

The direct factor Xa inhibitor rivaroxaban

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Since the 1920s, when heparin was discovered by a medical student in liver cell extracts and warfarin was synthesised from the dicoumarol found in spoiled cattle feed, these two agents have remained the mainstays of anticoagulation treatment. The broad range of indications for these medications, including prophylaxis of thromboembolic disease in surgical patients, as well as in patients with atrial fibrillation, prosthetic heart valves or unstable coronary syndromes,¹ has made these drugs frequently prescribed among patients aged 65 years or older. Unfractionated heparin has now been superseded by its low-molecular-weight counterparts (such as enoxaparin) in many clinical applications, and, although they facilitate outpatient therapy, there are significant limitations and complications of both heparin and warfarin therapies.² Heparins require parenteral administration and their use is associated with haemorrhage. Similarly, the risks of bleeding, the delayed onset of action, the numerous interactions with food and other medications, and the complexity of individualised dosing make warfarin a dangerous and inconvenient medication for patients and their treating doctors.^{3,4}

A new era in anticoagulation treatment

The lack of efficacy of heparin and warfarin for certain indications (such as arterial thromboembolic disease), the bleeding risks, and the inconvenience of therapy have provided much impetus for research into alternative anticoagulants. In recent years, a number of novel anticoagulant agents have emerged. These new anticoagulants, developed in an era of greater fundamental knowledge of haemostasis, involve the use of small, specific molecules designed to directly inhibit clotting factors within the clotting pathway, such as thrombin or activated factor X (Xa).

One novel anticoagulant to emerge recently was ximelagatran, an orally active direct thrombin inhibitor. Clinical trials demonstrated that ximelagatran's effectiveness in preventing strokes in patients with atrial fibrillation was similar to warfarin, with suggestions that it offered a comparable safety profile, as well as easier dose administration and a decreased need for monitoring.⁵ However, ximelagatran was dramatically withdrawn from the market in February 2006 when it was shown that some 6% of patients demonstrated abnormal liver functions subsequent to therapy.⁶ Other drugs that also inhibit thrombin have emerged, such as dabigatran etexilate, and this drug is currently in advanced clinical trials and limited clinical use in some countries.⁷⁻⁹

The factor Xa inhibitors

Several new anticoagulants have been developed to target factor Xa in the clotting pathway. Factor Xa is perceived as an ideal target for anticoagulation, as it is at the focal intersection of the intrinsic and extrinsic pathways and is the rate-limiting step in thrombin generation. Although the indirect factor Xa inhibitor fondaparinux, a synthetic pentasaccharide, has made its way into clinical practice, the need to provide this drug parenterally is a significant disadvantage. However, a number of orally active drugs have emerged that are specific, direct factor Xa inhibitors, including rivaroxaban, apixaban and razaxaban. Of these, rivaroxaban is the

ABSTRACT

- Warfarin and heparin are the traditional mainstay anticoagulant therapies for treating thromboembolic disease.
- These drugs, with a documented history of utility, also have inherent difficulties in usage; in particular, the complicated monitoring and numerous drug–drug interactions of warfarin, and the need for parenteral administration of heparins.
- New agents have recently emerged that target specific elements of the clotting pathway. Rivaroxaban, which inhibits activated factor X (Xa), is currently in clinical trials and is the most advanced factor Xa inhibitor.
- The drug offers once-daily oral dosing, with no need for injections, dose titration, or frequent blood tests to monitor the international normalised ratio. It has a rapid onset of action and, although there is no specific antidote, it has a short plasma elimination half-life (about 5–9 hours).
- Evidence from recently published large-scale phase III clinical trials shows rivaroxaban to be superior to enoxaparin for prophylaxis of venous thromboembolism after major orthopaedic surgery.
- Studies have shown rivaroxaban to have a sound safety profile, with an incidence of bleeding similar to enoxaparin in phase III clinical trials.
- Few side effects and drug–drug interactions between rivaroxaban and common medications have been found thus far, although some interactions with potent cytochrome P450 3A4 inhibitors have been observed.
- It is hoped that rivaroxaban may be used as a first-line anticoagulant for prophylaxis of venous thromboembolic disease in postsurgical patients.

