Cleveland Clinic Pharmacotherapy Update
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Rivaroxaban: A Novel Oral Anticoagulant

By: Tessa Ruble, Pharm.D.

Introduction: For over 50 years, warfarin was the only oral anticoagulant available in the United States.[1] It has been used for a variety of indications, including prevention and treatment of venous thromboembolism (VTE) in patients undergoing knee and hip replacement surgeries, as well as the prevention of stroke and systemic embolism in patients with atrial fibrillation.[2] Although warfarin has proven efficacy for these indications, its use is associated with various limitations including delayed onset of action, narrow therapeutic index necessitating continuous monitoring of the international normalized ratio (INR), and numerous food and drug interactions.[1] Other agents used for surgical thromboprophylaxis, such as enoxaparin and fondaparinux, must be given subcutaneously which may not be ideal for some patients. These shortcomings have prompted the development of new oral anticoagulants in an attempt to provide safer, more convenient alternatives. The first of these novel oral anticoagulants to arrive on the U.S. market was dabigatran (Pradaxa®; Boehringer Ingelheim Pharmaceuticals, Inc.), an oral direct thrombin inhibitor.[3] It received approval by the Food and Drug Administration (FDA) in October 2010, for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Less than 1 year later, the FDA approved rivaroxaban (Xarelto®; Janssen Pharmaceuticals, Inc.), an oral, direct factor Xa inhibitor, for the prevention of VTE in patients undergoing knee or hip replacement surgeries.[4] In November 2011, rivaroxaban became FDA-approved for the reduction of stroke risk in patients with nonvalvular atrial fibrillation.[5] However, this article will focus on rivaroxaban's role in VTE prevention associated with knee or hip replacement.

Mechanism of Action: Rivaroxaban is an oral, direct factor Xa inhibitor, which reversibly binds to the active site of factor Xa.[4] Within the coagulation cascade, the activation of factor Xa is the point of convergence of the extrinsic and intrinsic pathways whereby activated factor Xa transforms prothrombin (factor II) to thrombin (factor IIa) leading to thrombus formation and eventual clotting.[6,7] By blocking factor Xa, rivaroxaban interferes with the final steps in the coagulation process. Unlike fondaparinux, a parenteral irreversible factor Xa inhibitor, rivaroxaban directly targets factor Xa without antithrombin III mediation, and thus is able to affect both free and platelet-bound factor Xa.[6]

Pharmacokinetics: Rivaroxaban's pharmacokinetics are linear, with peak concentrations occurring within 2 to 4 hours after administration.[4] The drug has a fairly rapid onset of action with maximal factor Xa inhibition occurring within approximately 3 hours.[8,9] It achieves maximal absorption from the stomach, with a bioavailability of 80 to 100% follow-

ing a 10 mg dose.[4] Bioavailability is decreased by 26% in the proximal small intestine with further reductions in absorption as the drug passes through the rest of the intestinal tract. The steady-state volume of distribution of rivaroxaban is estimated to be 50 liters. Its terminal half-life is approximately 5 to 9 hours in patients aged 20 to 45 years and 11 to 13 hours in patients over 65 years of age. Although primarily metabolized by the liver, about one-third of its elimination occurs through the kidneys resulting in increased exposure in patients with renal impairment.

Select Clinical Trials: The **Re**gulation of **C**oagulation in **O**rthopedic Surgery to Prevent **D**eep Venous Thrombosis and Pulmonary Embolism (RECORD) studies were Phase III, multicenter, randomized, double-blind trials which compared rivaroxaban to enoxaparin for the prevention of VTE after orthopedic procedures. The RECORD 1 and 2 studies evaluated rivaroxaban versus enoxaparin for VTE prevention after hip arthroplasty. The RECORD 2 study specifically assessed the short-term use of enoxaparin compared with rivaroxaban. The RECORD 3 and 4 trials compared rivaroxaban versus enoxaparin for prevention of VTE after knee arthroplasty.

