

Rivaroxaban for thromboprophylaxis in major orthopedic surgery

Alternative to low-molecular-weight heparins is already approved in Europe and is anticipated to become available in the US later this year.

What's new, what's important

Venous thromboembolism (VTE) is a major problem in patients with cancer. According to the American Society of Clinical Oncology guidelines, all hospitalized cancer patients should be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications. Low-molecular-weight heparin is the preferred drug, and other options are heparin and warfarin, both of which require intense monitoring.

Rivaroxaban (BAY 59-7939), the first orally active direct factor Xa inhibitor, inhibits thrombin generation by both the intrinsic and tissue factor pathways. Clinical trials in patients undergoing hip replacement or knee surgery have shown it to be superior to enoxaparin (Lovenox), with an exceptionally safe side-effect profile for an anticoagulant. Bleeding risk is similar to that of enoxaparin.

The advantage of rivaroxaban is that it is an oral anticoagulant with a fixed dose of 10 mg/d. It does not require any monitoring of PT/INR (prothrombin time/international normalized ratio), and its potential for interactions with other drugs is limited. Other reported side effects, such as hepatic toxicity, should be monitored carefully.

Rivaroxaban is being evaluated by the US Food and Drug Administration for prevention of VTE in patients undergoing orthopedic surgery. Studies in patients with cancer are eagerly awaited.

—Jame Abraham, MD
Section Editor

Three recently reported randomized, double-blind phase III trials have shown the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939) to be superior to enoxaparin (Lovenox) anticoagulant therapy as thromboprophylaxis in patients undergoing total hip or knee arthroplasty. In all studies, bleeding risk was comparable between treatments.

Total hip arthroplasty

The RECORD1 (Regulation of Coagulation in Orthopedic Surgery

to Prevent Deep Vein Thrombosis and Pulmonary Embolism 1) study evaluated extended thromboprophylaxis (35 days) with both oral rivaroxaban and subcutaneous enoxaparin in patients undergoing total hip arthroplasty.¹ In this trial, 4,541 patients were randomized to receive oral rivaroxaban (10 mg/d) or subcutaneous enoxaparin (40 mg/d) for 35 days. Rivaroxaban was started 6–8 hours after wound closure; enoxaparin was started 12 hours before surgery and first given post surgery at 6–8 hours after wound closure.

Among the 3,153 patients included in the superiority efficacy analysis, the composite primary endpoint of deep vein thrombosis, nonfatal pulmonary embolism, or all-cause mortality at 36 days occurred in 18 (1.1%) of 1,595 rivaroxaban patients and 58 (3.7%) of 1,558 enoxaparin patients (absolute risk reduction, 2.6%; $P < 0.001$). The rate of major venous thromboembolism (VTE)—proximal deep vein thrombosis, nonfatal pulmonary embolism, or death due to VTE—was also significantly reduced in the rivaroxaban group when compared with the enoxaparin group (0.2% vs 2.0%; absolute risk reduction, 1.7%; $P < 0.001$).

Among the 4,433 patients included in the safety analysis, there was no difference between the rate of major bleeding (the primary safety endpoint) in the rivaroxaban group (6/2,209, or 0.3%) versus the enoxaparin group (2/2,224, or 0.1%; $P = 0.18$). On-treatment bleeding of any kind occurred in 6.0% and 5.9% of rivaroxaban- and enoxaparin-treated patients, respectively. Rates of any on-treatment adverse events (64.0% vs 64.7%) and drug-related adverse events (12.2% vs 11.9%) also were similar in the two groups.

Extended prophylaxis with rivaroxaban

The RECORD2 trial compared extended prophylaxis with rivaroxaban with a standard short-term regimen of enoxaparin in patients under-

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going total hip arthroplasty.² In this trial, 2,509 patients were randomized to receive rivaroxaban 10 mg/d for 31–39 days or enoxaparin 40 mg/d for 10–14 days, with dosing initiated as in the RECORD1 trial.

Among 1,733 patients in the modified intent-to-treat population, the composite primary endpoint of deep vein thrombosis, nonfatal pulmonary embolism, and all-cause mortality up to day 30–42 occurred in 17 (2.0%) of 864 rivaroxaban-treated patients versus 81 (9.3%) of 869 patients receiving enoxaparin (absolute risk reduction, 7.3%; $P < 0.0001$). Risk for major VTE was also significantly reduced in the rivaroxaban treatment group (0.6% vs 5.1%; absolute risk reduction, 4.5%; $P < 0.0001$).

