

Rivaroxaban: An oral direct inhibitor of factor Xa

MICHAEL P. GULSETH, JESSICA MICHAUD, AND EDITH A. NUTESCU

Anticoagulant agents are mainstays in the prevention and treatment of arterial and venous thrombosis. Several anticoagulants are available for the treatment and prevention of thrombosis, but the only oral agents available have been vitamin K antagonists (VKAs) such as warfarin. Although these traditional agents are effective, their use is complex from both the provider's and the patient's perspective.

Activated factor X (FXa) plays a critical role in the coagulation cascade by linking the intrinsic and extrinsic coagulation pathways and acting as the rate-limiting step in thrombin production. Inhibiting thrombin generation by blocking FXa with selective, direct and indirect FXa inhibitors has been validated as an effective antithrombotic approach. Indirect FXa inhibitors (e.g., fondaparinux, idraparinux) exert their effect via a cofactor (antithrombin), whereas direct inhibitors (e.g., rivaroxaban) block FXa directly.¹

The role of the FXa inhibitors as anticoagulants and as effective agents for the prevention and treat-

Purpose. The mechanism of action, pharmacodynamics, pharmacokinetics, efficacy in clinical trials, interactions, adverse effects and toxicity, and place in therapy of rivaroxaban are reviewed.

Summary. Rivaroxaban, the first oral, direct factor Xa (FXa) inhibitor to reach Phase III trials, inhibits thrombin generation by both the intrinsic and the tissue factor pathways. It has shown predictable, reversible inhibition of FXa activity, and it may have the ability to inhibit clot-bound FXa. Rivaroxaban is being evaluated for prevention of venous thrombosis in patients undergoing hip or knee arthroplasty, treatment of venous thrombosis, long-term use for secondary prevention of venous thrombosis, and prevention of stroke in atrial fibrillation. To date, only short-term trials have been reported, but rivaroxaban's safety and efficacy appear to be at least equivalent to those of traditional anticoagulants. The results of four studies of primary preven-

tion of venous thrombosis in patients undergoing orthopedic surgery suggest that rivaroxaban 10 mg daily is a promising alternative to low-molecular-weight heparins. Rivaroxaban appears to have a low potential for drug-drug or drug-food interactions. It offers the advantages of a fixed oral dose, rapid onset of action, and predictable and consistent anticoagulation effect, precluding the need for routine monitoring of anticoagulation.

Conclusion. Rivaroxaban is a promising alternative to traditional anticoagulants for the prevention and treatment of venous thromboembolism and for stroke prevention in atrial fibrillation; it offers once-daily oral administration without the need for routine monitoring.

Index terms: Mechanism of action; Pharmacokinetics; Rivaroxaban; Thrombolytic agents; Toxicity; Venous thrombosis
Am J Health-Syst Pharm. 2008; 65:1520-9

ment of venous and arterial thrombosis is supported by ample clinical evidence. Fondaparinux is at least as efficacious as low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) in the prevention of venous thromboembolism

(VTE) after orthopedic surgery, prevention of VTE after abdominal surgery, treatment of VTE, and treatment of patients with acute coronary syndromes.²⁻⁷ However, like UFH and LMWHs, fondaparinux cannot act directly against clot-bound FXa. This

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DOI 10.2146/ajhp070624

limitation has prompted research to develop direct FXa inhibitors, especially agents that have good oral bioavailability. Since these agents can be given in fixed doses and without routine anticoagulation monitoring, they have the potential to decrease demands on practitioners' time and hospital resources and to offer a less complex therapeutic regimen for patients. They could fulfill the need for anticoagulants that can be easily administered in both the inpatient and the outpatient setting.

This article describes the development of and preclinical and clinical data on the oral, direct FXa inhibitor nearest to marketing, rivaroxaban.

Pharmacology

Rivaroxaban (BAY 59-7939) is an oral direct,⁸ reversible,^{8,9} competitive,⁸ rapid,⁹ and dose-dependent^{8,10-15} inhibitor of FXa (Figure 1). FXa catalyzes the reaction that converts

factor II (prothrombin) to factor IIa (thrombin).⁸ Because FXa acts at the convergence of the contact activation (intrinsic) and tissue factor (extrinsic) pathways,⁸ inhibition of FXa activity by rivaroxaban inhibits thrombin generation via both pathways.^{11,16-19} Rivaroxaban inhibits FXa with more than 100,000-fold greater selectivity than other biologically relevant serine proteases, such as thrombin, trypsin, plasmin, factor VIIa, factor IXa, urokinase, and activated protein C.⁸

FXa catalyzes prothrombin activation via the prothrombinase complex, which consists of FXa, factor II, factor Va, calcium ions, and phospholipid assembled on the surface of activated platelets.⁸ In vitro, in addition to inhibiting free FXa, rivaroxaban inhibits FXa bound to the prothrombinase complex, raising the possibility that it could inhibit clot-bound FXa.^{8,20} This would be an advantage over UFH,