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furthest along in clinical development and has the strongest evidence to support its use as an anticoagulant.

Here, we outline the available evidence for rivaroxaban and its potential use in clinical practice. Levels of evidence (E1–E3) are graded according to the taxonomy of the National Health and Medical Research Council (NHMRC).¹⁰

Properties of rivaroxaban

Rivaroxaban is an oxazolidinone derivative that is a potent and selective direct inhibitor of factor Xa (see Box 1), binding the enzyme competitively and reversibly. Inhibition of factor Xa increases clotting times and decreases the formation of thrombin, the pivotal enzyme required for generation of fibrin, platelet activation and thrombus formation in venous thromboembolic disease and deep vein thrombosis (DVT).¹¹ Rivaroxaban has an oral bioavailability of about 80% and is well absorbed from the gastrointestinal tract, with food having no major effect on its absorption.¹² Plasma levels of rivaroxaban peak around 2.5–4 hours, and the drug has a terminal half-life of about 5–9 hours in

young people and 11–13 hours in older people.¹³ Rivaroxaban exhibits dual excretion, primarily by the kidneys (66%) but also by the biliary-faecal route (28%).^{12,13}

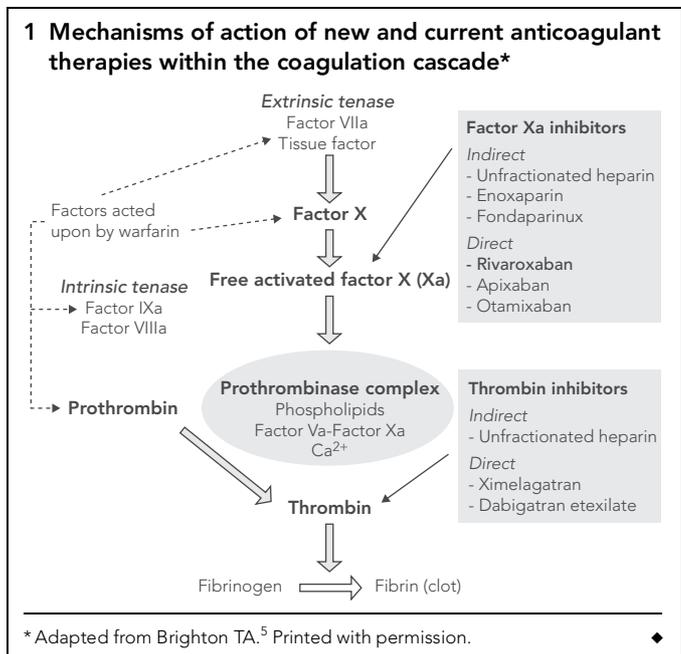
The espoused advantages of rivaroxaban, although similar to many novel anticoagulants in development, are numerous compared with warfarin and heparins (Box 2). Rivaroxaban has a rapid onset of action, high oral bioavailability (thus avoiding parenteral administration), and has predictable pharmacokinetic properties. Rivaroxaban can be administered without concurrent heparin, once daily in a fixed dose, without the need for individual monitoring and dose titration.^{3,11-13}

Clinical studies of rivaroxaban

While the complete therapeutic properties of rivaroxaban remain to be fully elucidated, current available evidence suggests it is a sound candidate to potentially replace enoxaparin and warfarin for certain indications. Rivaroxaban is currently undergoing multinational, multicentre, phase III clinical trials for a number of clinical indications, with recently published phase III studies in arthroplasty thromboprophylaxis demonstrating promising results.

Use of rivaroxaban as thromboprophylaxis after major orthopaedic surgery

The phase III RECORD (Regulation of Coagulation in Orthopaedic Surgery to Prevent DVT and Pulmonary Embolism [PE]) trials compared rivaroxaban with the standard treatment for venous thromboembolism (VTE), enoxaparin.¹⁴⁻¹⁶ The RECORD trials were randomised, double-blinded, double-dummy studies that evaluated the safety and efficacy of rivaroxaban in the prevention



