivaroxaban oral tablets (10 mg) for use in prophylaxis in deep vein thrombosis and pulmonary embolism in patients undergoing hip and knee replacement surgery. *Clin. Appl. Thromb. Haemost.* 15 (4), 389–394 (2009).
- **Website**
- 101 Xarelto®. Summary of Product Characteristics. www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_May2009.pdf (Accessed 24 October 2010).