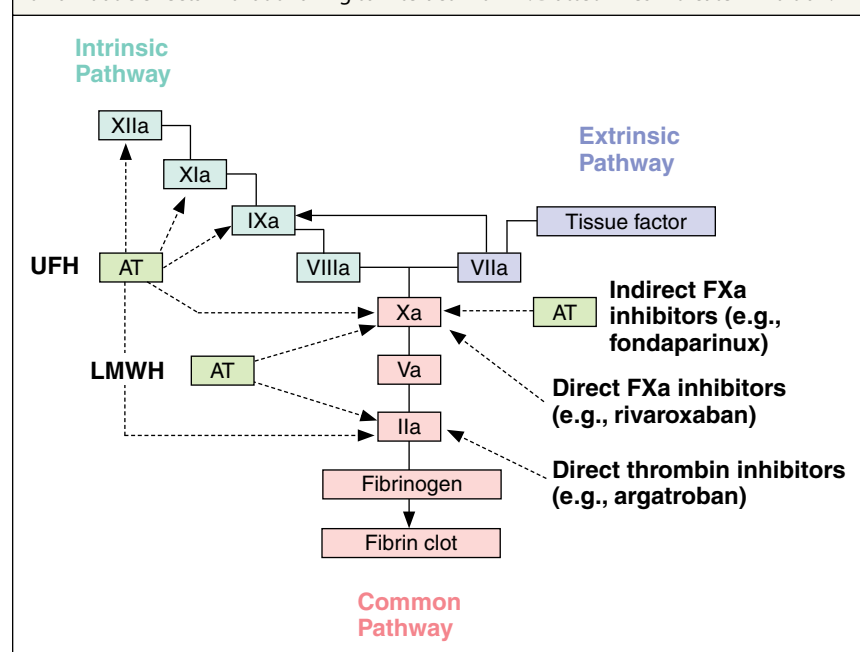
LMWHs, and fondaparinux, which when combined with antithrombin to exert their effect are too large to inhibit FXa in the prothrombinase complex.¹⁴

Effect on FXa activity. In Phase I and II studies, the pharmacodynamic properties of rivaroxaban were assessed by measuring inhibition of FXa activity and prolongation of the prothrombin time (PT) or activated partial thromboplastin time (aPTT). Inhibition of FXa activity correlated well with plasma concentration.^{11,14,15} At maximum inhibition, about 3 hours after administration, FXa activity was inhibited by approximately 20% with rivaroxaban 5 mg and up to 60–75% with rivaroxaban 60–80 mg. The inhibitory effect was maintained for about 8–12 hours.¹⁵ FXa activity did not completely return to baseline within 24 hours for rivaroxaban doses greater than 5 mg, making once-daily dosing of rivaroxaban a possibility.^{14,21} The efficacy of once-daily dosing will be more clear when in-progress trials evaluating once- and twice-daily dosing are published.

Effect on clotting assays. Since oral FXa inhibitors exert their effect at the junction of the two coagulation pathways, they would be expected to affect PT and aPTT.⁸ In fact, rivaroxaban prolongs both PT^{8,10,13-15,17,18} and aPTT^{10,13-15,17,18} in a dose-dependent manner, although PT may be more sensitive to rivaroxaban.⁸ PT prolongation due to rivaroxaban correlates well with the drug's plasma concentration^{14,15,22} and its inhibition of FXa activity.¹⁴ Rivaroxaban also prolongs dilute Russell viper venom time (dRVVT)^{17,18,23} in a dose-dependent manner,²³ and since prolongation of dRVVT suggests the presence of a lupus anticoagulant antibody, rivaroxaban may theoretically cause a false-positive diagnosis of antiphospholipid antibody syndrome.

Rivaroxaban was not monitored with any clotting assay, including antifactor Xa, aPTT, PT, or Interna-

Figure 1. Mechanisms of action of antithrombotic agents, other than warfarin, in the clotting cascade. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and indirect factor Xa (FXa) inhibitors bind with antithrombin (AT) and increase its inhibition of certain clotting factors. The UFH–AT complex inhibits factors XIIa, XIa, IXa, Xa, and IIa, whereas the LMWH–AT complex inhibits factors Xa and IIa. Indirect FXa inhibitors in complex with AT inhibit FXa only. Direct inhibitors of FXa and thrombin (factor IIa) exert antithrombotic effects without having to interact with AT. Dotted lines indicate inhibition.



tional Normalized Ratio (INR), in published clinical trials.²⁴⁻²⁷ Whether certain patients would require laboratory monitoring during rivaroxaban therapy is not clear. Table 1 summarizes the pharmacodynamic properties of rivaroxaban.

Pharmacokinetics

Absorption and distribution.