2 Comparison of rivaroxaban with warfarin and enoxaparin

Property	Warfarin	Enoxaparin	Rivaroxaban
Mechanism of action	Reduced synthesis of functional prothrombin and other clotting factors	Indirect inhibition of activated factor X (Xa)	Direct inhibition of factor Xa
Administration	Oral	Parenteral	Oral
Onset of action	36–72 hours	3–5 hours	2.5–4 hours
Duration of action	48–96 hours	12 hours	24 hours
Elimination half-life	20–60 hours	4.5–7 hours	5.7–9.2 hours
Effective anticoagulant	Yes	Yes	Yes (superior to enoxaparin in phase III studies)
Risk of haemorrhage	Significant	Significant	Equivalent to enoxaparin in most studies
Stable, predictable pharmacokinetics	No	Yes	Yes
Interactions with diet and alcohol	Yes	Some exist (eg, alcohol abstinence recommended)	Low potential
Dosing	Individualised to each patient and target international normalised ratio (INR)	Fixed dose dependent on patient's weight	Fixed dose dependent on indication
Monitoring	INR every 2 weeks	Not monitored	No routine monitoring required; can be monitored by factor Xa inhibition in plasma
Dose adjustment	Frequent	Rarely required	Not required
Use in severe liver disease	Problematic	Metabolised by hepatic route	Not studied (primarily renally excreted)
Use in severe renal disease	Yes	Yes (dose adjusted)	No (primarily renally excreted)
Reversibility after cessation	Slow elimination and reversal of antithrombotic effect	Antithrombotic effect reversed after about 5 hours	Reversal of factor Xa inhibition dependent on plasma concentration and half-life (about 5–9 hours)
Antidote	Rapid reversal with plasma or factor replacement; slow reversal with vitamin K	Protamine sulphate (effectively reverses 60% of enoxaparin)	None available; possible removal by dialysis

of VTE in patients undergoing major orthopaedic surgery (hip or total knee arthroplasty) (Box 3). The primary efficacy endpoint in each trial was a composite of DVT (either symptomatic or detected by bilateral venography), non-fatal PE, or death from any cause at follow-up (range, 13–42 days). The primary safety endpoint was the incidence of major bleeding.

All three RECORD trials found a lower incidence of VTE in the rivaroxaban group compared with the enoxaparin group, and statistically significant reductions in absolute risk of VTE with rivaroxaban (Box 3).^{14–16} The RECORD 1 and 3 trials found that rivaroxaban reduced the relative risk of VTE compared with enoxaparin.^{14,16} The RECORD 2 trial aimed to compare extended thromboprophylaxis with rivaroxaban (oral dose of 10 mg rivaroxaban once daily for 31–39 days, with placebo injection for 10–14 days) against short-term thromboprophylaxis with enoxaparin (40 mg enoxaparin subcutaneously once daily for 10–14 days, with placebo tablet for 31–39 days) in patients who had undergone total hip arthroplasty. The results (Box 3) allowed investigators to conclude that extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of VTE, including symptomatic events, in patients undergoing total hip arthroplasty (E2).¹⁵

On the basis of the results of these phase III trials, the investigators concluded that rivaroxaban has clearly superior efficacy to enoxaparin in the prophylaxis of VTE after major orthopaedic surgery (E2). These trials also showed that both drugs have a similar safety profile with regard to major bleeding (E2).

Use of rivaroxaban in the treatment of deep vein thrombosis and pulmonary embolism

A pair of phase II trials, the ODIXa-DVT study and the EINSTEIN-DVT trial, investigated twice-daily and once-daily dosing of rivaroxaban, respectively, in the treatment of symptomatic proximal DVT.^{17–19} Each of these studies was a prospective, randomised, double-blinded, multicentre trial that compared the efficacy and safety of rivaroxaban against standard therapy for VTE — low-molecular-weight heparin and a vitamin K antagonist (VKA). Each study enrolled more than 500 patients.