Patients were randomized to receive oral rivaroxaban 10 mg once daily for 31 to 39 days in RECORD 1 (n=2266) and RECORD 2 (n=1252) or subcutaneous enoxaparin 40 mg once daily for 31 to 39 days in RECORD 1 (n=2275) and 10 to 14 days in RECORD 2 (n=1257).[10,11] Rivaroxaban was initiated at least 6 to 8 hours after wound closure while enoxaparin was started 12 hours preoperatively and restarted 6 to 8 hours after wound closure. Follow-up occurred through 30 to 35 days after the last dose of study drug. Participants ≥18 years of age scheduled to undergo elective total hip arthroplasty were eligible. Major exclusion criteria included staged bilateral total hip replacement, active bleeding or high risk for bleeding, any contraindications to enoxaparin or conditions which would necessitate its dosage adjustment. The primary efficacy endpoint for RECORD 1 and 2 was the composite of deep-vein thrombosis (DVT), nonfatal pulmonary embolism (PE), and all-cause mortality at 36 days (range 30 to 42). The main secondary efficacy endpoint was major VTE, defined as the composite of proximal DVT, nonfatal PE, and death from VTE. The primary safety endpoint was major bleeding, defined as fatal bleeding, bleeding in a critical organ (e.g., retroperitoneal, intracranial, intraocular, intraspinal), required reoperation, or clinically overt non-surgical site bleeding causing a drop in hemoglobin of at least 2 g/dL or the need for transfusion of two or more units of whole blood or packed red blood cells. Both studies utilized a modified intent-to-treat (ITT) group to determine treatment superiority and a specific safety population to assess adverse events. The key results of both trials are listed in Table 1. In both studies, rivaroxaban was found to be superior to enoxaparin in preventing DVT, nonfatal PE, and all-cause mortality, as well as preventing major VTE in patients undergoing hip arthroplasty. There was no statistically significant difference in rate of major bleeding between these agents. Other adverse events were also similar between the two treatment groups. However, there was a higher percentage of patients receiving enoxaparin who experienced an elevation in alanine aminotransferase (ALT) greater than three times the upper limit of normal compared to patients receiving rivaroxaban (4.7% versus 1.6%, respectively). The authors of the RECORD 1 and 2 studies concluded rivaroxaban was significantly more effective in preventing VTE in patients undergoing hip arthroplasty compared to enoxaparin with a comparable safety profile.

In RECORD 3, patients were randomized to receive oral rivaroxaban 10 mg once daily beginning 6 to 8 hours after wound closure (n=1254) or subcutaneous enoxaparin 40 mg once daily, initiated 12 hours prior to surgery and continued 6 to 8 hours after wound closure (n=1277).[12] The treatment groups in RECORD 4 were randomized to receive rivaroxaban 10 mg once daily (n=1584) or subcutaneous enoxaparin 30 mg every 12 hours (n=1564).[13] All patients received study medication for 10 to 14 days, with follow-up extending 30 to 35 days after the last dose of study drug. Major exclusion criteria were active bleeding or high risk for bleeding, and any contraindications to enoxaparin or conditions which would necessitate its dosage adjustment. The primary endpoint was the composite of DVT, nonfatal PE, or all-cause mortality within 13 to 17 days following surgery. The main secondary efficacy endpoint was major VTE, while the primary safety endpoint was the incidence of major bleeding, as defined previously in the RECORD 1 and 2 trials. A modified ITT population was used to determine superiority and a specific safety population was utilized to assess adverse effects. The key results for these trials are reported in Table 2. In both studies, rivaroxaban was found to be superior to enoxaparin in preventing DVT, nonfatal PE, and all-cause mortality in patients undergoing total knee arthroplasty. For the prevention of major VTE, rivaroxaban was found to be superior only to the enoxaparin 40 mg once daily regimen although it was deemed noninferior to the enoxaparin 30 mg every 12 hour regimen. There was no difference in the rates of major bleeding between the two treatment groups in either study. Other adverse event rates were also similar, with the exception of elevated ALT levels greater than three times the upper limit of normal, which occurred more frequently in the enoxaparin group in RECORD 4. The authors of both trials concluded that rivaroxaban was superior to enoxaparin for thromboprophylaxis following total knee arthroplasty with a similar bleeding rate.