Rivaroxaban is a nonbasic⁸ compound that is absorbed rapidly^{14,32} with 60–80% bioavailability^{15,18} after oral administration. Its pharmacokinetics is dose dependent,^{14,15,31} with peak plasma concentrations (C_{\max}) occurring 2.5–4 hours after an oral tablet dose (Table 2).^{12,15,28} Rivaroxaban is bound extensively ($\approx 90\%$) to plasma proteins.³¹

Compared with fasting patients, patients who were fed had higher but delayed maximum concentrations ($C_{\max} = 158 \mu\text{g/L}$ [fed] and time to maximum concentration [t_{\max}] = 4 hours [fed] versus $C_{\max} = 113 \mu\text{g/L}$ [fasting] and $t_{\max} = 2.75$ hours [fasting]) and a higher area under the concentration–time curve (AUC) ($1107 \mu\text{g} \times \text{hours/L}$ [fed] versus $808 \mu\text{g} \times \text{hours/L}$ [fasting]).³⁰ These differences in pharmacokinetics translated to slightly reduced pharmacodynamic values in the fasting state, with the maximum PT prolongation being smaller and delayed by 1.5 hours, and the maximum inhibition of FXa activity slightly lower as well. These studies have led rivaroxaban to be administered with food or within 2 hours of eating in all published clinical trials.²⁴⁻²⁷ Increases in gastric pH caused by ranitidine or an aluminum hydroxide and magnesium hydroxide antacid had no effect on the pharmacokinetic or pharmacodynamic properties of rivaroxaban.³⁰

Elimination. About 30% of rivaroxaban is excreted unchanged in the urine^{1,14,34}; other routes of elimination include fecal elimination¹⁵ and hepatic metabolism primarily via cytochrome P-450 (CYP) isozyme 3A4.^{35,36} Patients with renal or he-

Table 1.

Pharmacodynamics of Rivaroxaban

Variable ^a	Value
Maximum FXa activity inhibitory effect (E_{\max}) for multiple doses of 5 mg twice daily to 30 mg twice daily	20–70% depending on dose ^{12,15,28}
Time to E_{\max}	1–4 hr ^{12,15,29,30}
Half-life of FXa activity inhibition	6–7 hr ¹⁴
Maximum PT prolongation for multiple doses of 5–30 mg twice daily	1.3–2.6 times baseline depending on dose ^{12,15,28}
Time to maximum PT prolongation	1–4 hr ^{15,29,30}
Maximum aPTT prolongation for multiple doses of 5–30 mg twice daily	1.3–1.8 times baseline depending on dose ^{12,15,28}
Time to maximum aPTT prolongation	1–4 hr ^{15,29,31}

^aFXa = activated factor X, PT = prothrombin time, aPTT = activated partial thromboplastin time.

Table 2.

Steady-State Pharmacokinetics of Rivaroxaban in Multiple-Dose Pharmacokinetic Studies^{15,33}

Variable ^a	5 mg b.i.d.	10 mg b.i.d.	20 mg b.i.d.	30 mg b.i.d.
C_{\max} ($\mu\text{g/L}$)	39.7–85.3	65.2–158	141–318.1	451.9
t_{\max} (hr) ^b	3.00	2.98	2.50	3.02
AUC ($\mu\text{g} \times \text{hr/L}$)	458.5–531	863.8–915	1903.0–1982	2782.0
$t_{1/2}$ (hr)	7.0	7.6	NA	NA

^a C_{\max} = maximum plasma concentration, t_{\max} = time to maximum plasma concentration, AUC = area under the concentration–time curve, $t_{1/2}$ = elimination half-life, NA = data not available.

^bDose administered with a meal.

patic impairment may be at risk for supratherapeutic levels, as discussed below.

The elimination half-life of rivaroxaban was approximately seven hours for usual doses in multiple-dose pharmacokinetic studies; it ranged from four to nine hours depending on the dose and number of doses received before pharmacokinetic data were collected.^{12,15,28} No significant accumulation was noted when multiple doses were administered.

Effect of age. When rivaroxaban was evaluated in subjects >75 years of age compared with subjects 18–45 years, the AUC was significantly higher in the elderly population.^{37,38} Not surprisingly, total and renal clearance were found to be inversely correlated with age and creatinine clearance (CL_{cr}).^{22,33,37,38} These find-

ings are reflected in the increased AUCs of PT prolongation and of FXa-activity inhibition in older patients. Time to maximum FXa-activity inhibition, time to maximum PT prolongation, and C_{\max} are unaffected by age.^{37,38} Whether the dose ought to be adjusted for the elderly population is not clear.