The ODIXa-DVT study compared various doses of oral rivaroxaban (2.5, 5, 10, 20 and 30 mg, twice daily) with 40 mg subcutaneous enoxaparin followed by a VKA.^{17,18} The primary efficacy endpoint was the reduction in thrombotic burden, assessed at Day 21 by compression ultrasonography. The primary safety endpoint was the incidence of major bleeding. The results of the ODIXa-DVT trial showed that the primary efficacy endpoints for the tested doses of rivaroxaban ranged between 7% and 18%, compared with 17% for the combined enoxaparin–VKA group. In terms of the safety endpoint, it was shown that as the dose of rivaroxaban increased, so did the frequency of major bleeding complications ($P=0.045$). However, the study found that there was no statistically significant difference in the rate of bleeding complications between rivaroxaban (occurring in 2.9%–7.5% of patients) and enoxaparin–VKA (occurring in 8.8% of patients) (E2).¹⁷

The EINSTEIN-DVT trial, which was a partner phase II study and similar in design to the ODIXa-DVT trial, evaluated once-daily dosing of rivaroxaban against 40 mg enoxaparin and a VKA for treatment of VTE.¹⁹ The efficacy endpoint was the deterioration in thrombotic burden, which was assessed by an ultrasound and perfusion lung scan performed at 12 weeks and compared with the results obtained at baseline. The EINSTEIN-DVT trial demonstrated this efficacy outcome in 5.4%–6.6% of patients randomly assigned to receive rivaroxaban, compared with 9.9% of those given enoxaparin–VKA. This trial again demonstrated that rivaroxaban has highly comparable efficacy to the current standard treatment for

oxaban, respectively, in the treatment of symptomatic proximal DVT.^{17–19} Each of these studies was a prospective, randomised, double-blinded, multicentre trial that compared the efficacy and safety of rivaroxaban against standard therapy for VTE — low-molecular-weight heparin and a vitamin K antagonist (VKA). Each study enrolled more than 500 patients.

3 Summary of phase III studies of rivaroxaban for prophylaxis against venous thrombosis after major orthopaedic surgery

Study	RECORD 1 ¹⁴	RECORD 2 ¹⁵	RECORD 3 ¹⁶
Design	Double-blind RCT	Double-blind RCT	Double-blind RCT
Type of surgery	Hip arthroplasty	Hip arthroplasty	Total knee arthroplasty
Study intervention	Rivaroxaban group: rivaroxaban 10 mg 6–8 h after surgery then once daily Control group: enoxaparin 40 mg 12 h before surgery then once daily		
Treatment duration	36 days	30–42 days	13–17 days
Total no. of patients in trial	4541	2509	2541
No. of patients in group, rivaroxaban (control)	1595 (1558) [§]	1252 (1257) [§]	824 (878) [§]
Primary efficacy outcome,* rivaroxaban (control)	1.1% (3.7%) [¶]	2.0% (9.3%) [¶]	9.6% (18.9%) [¶]
Major VTE,† rivaroxaban (control)	0.2% (2.0%) [¶]	0.6% (5.1%) [¶]	1.0 (2.6%) [¶]
Incidence of DVT, rivaroxaban (control)	0.8% (3.4%) [¶]	1.6% (8.2%) [¶]	9.6% (18.2%) [¶]
Incidence of PE, rivaroxaban (control)	0.3% (0.1%) [§]	0.1% (0.5%) [§]	0.0% (0.3%) [§]
Death during on-treatment period, rivaroxaban (control)	0.3% (0.3%) [§]	0.2% (0.5%) [§]	0.0% (0.2%) [§]
Major bleeding,‡ rivaroxaban (control)	0.3% (0.1%) [§]	<0.1% (<0.1%) [§]	0.6% (0.5%) [§]
Absolute VTE risk reduction, rivaroxaban (95% CI)	2.6% (1.5%–3.7%) [¶]	7.3% (5.2%–9.4%) [¶]	9.2% (5.9%–12.4%) [¶]
Relative VTE risk reduction, rivaroxaban v enoxaparin	88% [¶]	—	49% [¶]

RECORD = Regulation of Coagulation in Orthopaedic Surgery to Prevent DVT and PE. RCT = randomised controlled trial. VTE = venous thromboembolism. DVT = deep vein thrombosis. PE = pulmonary embolism. * Primary efficacy outcome is a composite of DVT (symptomatic or detected by bilateral venography), PE or any-cause mortality for the given follow-up period. † Major VTE is proximal DVT, non-fatal PE or death from VTE. ‡ Major bleeding is fatal bleeding, bleeding in a critical organ (retroperitoneal, intracranial, intraocular or intraspinal bleeding), bleeding that required reoperation, or bleeding that caused a fall in haemoglobin of at least 2 g/dL (excluding surgical site bleeding). § No significant difference between rivaroxaban and control groups at $P < 0.001$. ¶ Significant difference between rivaroxaban and control groups at $P < 0.001$.