In the safety population of 2,457 patients, on-treatment bleeding of any kind occurred in 81 (6.6%) of 1,228 patients given rivaroxaban versus 68 (5.5%) of 1,229 patients receiving enoxaparin ($P = 0.25$); major bleeding occurred in 1 patient ($< 0.1\%$) in

each group. Rates of on-treatment adverse events again were similar in the two groups (62.5% vs 65.7%), as were rates of discontinuation due to adverse events (3.8% vs 5.2%).

Total knee arthroplasty

In the RECORD3 trial,³ 2,531 patients undergoing total knee arthroplasty were randomized to receive rivaroxaban (10 mg) or enoxaparin (40 mg) for 10–14 days, with treatment initiated as in the other phase III RECORD trials. In the modified intent-to-treat population of 1,702 patients, the composite primary endpoint of deep vein thrombosis, nonfatal pulmonary embolism, and all-cause mortality within 13–17 days occurred in 79 (9.6%) of 824 rivaroxaban-treated patients versus 166 (18.9%) of 878 enoxaparin-treated patients (absolute risk reduction, 9.2%; $P < 0.001$). Further, the risk of major VTE was significantly reduced in the rivaroxaban group when compared with the enoxaparin

group (1.0% vs 2.6%; absolute risk reduction, 1.6%; $P = 0.01$).

In the safety population of 2,459 patients, major bleeding occurred in 7 (0.6%) of 1,220 rivaroxaban-treated patients and 6 (0.5%) of 1,239 patients given enoxaparin ($P = 0.77$); there was no significant difference between groups with regard to the rate of any bleeding (4.9% vs 4.8%). Rates of adverse events of all types (63.6% vs 68.1%) and drug-related adverse events (12.0% vs 13.0%) were similar in the two groups.

References

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From the Oncologist's Perspective

Promising alternative to current drugs for thromboprophylaxis, but studies in cancer patients are lacking

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Rivaroxaban (BAY 59-7939) is approved in Europe for venous thromboembolism (VTE) thromboprophylaxis following orthopedic surgery and is currently being evaluated by the Food and Drug Administration (FDA) here in the United States for the same indication. It is a direct factor Xa inhibitor that inhibits throm-

bin generation by both the intrinsic and tissue factor pathways. Because it acts at the convergence of these two pathways, it prolongs both the prothrombin time (PT) and the activated partial thrombin time in a dose-dependent fashion.^{1–3}

Dose-finding studies leading to the phase III RECORD (Regulation of Coagulation in Orthopedic Sur-

gery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) series of clinical trials suggested that an oral dose of 10 mg once daily for thromboprophylaxis was suitable for further investigation.^{4–6} Subsequently, in the RECORD1, RECORD2, and

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RECORD3 modified intention-to-treat analyses, rivaroxaban (10 mg/d) has been reported to be superior to enoxaparin (Lovenox, 40 mg/d) for thromboprophylaxis following total hip or knee replacement.

It is important to appreciate that these doses are probably not comparable, in that rivaroxaban at 10 mg/d is most likely closer to a “full” therapeutic dose, whereas enoxaparin at 40 mg/d is a low prophylactic dose. However, few major bleeding events were noted, and no significant differences in the incidence of major bleeding events between the comparator arms were seen in any of these three studies.⁷⁻⁹

Clinical pharmacology

Rivaroxaban inhibits free factor Xa and prothrombinase activity and may inhibit clot-bound factor Xa. It offers the advantages of a fixed oral dose with rapid onset of action. Plasma concentrations reach a peak within 2.5 to 4 hours. It has a predictable anticoagulation effect, which precludes the need for routine monitoring. The oral bioavailability of rivaroxaban is about 80%, and no significant accumulation of the drug occurs once the plasma concentration reaches steady-state levels.^{4-5,10-13}