Effect of renal insufficiency. As previously stated, the clearance of rivaroxaban has been correlated with CL_{cr} . In a study of subjects with renal insufficiency, AUC was 44%, 52%, and 64% higher in mild (CL_{cr} , 50–79 mL/min), moderate (CL_{cr} , 30–49 mL/min), and severe (CL_{cr} , <30 mL/min) renal insufficiency, respectively, compared with the control ($p < 0.05$).³⁴ Importantly, the AUC of FXa activity inhibition increased by 50%, 86%, and 100%, respectively ($p < 0.01$), and the AUC of PT prolongation

increased by 33%, 116%, and 144%, respectively ($p < 0.001$). There are no recommendations at this time for adjusting dosages of rivaroxaban in patients with renal insufficiency; however, patients with an estimated CL_{cr} of <30 mL/min have been excluded from published clinical trials,²⁴⁻²⁷ and a dosage adjustment is being used for moderate renal insufficiency (CL_{cr} , 30–49 mL/min) in atrial fibrillation trials.^{39,40} These data suggest that it may be possible to use PT and FXa activity to monitor rivaroxaban, but target ranges have not been established.

Effect of hepatic insufficiency. In subjects with mild hepatic disease (Child-Pugh class A), no clinically relevant differences in the pharmacokinetics and pharmacodynamics of rivaroxaban were found.³⁵ However, in patients with moderate disease (Child-Pugh class B), there was a moderate decrease in total body clearance of the drug, which resulted in a statistically significant increase in AUC with a subsequent moderate increase in FXa activity inhibition and PT prolongation. Patients with severe liver disease have been excluded from published rivaroxaban clinical trials.²⁴⁻²⁷

Effect of obesity. Rivaroxaban has been compared among different weight groups (≤ 50 , 70–80, and >120 kg).^{31,41} In the higher weight groups, PT was slightly less prolonged or had a lower AUC, and the maximum inhibition of FXa activity was slightly lower. In the lower weight group, C_{max} was slightly higher, half-life was two hours longer, and aPTT was slightly more prolonged. Significant dosage adjustment is not likely to be needed in underweight or overweight patients.

Effect of gender and race. No differences were found between the sexes with regard to any pharmacokinetic or pharmacodynamic property.^{37,38,41} All pharmacokinetic studies so far either have specified Caucasians as the population included^{14,15,31} or have

not reported on the racial makeup of the population.^{28,32,34,35,37,38,41-44}

Phase II trials for VTE prophylaxis

Two studies, ODIxa-HIP²⁵ ($n = 548$) and ODIxa-OD-HIP²⁶ ($n = 618$), have evaluated rivaroxaban use to prevent VTE after total hip arthroplasty (THA). Both trials were randomized, double-blind, double-dummy, multicenter studies comparing rivaroxaban with preoperatively started enoxaparin 40 mg given subcutaneously (s.c.) every 24 hours. Rivaroxaban was started 6–8 hours after surgery in both trials. All patients underwent mandatory bilateral venography after five to nine days of therapy. The key difference in the trials was that ODIxa-HIP used rivaroxaban in a twice-daily regimen (2.5, 5, 10, 20, and 30 mg) and ODIxa-OD-HIP used a once-daily regimen (5, 10, 20, 30, and 40 mg). In ODIxa-HIP, rates of the composite endpoint of asymptomatic and symptomatic VTE plus all-cause mortality were 7–18%, compared with 17% for enoxaparin. In ODIxa-OD-HIP, rates of the same composite endpoint were 6.4–14.9%, compared with 25.2% for enoxaparin. In ODIxa-HIP, major bleeding occurred in 0.8–5.4% of rivaroxaban patients, compared with 1.5% for enoxaparin. In ODIxa-OD-HIP, major bleeding occurred in 0.7–5.1% of rivaroxaban patients, compared with 1.9% for enoxaparin. Both trials showed no significant dose response for efficacy but did find a significant dose–response relationship for bleeding.

ODIxa-KNEE ($n = 366$) evaluated rivaroxaban use to prevent VTE after total knee arthroplasty (TKA).²⁷ It was a randomized, double-blind, double-dummy, multicenter study comparing rivaroxaban (2.5, 5, 10, 20, and 30 mg) every 12 hours, started 6–8 hours after surgery, with enoxaparin 30 mg s.c. every 12 hours started 12–24 hours after surgery. All patients underwent mandatory

bilateral venography after five to nine days of therapy. The rates of the composite endpoint of asymptomatic and symptomatic VTE plus all-cause mortality were 23.3–40.4%, compared with 44.3% for enoxaparin. Major bleeding occurred in 0–7.5% of rivaroxaban patients, compared with 1.9% for enoxaparin. As in the previous studies, no significant dose response was demonstrated for efficacy but a significant dose response for bleeding was present.