VTE. However, investigators also made the important observation that there appeared to be a decreased incidence of bleeding associated with once-daily dosing, and the optimal dose for safety and efficacy was between 15 mg and 20 mg administered once daily (E2).^{17,19} As a result of this performance in phase II trials, a 20 mg once-daily dose of rivaroxaban is currently being evaluated in phase III trials for the treatment of patients with symptomatic DVT or PE.

Use of rivaroxaban for other clinical indications

Rivaroxaban is also undergoing phase III trials for a number of other indications. Currently, a 20 mg dose of rivaroxaban is being trialled against warfarin for the prevention of stroke in patients with non-valvular atrial fibrillation. Another phase III study (the ATLAS ACS-TIMI 46 trial) is investigating the use of rivaroxaban in acute coronary syndromes as an adjunct to aspirin in reducing the risk of further cardiovascular events. The results of these studies are anticipated within the next 6 to 18 months, and the outcomes are likely to be illuminating in demonstrating the potential utility of rivaroxaban in these clinical applications.

Safety profile and drug interactions of rivaroxaban

While the efficacy and safety of rivaroxaban have been demonstrated by phase III trials, there have also been numerous studies to assess potential interactions of rivaroxaban with foods and other drugs. Kubitz and colleagues performed four randomised studies, two of which assessed the interaction of rivaroxaban with food.²⁰ No significant food–drug interactions were found, nor were there any major disturbances to any of the pharmacological parameters studied (E3).²⁰

In another phase II study performed by the same researchers, the safety, tolerability and pharmacokinetics of the combination of rivaroxaban and the non-steroidal anti-inflammatory drug (NSAID) naproxen were investigated.²¹ Patients were allocated to receive naproxen alone, rivaroxaban alone or a combination of both drugs. The results demonstrated no interactions in the mechanisms between rivaroxaban and naproxen, and also showed that the addition of naproxen did not affect prothrombin time or platelet aggregation, although a significant increase in bleeding was observed in the combination group. However, this increase in bleeding was less than when naproxen was administered alone, and further studies are underway to confirm the safety of this drug combination.²¹

An important phase I trial was performed to determine if aspirin influenced the safety and efficacy of rivaroxaban.²² In all the subjects studied, this combination was tolerated, and aspirin did not affect either the factor Xa inhibition activity of rivaroxaban or prolongation of the prothrombin time. Additionally, it was determined that rivaroxaban did not interfere with the effects of aspirin on platelet aggregation, suggesting this combination should pose no appreciable clinical interaction (E3).²²

Clinical trials undertaken thus far to assess potential interactions of rivaroxaban with common drugs have found no significant interactions with aspirin, NSAIDs, antacids, histamine H₂-receptor antagonists or digoxin (E3).²⁰⁻²² However, recent evidence has shown that rivaroxaban demonstrates pharmacological interactions with potent inhibitors of cytochrome P450 3A4, including drugs such as ketoconazole, macrolides (such as clarithromycin) and protease inhibitors (such as the antiretroviral drug atazanavir).²³ Further studies are required to determine potential interactions between rivaroxaban and other drugs, but

4 Drug profile summary of rivaroxaban

Mechanism of action: Direct inhibition of activated factor X (Xa) decreases the formation of thrombin, an essential enzyme for fibrin formation, platelet activation and subsequent generation of venous thromboembolism and deep vein thromboses.

Dosage: Phase II and phase III clinical trials suggest that a dose of 10 mg is optimal for prophylaxis of thromboembolic disease.^{17,19} The treatment dose of 20 mg once daily is currently being evaluated in phase III treatment studies.

Administration: Once daily, orally.

Indications: It is anticipated that rivaroxaban will be marketed for indications similar to those approved for enoxaparin by the United States Food and Drug Administration, such as prophylaxis against thromboembolic disease in postsurgical patients.²⁴ Other potential indications for rivaroxaban (eg, in atrial fibrillation, acute coronary syndromes and treatment of established thromboembolic disease) are currently being investigated.