The drug is hepatically metabolized via the P450 system (specifically by the isoenzyme CYP3A4) and is excreted in the urine (66%, with 36% as unchanged drug) and feces. In vitro studies suggest that rivaroxaban may interact with strong CYP3A4 inhibitors. At this time, there is a recommendation to avoid concomitant systemic treatment with strong CYP3A4 and P-glycoprotein (P-gp) inhibitors, but as safety data and experience with this drug accrue, this recommendation may change.^{14,15} Extremes in body weight influence the volume of distribution of rivaroxaban, but this effect has not been found to be significant, and currently it is not recommended that dosage adjustments be made for

underweight or obese patients.^{5,16}

Rivaroxaban appears to have low potential for drug-drug or drug-food interactions. Specifically, no significant interactions have been noted with aspirin or other nonsteroidal anti-inflammatory drugs, antacids, histamine-2 antagonists (such as ranitidine), or digoxin.¹⁷⁻¹⁹ In clinical trials of rivaroxaban, patients were excluded who were pregnant or had active bleeding, intracerebral or gastrointestinal bleeding within the past 6 months, neurosurgery within the past 4 weeks, an active peptic ulcer, a known bleeding disorder, prolonged PT/INR (international normalized ratio), low platelet counts, severe liver disease, and/or kidney function impairment (creatinine clearance < 30 mL/min). These exclusion criteria are similar to the contraindications and precautions that are recommended before using warfarin or enoxaparin. Until specific recommendations are made for rivaroxaban, caution should be exercised in patients with these conditions.

Safety

Thus far, rivaroxaban has proven to be safe. As mentioned, the rate of major bleeds observed in patients treated with this drug or enoxaparin is similar. However, a higher incidence of bleeding has been reported with twice-daily versus once-daily dosing of rivaroxaban.⁸

The most commonly reported side effects are headache, mild nausea, and vomiting. No clinically significant changes have been seen in bleeding time, blood pressure, heart rate, electrocardiographic findings, vital signs, or laboratory parameters (except for the results of clotting tests). Rivaroxaban does not prolong the QTc interval.²⁰

Information on the potential liver toxicity of rivaroxaban is limited. In phase II/III studies, a small number of patients experienced increases in their liver enzymes, and similar in-

creases were seen in the enoxaparin group. In all the published trials of rivaroxaban to date, patients have received relatively short courses of drug therapy (6–12 weeks), whereas the problems of hepatotoxicity reported with the direct thrombin inhibitor ximelagatran, which caused it to be removed from the market, occurred with long-term use, such as for prevention of stroke in patients with atrial fibrillation and for secondary prophylaxis of VTE.

It will be important to follow the results of trials evaluating long-term rivaroxaban therapy to look for liver toxicity or other adverse effects that may arise.⁸ Phase III trials of rivaroxaban for stroke prevention in non-valvular atrial fibrillation, prevention of VTE in hospitalized medically ill patients, treatment and secondary prevention of VTE, and secondary prevention of major cardiovascular events in patients with acute coronary syndromes are ongoing. Details of these trials are available at the National Institutes of Health's Clinical-Trials.gov Web site.

Use in cancer patients

Several studies have demonstrated the unpredictable anticoagulant responses of cancer patients to warfarin, resulting in both subtherapeutic and supratherapeutic INR values.²¹⁻²³ The low-molecular-weight heparins (LMWHs) have been extensively used in cancer patients. Due to their effective inhibition of factor Xa, they are generally deemed to be a safer alternative to warfarin for both therapeutic and prophylactic anticoagulation, especially in patients receiving chemotherapy.^{22,24-26} However, patients often express difficulty and discomfort in self-administering the injectable LMWHs, making compliance an issue with these agents. Further studies are needed to elucidate rivaroxaban's exact role in this patient population, but it may represent a promising alternative to currently available agents.

Summary

Rivaroxaban is an oral direct factor Xa inhibitor that appears to be promising in the area of VTE prophylaxis following orthopedic surgery. It is anticipated that it will gain FDA approval for this indication later this year. Further studies are ongoing to assess its role in secondary VTE prophylaxis, treatment of pulmonary embolism and deep vein thrombosis, and stroke prevention in patients with atrial fibrillation. As data from studies of its use in medically ill patients mature, evidence regarding the potential use of rivaroxaban in cancer patients may become available through indirect or subset analyses, but studies looking at its specific thromboprophylactic role in this population have yet to be performed.

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