Phase II trials for VTE treatment

Two studies, ODIxa-DVT²⁴ ($n = 528$) and EINSTEIN-DVT⁴⁵ ($n = 449$), have evaluated rivaroxaban use to treat deep venous thrombosis (DVT). Both trials were randomized, partially blind, multicenter studies comparing rivaroxaban with a heparin therapy (LMWH or UFH) combined with VKA therapy. Both trials lasted for 12 weeks. ODIxa-DVT used rivaroxaban at doses of 10, 20, or 30 mg orally twice daily and 40 mg orally once daily, and the primary efficacy endpoint was improvement in thrombotic burden without recurrent VTE or VTE-related death at day 21. Rivaroxaban efficacy rates were 43.8–59.2%, compared with 45.9% for enoxaparin and a VKA. Major bleeding rates during the 12 weeks of therapy were 1.7–3.3% for rivaroxaban, compared with no major bleeding in the enoxaparin–VKA arm. EINSTEIN-DVT used rivaroxaban at doses of 20, 30, or 40 mg orally once daily, and the primary efficacy endpoint was the composite of symptomatic, recurrent VTE and deterioration of thrombotic burden at week 12. Rivaroxaban efficacy rates were 5.4–6.6%, compared with 9.9% for LMWH or UFH and a VKA. Major bleeding rates during the 12 weeks of therapy were 0–1.5% for rivaroxaban, compared with 1.5% in the group treated with LMWH or UFH and a VKA.

A reanalysis of the ODIxa-DVT and EINSTEIN-DVT studies was

conducted ($n = 1156$).⁴⁶ For ODIXa-DVT, rivaroxaban rates of symptomatic DVT or pulmonary embolism (PE) and deterioration of thrombotic burden at week 12 were 1.1–3%, compared with 1% for enoxaparin-VKA. Rates of the same endpoint at week 12 in the EINSTEIN DVT rivaroxaban groups were as stated above for the original study. Both twice- and once-daily dosing of rivaroxaban were as effective and safe as standard therapy at three months, but thrombus regression at 3 weeks was greater with rivaroxaban twice daily than with once-daily dosing. When both studies were analyzed for bleeding rates over 12 weeks, daily dosing seemed to convey a slight advantage (note data presented above). Because of the data on regression of thrombotic burden at 21 days and bleeding over 12 weeks, Phase III trials are focusing on initial twice-daily dosing for 21 days followed by long-term daily dosing of rivaroxaban.

Phase III trials

An extensive Phase III clinical trials program is under way for rivaroxaban. The agent is being evaluated for indications that include prevention of venous thrombosis in patients undergoing major orthopedic

surgery (hip or knee replacement), treatment of venous thrombosis (DVT and PE), secondary prevention of venous thrombosis for an extended duration, and prevention of stroke in atrial fibrillation. Three completed studies of primary prevention of venous thrombosis in patients undergoing orthopedic surgery are discussed below. Table 3 summarizes critical differences in study design among the Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of Deep Vein Thrombosis and Pulmonary Embolism (RECORD) trials. Phase III trials in progress for other indications are summarized in Table 4.

RECORD1 was a trial evaluating the efficacy of rivaroxaban versus enoxaparin for VTE prophylaxis in THA.⁴⁷ This trial randomized, in a double-blind fashion, 4541 patients undergoing THA to rivaroxaban 10 mg p.o. daily starting six to eight hours after surgery or enoxaparin 40 mg s.c. starting the evening before surgery and restarting six to eight hours after surgery and then daily thereafter. Both treatment arms were continued for 31–39 days; all patients underwent mandatory bilateral venography the next day. The primary treatment outcome was

total frequency of VTE plus all-cause mortality, and the primary safety outcome was major bleeding.

In the primary efficacy analysis ($n = 1595$ for rivaroxaban and $n = 1558$ for enoxaparin), the frequency of VTE or mortality was 1.1% for rivaroxaban and 3.7% for enoxaparin ($p < 0.001$). The frequency of the secondary outcome—major VTE (proximal DVT, PE, or VTE-related death)—was 0.2% in rivaroxaban patients and 2% in enoxaparin patients ($p < 0.001$). Major bleeding rates were 0.3% for rivaroxaban and 0.1% for enoxaparin ($p = 0.178$). Nonmajor bleeding rates were also comparable.

The investigators concluded that rivaroxaban was significantly more effective than enoxaparin for extended (roughly 35 days) VTE prophylaxis following THA, with similar bleeding rates in this trial. It is unclear whether rivaroxaban would maintain its superiority if enoxaparin were given at a dosage of 30 mg s.c. every 12 hours.