Table 1: Summary of Key Results RECORD 1 and 2[10,11]

	RECORD 1			RECORD 2		
Treatment	**Rivaroxaban 10 mg daily % affected (No. with event/total)**	**Enoxaparin 40 mg daily % affected (No. with event/total)**	**Absolute Risk Reduction (ARR)**	**Rivaroxaban 10 mg daily % affected (No. with event/total)**	**Enoxaparin 40 mg daily % affected (No. with event/total)**	**Absolute Risk Reduction (ARR)**
Primary Outcome*	1.1% (18/1595)	3.7% (58/1558)	2.6% (P<0.001)	2.0% (17/864)	9.3% (81/869)	7.3% (P<0.0001)
Major VTE*	0.2% (4/1686)	2.0% (33/1678)	1.7% (P<0.001)	0.60% (6/961)	5.1% (49/962)	4.5% (P<0.0001)
Major Bleeding†	0.3% (6/2209)	0.1% (2/2224)	P=0.18	<0.1% (1/1228)	<0.1% (1/1229)	P=NR

*Results for Modified Intent-to-Treat Population
†Results for Safety Population
VTE=Venous Thromboembolism
NR=Not Reported

Table 2: Summary of Key Results RECORD 3 and 4 [12,13]

	RECORD 3			RECORD 4		
Treatment	**Rivaroxaban 10 mg daily % affected (No. with event/total)**	**Enoxaparin 40 mg daily % affected (No. with event/total)**	**Absolute Risk Reduction (ARR)**	**Rivaroxaban 10 mg daily % affected (No. with event/total)**	**Enoxaparin 30 mg every 12 hours % affected (No. with event/total)**	**Absolute Risk Reduction (ARR)**
Primary Outcome*	9.6% (79/824)	18.9% (166/878)	9.2% (P<0.001)	6.9% (67/965)	10.1% (97/959)	3.19% (P<0.0118)
Major VTE*	1.0% (9/908)	2.6% (24/925)	1.6% (P=0.01)	1.2% (13/1122)	2.0% (22/1112)	0.80% (P=0.1237)
Major Bleeding†	0.6% (7/1220)	0.5% (6/1239)	P=0.77	<0.7% (10/1526)	0.3% (4/1508)	P=0.1096

*Results for Modified Intent-to-Treat Population
†Results for Safety Population
VTE=Venous Thromboembolism
NR=Not Reported

Adverse Reactions: The most common adverse event reported in the RECORD trials was overall bleeding occurring in approximately 5% of patients receiving rivaroxaban.[4] Major bleeding was reported in approximately 0.3 to 0.6% of rivaroxaban-treated patients. The drug has also been associated with fatal bleeding occurring in approximately 0.1% of patients. Other reactions noted in ≥1% of patients include wound secretions, pain in extremities, muscle spasm, syncope, pruritus, and blisters. The overall incidence rate of adverse effects leading to permanent cessation of rivaroxaban therapy in the RECORD studies was 3.7%.

Black Box Warning: Patients who are anticoagulated and receiving neuraxial anesthesia or undergoing spinal puncture are at an increased risk of developing epidural or spinal hematomas, which may lead to long-term or permanent paralysis.[4] Certain factors such as use of indwelling epidural catheters, concurrent use of antiplatelet/anticoagulant agents, history of traumatic or repeated epidural or spinal punctures, and history of spinal deformity or spinal surgery can increase the incidence of this adverse event in rivaroxaban-treated patients. In order to help prevent this serious complication from occurring, an epidural catheter should not be removed for at least 18 hours after the last rivaroxaban dose and the next scheduled dose should not be given earlier than 6 hours after catheter removal.

Drug Interactions: Rivaroxaban is a substrate of the cytochrome P450 (CYP) 3A4/5 and CYP2J2 enzymes as well as P-glycoprotein (P-gp) and ATP-binding cassette G2 (ABCG2) transporters.[4] Inhibitors or inducers of these CYP 450 enzymes and transporter systems can alter rivaroxaban clearance which may significantly increase the drug's bleeding risk or reduce its therapeutic effect, respectively. Therefore, coadministration of rivaroxaban with certain combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, conivaptan) and combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's wort) should be avoided. Furthermore, concomitant use of rivaroxaban with other anticoagulants except during a therapeutic transition period is not recommended. Rivaroxaban-treated patients should be observed for increased bleeding during concomitant use with nonsteroidal antiinflammatory agents (NSAIDs) or aspirin. Rivaroxaban should only be used if the benefit outweighs the risk in patients with renal impairment currently receiving weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, amiodarone, ranolazine, dronedarone, felodipine) and in patients on clopidogrel therapy.