Adverse effects: Few side effects of rivaroxaban have been reported in clinical trials to date. The most common adverse effects observed include headache, with some patients reporting nausea and vomiting (E3¹⁰).²⁰ Small numbers of patients in clinical trials showed elevated liver functions, but this was not dissimilar to those treated with enoxaparin.^{20,22,23}

Contraindications and precautions: Clinical trials to date have excluded people with renal failure (as the drug is renally excreted). Prudent clinical practice would imply that precautions similar to those for warfarin should be applied to rivaroxaban: patients with active bleeding, intracerebral or gastrointestinal bleeding within the past 6 months, neurosurgery within the past 4 weeks, active peptic ulcer disease, a known bleeding disorder, prolonged prothrombin time/international normalised ratio, pregnancy, thrombocytopenia, impaired kidney function, or certain malignancies.^{14,15}

Interactions: Current available evidence shows no significant drug interactions between rivaroxaban and non-steroidal anti-inflammatory drugs, aspirin, antacids, histamine H₂-receptor antagonists, and digoxin.²⁰⁻²² Evidence shows that rivaroxaban has interactions with potent cytochrome P450 3A4 inhibitors, such as ketoconazole, macrolides, and protease inhibitors.²³ ◆

the results so far demonstrate that rivaroxaban appears to be largely clinically safe (E3).

Given that research to date has shown rivaroxaban to be a viable anticoagulant, the manufacturers have sought licensing approval in Europe. As licensing in Australia may soon follow, it is important that all clinicians treating patients with anticoagulants be aware of the potential advantages of rivaroxaban. A summary of rivaroxaban's medicinal profile is provided in Box 4.

Conclusion

The high level of evidence published in the clinical studies of rivaroxaban indicates that it is a promising alternative anticoagulant. Large, multicentre, multinational randomised controlled trials have shown that rivaroxaban is clearly superior to enoxaparin in the prevention of VTE after orthopaedic surgery (E2), and that there is no appreciable increase in the incidence of major or fatal bleeding (E2). The safety of rivaroxaban for mainstream clinical use has also been illustrated by its few interactions with other drugs (E3) and few side effects (E3) in studies so far.

5 Important messages for patients

- Rivaroxaban is a drug with anticoagulating effects similar to warfarin and enoxaparin.
- Unlike warfarin, rivaroxaban does not require frequent blood tests for monitoring.
- Unlike enoxaparin, rivaroxaban does not require administration via injection.
- Rivaroxaban has low potential for interaction with diet and other common medications.
- Rivaroxaban may interact with some drugs, such as the antifungal drug ketoconazole, macrolide antibiotics (eg, clarithromycin, erythromycin, roxithromycin), or antiretroviral drugs (eg, atazanavir).
- Rivaroxaban is not yet marketed in Australia. ◆

A salient observation is that a number of patient groups have been excluded from the clinical evaluation of rivaroxaban, including pregnant and lactating women, patients being treated for HIV, patients with renal impairment (calculated creatinine clearance < 30 mL/min), and patients with clinically significant liver disease. Further studies of the use of rivaroxaban in patients with varying degrees of renal and liver dysfunction are necessary.

The ease of dosing and administration and decreased need for monitoring of patients treated with rivaroxaban, combined with superior outcomes, make it an attractive anticoagulant for the future. Clinical trials are underway studying the use of rivaroxaban for various indications, such as the treatment of vein thromboses and the prevention of stroke in patients with atrial fibrillation and acute coronary syndromes, and it is hoped that rivaroxaban will reduce the burden of disease caused by these conditions. However, in the interim, rivaroxaban has been proven to be a highly effective and exciting new oral anticoagulant drug. With the concurrent development of other orally active direct factor Xa inhibitors, such as apixaban, rivaroxaban will potentially benefit many patients at risk of venous thromboembolic disease. Important messages for patients are shown in Box 5.

Competing interests

Timothy Brighton has received an honorarium from Bayer for an advisory role on Steering Committees for the EINSTEIN phase II and III clinical studies.

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