RECORD2 was also a trial evaluating the efficacy of rivaroxaban versus enoxaparin for VTE prophylaxis in THA.⁴⁸ This trial randomized, in a double-blind fashion, 2509 patients undergoing THA to rivaroxaban 10

Table 3.
Comparison of RECORD^a Phase III Trials

Variable	Hip Surgery Trials		Knee Surgery Trials	
	RECORD1 ⁴⁷	RECORD2 ⁴⁸	RECORD3 ⁴⁹	RECORD4 ⁵³
Daily rivaroxaban dose (mg)	10	10	10	10
Enoxaparin dosage (mg)	40 daily	40 daily	40 daily	30 twice daily
Duration (days)	31–39	Rivaroxaban: 31–39 Enoxaparin: 10–14	10–14	10–14
Efficacy summary	Rivaroxaban superior to enoxaparin	Extended-duration rivaroxaban superior to short-term enoxaparin	Rivaroxaban superior to enoxaparin	Rivaroxaban similar to enoxaparin
Bleeding rate	Rivaroxaban similar to enoxaparin	Rivaroxaban similar to enoxaparin	Rivaroxaban similar to enoxaparin	Rivaroxaban similar to enoxaparin

^aRegulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of Deep Vein Thrombosis and Pulmonary Embolism.

mg p.o. daily starting six to eight hours after surgery and continuing for 31–39 days or enoxaparin 40 mg s.c. starting the evening before surgery and then daily for only 10–14 days. All patients underwent mandatory bilateral venography when the extended treatment group (rivaroxaban patients) was finished (around days 31–39 in all patients). The primary treatment outcome was total frequency of VTE plus all-cause mortality, and the primary safety outcome was major bleeding.

In the primary efficacy analysis ($n = 869$ for rivaroxaban and $n = 864$ for enoxaparin), the frequency of VTE or mortality was 2% for rivaroxaban and 9.3% for enoxaparin ($p < 0.001$). The frequency of the secondary outcome—major VTE (combination of proximal DVT, PE, or VTE-related death)—was 0.6% in rivaroxaban patients and 5.1% in enoxaparin patients ($p < 0.001$). Major bleeding rates were 0.1% for rivaroxaban and 0.1% for enoxaparin. Rates of any bleeding were also comparable.

The investigators concluded that extended-duration rivaroxaban was significantly more effective than short-term enoxaparin for VTE prophylaxis following THA. Considering that the two treatments were of unequal length, it is not surprising that rivaroxaban outperformed

enoxaparin; the benefits of extended VTE prophylaxis after THA are well documented.^{2,51} This study helped confirm previous findings, but it did not necessarily show head-to-head superiority to enoxaparin, as was seen in the RECORD1 trial.

RECORD3 was a trial evaluating the efficacy of rivaroxaban versus enoxaparin for VTE prophylaxis in TKA.^{49,52} This trial randomized, in a double-blind fashion, 2531 patients undergoing TKA to rivaroxaban 10 mg p.o. daily starting 6–8 hours after surgery or enoxaparin 40 mg s.c. once daily starting 12 hours before surgery. Both treatment arms were continued for 10–14 days, after which patients were required to undergo venography. The primary treatment outcome was total frequency of VTE plus all-cause mortality, and the primary safety outcome was major bleeding.

In this trial, 1254 patients were randomized to rivaroxaban and 1277 to enoxaparin. In the primary efficacy analysis ($n = 824$ for rivaroxaban and $n = 878$ for enoxaparin), the frequency of VTE or mortality was 9.6% for rivaroxaban and 18.9% for enoxaparin ($p < 0.001$). The frequency of the secondary outcome—major VTE (combination of proximal DVT, PE, or VTE-related death)—was 1% in rivaroxaban patients and 2.6%

in enoxaparin patients ($p = 0.01$). Symptomatic VTE occurred in 0.7% of rivaroxaban patients and 2% of enoxaparin patients ($p = 0.005$). Major bleeding rates were 0.6% for rivaroxaban and 0.5% for enoxaparin. Nonmajor bleeding rates were also comparable.

The investigators concluded that rivaroxaban was significantly more effective than enoxaparin for VTE prophylaxis following TKA, with similar bleeding rates. It is unclear whether rivaroxaban would maintain its superiority in this trial if enoxaparin were dosed in the North American fashion of 30 mg s.c. every 12 hours, although early non-peer-reviewed results from RECORD4 appear promising.⁵³

Drug interactions

Few studies are available for evaluating drug interactions with rivaroxaban. One trial showed that rivaroxaban does not significantly interact with digoxin.⁵⁴ In vitro studies suggest a moderate potential for rivaroxaban to interact with strong CYP3A4 inhibitors, but rivaroxaban did not inhibit or induce any major CYP450 enzyme.⁵⁵

The combination of enoxaparin and rivaroxaban prolonged PT by 38% and aPTT by 18% compared with enoxaparin alone, and the com-

Table 4.
Phase III Studies of Rivaroxaban for Indications Other Than Orthopedic Surgery^a

Medication	Study Name	ClinicalTrials.gov Identifier	Indication ^b	Comparator
Rivaroxaban	NA ^c	NCT00494871	Stroke prevention due to atrial fibrillation	Warfarin
Rivaroxaban	ROCKET AF	NCT00403767	Stroke prevention due to atrial fibrillation	Warfarin
Rivaroxaban	EINSTEIN-DVT	NCT00440193	Treatment of acute DVT	Enoxaparin and VKA ^d
Rivaroxaban	EINSTEIN-PE	NCT00439777	Treatment of acute PE	Enoxaparin and VKA
Rivaroxaban	EINSTEIN-Extension	NCT00439725	Extended treatment of VTE to prevent recurrence	Placebo

^aAs listed at www.clinicaltrials.gov.