Pregnancy and Lactation: Rivaroxaban is classified as pregnancy-risk category C due to the lack of adequate and well-controlled studies in pregnant women.[4] Rivaroxaban crosses the placenta in animals and has been shown to produce serious maternal hemorrhagic complications in rats and an increased incidence of pregnancy loss and fetal toxicities in rabbits. Dosing in pregnancy has not been established. Rivaroxaban should only be used in pregnant women if the benefit outweighs the risk of maternal and fetal bleeding. Pregnant women receiving this medication should be closely monitored for signs or symptoms of blood loss (e.g., drop in hemoglobin/hematocrit, hypotension, fetal distress). Currently, it is not known whether rivaroxaban and/or its metabolites are excreted in human milk. Due to the potential for drug-related severe adverse reactions in nursing infants, the decision should be made to either discontinue rivaroxaban or breastfeeding, taking into account the importance of the drug to the mother.

Pediatric Use: There are currently no data on safety and efficacy of rivaroxaban in pediatric patients.[4]

Dose and Administration: The recommended dose of rivaroxaban for the prevention of VTE is 10 mg once daily for 35 days following hip replacement surgery and 12 days following knee replacement surgery.[4] It should be initiated at least 6 to 10 hours following surgery after hemostasis has been achieved. The drug may be taken without regard to meals. If a dose is missed, it is recommended to administer the dose as soon as possible on the same day. Rivaroxaban may be crushed and administered via a gastric feeding tube; enteral administration directly into other areas of the gastrointestinal (GI) tract (e.g., proximal small intestine) is not recommended due to inadequate absorption. Rivaroxaban should be avoided in patients with a severe renal impairment (i.e., CrCl <30 mL/min), moderate or severe hepatic dysfunction (i.e., Child-Pugh B or C), and hepatic disease with coagulopathy. Rivaroxaban-treated patients with a CrCl of 30 to 49 mL/min should be closely observed for signs and symptoms of bleeding; the drug should be discontinued in cases of acute renal failure. Patients aged ≥65 years have demonstrated an elevated exposure to rivaroxaban, likely due to an age-related decline in renal function; therefore, assessment of renal function should be completed prior to initiating therapy. Elderly patients should be carefully monitored for signs and symptoms of bleeding. It is recommended that rivaroxaban be discontinued at least 24 hours before surgery or other procedures and may be restarted afterwards once hemostasis has been established.

Monitoring: While monitoring parameters have not been determined for rivaroxaban, it has been shown to provide dose-dependent inhibition of factor Xa activity in addition to prolonging the prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT).[4] Similar to direct thrombin inhibitors, there is currently no antidote or direct reversal agent for rivaroxaban. In the event of bleeding, rivaroxaban should be discontinued and supportive therapy initiated. Rivaroxaban is highly protein bound, thus removal via dialysis is not likely. Protamine sulfate and Vitamin K are not expected to have an impact on rivaroxaban's anticoagulant activity. There are no data demonstrating the efficacy of antifibrinolytic agents (e.g., tranexamic acid, aminocaproic acid) or systemic hemostatics (e.g., desmopressin and aprotinin) as reversal agents. Although not evaluated in clinical trials, prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered to counteract rivaroxaban's pharmacodynamic effects.

Cost and Formulary Status: The dosage of rivaroxaban available for DVT prophylaxis in patients undergoing knee or hip replacement surgery is 10 mg.[4] The average wholesale price (AWP) of a rivaroxaban 10 mg tablet is approximately $9.00; therefore, the AWP of a 30-day supply of medication would be about $270.[14] Rivaroxaban was added to the CCHS Formulary in October 2011; its use is restricted for the indication of thromboprophylaxis in adult patients following orthopedic surgery and as requested by vascular medicine.

Conclusion: Oral administration of rivaroxaban makes it a valuable alternative to enoxaparin and fondaparinux, while advantages over warfarin include quicker onset of action, fixed dosing regimen, fewer drug interactions, and no requirement for coagulation monitoring. Nevertheless, there are limitations with rivaroxaban therapy. Without established monitoring parameters, the risk of bleeding cannot be easily determined. In addition, there is currently no specific antidote for reversal in the event of severe bleeding. Aside from these potential issues, rivaroxaban is an effective alternative for thromboprophylaxis following orthopedic surgery.

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Formulary Update

The CCHS Medical Staff Pharmacy and Therapeutics Committee met on November 29, 2011 and the Cleveland Clinic Local Pharmacy and Therapeutics Committee met on December 13, 2011; the following decisions were made:

Adults:

Additions to the CCHS Formulary:

Cardiovascular/Thrombosis:

1. **Fondaparinux** is now available in a **generic formulation** and this will be the product on the formulary. Brand fondaparinux (Arixtra®) will no longer be on the formulary.