^bDVT = deep venous thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.

^cNA = not available.

^dVKA = vitamin K antagonist.

bination similarly increased anti-FXa levels compared with enoxaparin or rivaroxaban alone.⁴⁴ No pharmacokinetic interaction was noted. The authors concluded that the interaction was not clinically significant and that enoxaparin and rivaroxaban may be used together or sequentially.

Rivaroxaban was not shown to influence the antiplatelet effect of aspirin, clopidogrel, or abciximab in primates.⁵⁶ In humans, the addition of aspirin to rivaroxaban did not change collagen-activated platelet aggregation; it did increase bleeding time, although the difference was considered small compared with aspirin alone.^{29,43,57} The combination did result in earlier pharmacodynamic effects and slightly greater clotting test duration.²⁹ Aspirin did not affect the pharmacokinetics of rivaroxaban.^{29,43,57} Even though the addition of aspirin to rivaroxaban had only minor effects on rivaroxaban's pharmacodynamics and did not affect rivaroxaban's pharmacokinetics, there is still a possibility of increased bleeding events with the combination.

FXa activity inhibition, PT prolongation, aPTT prolongation, and platelet aggregation were not influenced by naproxen combined with rivaroxaban.^{30,42,57} Compared with rivaroxaban alone, which has not been shown to prolong bleeding time,^{10,12,13,28,29,57} the addition of naproxen prolonged bleeding time.^{30,42,57} Naproxen was reported to not influence the pharmacokinetics of rivaroxaban,⁵⁷ but other studies have reported that the combination caused a slight increase ($\approx 10\%$) in rivaroxaban's AUC and C_{\max} .^{30,42} As with aspirin, although the pharmacokinetics and pharmacodynamics are not significantly changed with the combination of naproxen and aspirin, larger studies are needed to determine whether naproxen's inhibitory effects on platelet aggregation increase the risk of bleeding in patients taking rivaroxaban.

Adverse effects

Bleeding. As would be expected, the major safety issue involving an oral FXa inhibitor, like any other anticoagulant, is bleeding. The bleeding rates for rivaroxaban were discussed above. So far, bleeding has been comparable to other active comparators and seems to be dependent on the dose. Access to data on other common adverse effects, such as headache and nausea, is limited, since rivaroxaban is not yet approved for marketing. However, ximelagatran, an oral direct thrombin inhibitor, did not achieve FDA marketing approval largely because of liver toxicity issues, despite its promising efficacy.⁵⁸ This has led to intense interest in closely examining the potential liver toxicity of other emerging oral anticoagulants.

Hepatotoxicity. Information on potential liver toxicity due to rivaroxaban is limited at this time. In ODIXa-DVT ($n = 604$ in the safety analysis), alanine transaminase (ALT) elevations to greater than three times normal occurred in 1.9–4.3% of patients in the rivaroxaban groups compared with 21.6% in the enoxaparin–warfarin group.²⁴ Half of the rivaroxaban ALT elevations occurred in the first 21 days; after the first 21 days, the rate of ALT elevation to greater than three times normal was 1.9% for rivaroxaban and 0.9% for enoxaparin–warfarin. The overall mean time of ALT elevations to greater than three times normal was 10.5 days for rivaroxaban and 7 days for enoxaparin–warfarin. In the rivaroxaban group, three patients discontinued therapy because of elevated liver enzymes. For patient 1, ALT increases started immediately after therapy was initiated; therapy was discontinued on day 5 and ALT normalized uneventfully. Patient 2 had elevated ALT levels at study initiation and never received rivaroxaban. Patient 3 had rivaroxaban 40 mg stopped after 23 days because of a diagnosis of hepatitis B with raised

ALT. This patient died of acute liver failure 48 days after starting therapy. This death was likely due to a fatal hepatitis B infection, but rivaroxaban could not be excluded as a contributing factor to the liver failure. The abstract of the EINSTEIN-DVT study, in which the number of patients in the safety analysis was not reported, stated that “no signal for liver toxicity with rivaroxaban was observed during the 12 weeks of treatment.”⁴⁵

In the ODIXa-HIP study ($n = 704$ in the safety analysis), ALT elevations to greater than three times normal ranged from 3.9% to 6.4% in rivaroxaban groups compared with 11.2% in the enoxaparin group.²⁵ ALT elevations greater than three times normal, combined with a twofold increase in bilirubin (an indicator of potential serious drug-induced liver injury), did not occur in any rivaroxaban patients. In the ODIXa-OD-HIP study ($n = 845$ in the safety analysis), ALT elevations to greater than three times normal ranged from 3% to 5.4% in the rivaroxaban groups compared with 7.1% in the enoxaparin group.²⁶ A single rivaroxaban patient had an ALT elevation greater than three times normal combined with a twofold increase in bilirubin three hours after receiving study medication. This patient continued on therapy uneventfully. In the ODIXa-KNEE study ($n = 613$ in the safety analysis), four rivaroxaban patients had ALT or aspartate transaminase levels elevated to greater than three times normal combined with bilirubin greater than two times normal.²⁷ The study report stated that “both patients with elevated ALT and bilirubin remained on study medication without any clinical symptoms, with liver function tests returning to normal by follow-up.” This statement apparently pertains to two patients; the article did not note the outcome of the other two patients. A combined analysis of the ODIXa-HIP and ODIXa-KNEE studies found that ALT elevations

to greater than three times normal ranged from 3.8% to 6% in the rivaroxaban groups compared with 7.7% in the enoxaparin groups.⁵⁹ No information on potential liver toxicity was published in the abstracts for RECORD1, 2, or 3.^{47,48,52}

Factors in evaluating adverse effects. It is important to note that all published or presented clinical trials of rivaroxaban have been relatively short (the longest was 12 weeks), whereas the problems with ximelagatran occurred after long-term use for indications such as secondary VTE prophylaxis or stroke prevention in atrial fibrillation.⁵⁷ Because of its very low oral bioavailability, ximelagatran was formulated as a prodrug, which may have contributed to the safety issue. Rivaroxaban is not formulated as a prodrug. It will be important for clinicians to pay close attention to the results of long-term trials such as EINSTEIN and ROCKET AF to detect any indications of liver toxicity or other potential adverse effects that may surface with long-term use. At this point, it is uncertain whether the different mechanism of action of rivaroxaban, when compared with ximelagatran and dabigatran (a direct thrombin inhibitor in development), will prevent it from causing liver toxicity.

Anticoagulation reversal

Only recombinant factor VIIa (rFVIIa) has been studied as a method of reversing anticoagulation induced by rivaroxaban. Rivaroxaban's effects in humans and rats were par-

tially reversed by rFVIIa, as measured by bleeding time, PT prolongation, and other clotting tests, without affecting inhibition of FXa.⁶⁰⁻⁶²

Other oral Xa agents in development

Several oral FXa inhibitors are in development (Table 5), although rivaroxaban is in the most advanced stage of development. Apixaban is another direct, oral FXa inhibitor that has entered Phase III trials, and clinical efficacy and safety data are awaited.

Place in therapy

Rivaroxaban is a promising new oral anticoagulant that could become an attractive alternative to traditional treatments such as warfarin and may have a significant impact on the current approach to treating thromboembolic disorders. It can be administered as a fixed oral dose, once or twice daily. It has a rapid onset of action and provides a predictable and consistent anticoagulation effect without the need for routine coagulation monitoring. In addition, it appears to have a low potential for drug-drug or drug-food interactions. Results from Phase II and Phase III trials suggest that rivaroxaban is an effective anticoagulant. Thus far, rivaroxaban has been administered only for short time periods; any significant long-term adverse effects (e.g., hepatotoxicity) remain to be observed and analyzed in future trials. Rivaroxaban is being evaluated for the prevention of

venous thrombosis in patients undergoing major orthopedic surgery (hip or knee replacement), treatment of venous thrombosis (DVT and PE), secondary prevention of venous thrombosis for an extended duration, and prevention of stroke in atrial fibrillation. Four primary venous thrombosis prevention studies have been completed in patients undergoing orthopedic surgery, and rivaroxaban appears to be a promising alternative to LMWH. The results of ongoing studies in VTE treatment and stroke prevention in atrial fibrillation will further define the role of rivaroxaban in comparison with traditional warfarin anticoagulation. A regulatory filing to the European Agency for the Evaluation of Medicinal Products (EMA) was submitted in October 2007, and a filing with FDA is planned in 2008 for the prevention of VTE in patients undergoing major orthopedic surgery.

Conclusion

Rivaroxaban is a direct FXa inhibitor that appears to offer promise for the prevention and treatment of VTE and for stroke prevention in atrial fibrillation; it offers once-daily oral administration without the need for frequent monitoring.

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Table 5.
Oral Xa Inhibitors in Development

Medication	Phase	Manufacturer
Rivaroxaban (BAY 59-7939)	III	Bayer and Johnson & Johnson
Apixaban (BMS-562247)	II and III	Bristol-Myers Squibb and Pfizer
LY-517717	II	Eli Lilly and Company
YM-150	II	Astellas Pharma
DU-176b	II	Daiichi Sankyo
PRT-054021	II	Portola Pharmaceuticals

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