Ophthalmology:

1. **Aflibercept (Eylea™):** It is a vascular endothelial growth factor (VEGF) inhibitor FDA-approved for the treatment of neovascular (wet) age-related macular degeneration (AMD). The recommended dose of aflibercept is 2 mg (0.05 mL) intravitreally in the eye every 4 weeks (monthly) for the first 3 months followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Aflibercept will be **restricted** to the Department of Ophthalmology for **outpatient use only**.

Transplant:

1. **Everolimus (Zortress®):** It is an inhibitor of the mammalian target of rapamycin (mTOR), like sirolimus. It is FDA-approved for use in renal cell carcinoma (Afinitor®) and is already on formulary for this indication **restricted** to continuation of home therapy. Everolimus was also recently approved for prophylaxis of kidney transplant rejection under the trade name Zortress®. Everolimus is approved for use in combination with a calcineurin inhibitor and is administered orally, twice daily in transplant patients. **Please note:** There is a 10-fold difference in dosing (tablet strengths) between the two product formulations:
   Everolimus (Afinitor®): 2.5 mg, 5 mg, 10 mg (renal cell carcinoma)
   Everolimus (Zortress®): 0.25 mg, 0.5 mg, 0.75 mg (transplant rejection prophylaxis)
   Everolimus **must be ordered by a staff physician** in accordance with the oral chemotherapy policy #04-003 for inpatients regardless of whether it is ordered for a transplant or oncology indication.

Deletion from the CCHS Formulary

1. **Drotrecogin alfa (Xigris®):** This medication was voluntarily withdrawn from the U.S. Market by Lilly following the results of the PROWESS-SHOCK study, in which the drug failed to show a survival benefit for patients with severe sepsis and septic shock. As of October 25, 2011, drotrecogin alfa treatment should not be started in new patients and should be stopped in patients currently being treated with drotrecogin alfa.

Changes in Current CCHS Formulary Restrictions:

1. **Fondaparinux generic:** This medication will be available on the formulary with **no restrictions** (i.e., previous restrictions to the Department of Hematology/Oncology, the Department of Vascular Medicine, and select physicians from the Department of Internal Medicine (IMPACT Center) **will be removed**).
2. **Methylnaltrexone (Relistor®):** This medication will be available on the formulary with **no restrictions** (i.e., previous restrictions to the Department of Hematology and Medical Oncology and Palliative Care Medicine, and Pain Management/Pain Medicine **will be removed**).
3. **Denosumab (Prolia®):** The current formulary restrictions on this medication have been **expanded** to include the two new FDA-approved indications for denosumab: 1.) Treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) and 2.) Treatment of bone loss in women with breast cancer receiving aromatase inhibitor (AI) therapy. The drug continues to be restricted to **outpatient use only**. The FDA-approved dosing for denosumab for these two new indications is 60 mg subcutaneously every 6 months.
4. **Alefacept (Amevive®):** The current formulary restriction for alefacept has been **expanded** to include use by **Transplant Physicians** for the treatment of **graft-versus-host-disease** (GVHD). However, due to manufacturing issues, alefacept is not currently available.
5. **Budesonide (Entocort®EC):** The current formulary restriction for budesonide has been **expanded** to include use by **Transplant Physicians** for the treatment of **graft-versus-host-disease** (GVHD).

Adults:

FDA Safety Alert:

1. An FDA Safety Alert was reviewed regarding **ondansetron** use and associated ECG changes. It was decided to leave the current 5HT3 receptor antagonists for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) on the CCHS Formulary with no changes and to re-address the 5HT3 receptor antagonists' formulary status, interchange program, and/or restrictions when the manufacturer's QT prolongation trial is completed and results are published.

Adults:

Order Set Update:

1. **Rivaroxaban (Xarelto®):** Rivaroxaban 10 mg daily has recently been added to the venous thromboembolism (VTE) prophylaxis order set in the special circumstances section with a notation that it is for orthopedic patients.

Children's Hospital/Pediatrics:

The CCHS Pediatric Medical Staff Pharmacy and Therapeutics Committee meeting was cancelled for the 4th quarter; therefore, no changes were made to the Children's Hospital/Pediatric Formulary.