Upon successful completion of this article, the pharmacist should be able to:

1. List the advantages and disadvantages of currently available anticoagulants.
2. Discuss the role of Factor Xa (FXa) in the coagulation cascade and the rationale for selected FXa inhibition as a target for drug development.
3. Discuss the pharmacology of apixaban and rivaroxaban: mechanism of action, pharmacokinetics and pharmacodynamics.
4. Discuss the clinical data with rivaroxaban.
5. Discuss the clinical data with apixaban.

INTRODUCTION

Arterial and venous thromboses are major causes of morbidity and mortality. Arterial thrombosis is the most common cause of myocardial infarction, ischemic stroke, and limb gangrene. Venous thrombosis, such as deep vein thrombosis (DVT), may lead to pulmonary embolism (PE), which can be fatal. Anticoagulants are the foundation for prevention and treatment of venous and arterial thromboembolic diseases. Heparins and vitamin K antagonists were discovered more than 60 years ago and have proven effectiveness. However, there are drawbacks with their use. Unfractionated heparin (UFH) requires parenteral administration and individualized dosing due to variable intra-patient response. Moreover, a specific test, the activated partial thromboplastin time (aPTT), must be monitored to ensure adequate anticoagulation. Adverse effects are also problematic and include bleeding, thrombocytopenia, and osteoporosis with prolonged use.

Vitamin K antagonists (VKAs) are the only oral agents available and have been the cornerstone of chronic anticoagulation therapy. Warfarin is the VKA of choice in the United States with an estimated 2 million people on chronic warfarin therapy. Warfarin has a proven efficacy and has multiple indications: 1) prophylaxis and/or treatment of venous thromboembolism, 2) prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and 3) to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. Similar to UFH, warfarin needs individualized dosing and regular monitoring. It interacts with numerous drugs and foods. Warfarin also shares a risk for bleeding, as it has been reported that 26,000 to 210,000 major bleeding events are attributed to warfarin therapy annually. Despite these limitations, VKAs continue to be the drug of choice when chronic oral
Anticoagulation is necessary because a more attractive alternative is not yet available.

Owing to the many limitations of warfarin and heparin, there has been considerable interest in developing an alternative anticoagulant. Experts agree on characteristics of an "ideal anticoagulant." They are: 1) availability for oral and parenteral administration; 2) no need for close coagulation monitoring; 3) no need for individualized dosing; 4) a wide therapeutic window; 5) an appropriate half-life that allows for once or twice daily dosing regimen; 6) rapid onset and offset of action; and 7) minimal drug or food interactions. Researchers continue to search for this "ideal anticoagulant." With advances in drug design based on structure and function and improved understanding of the process of coagulation, development of new anticoagulants has expanded in recent years.

**Anticoagulants** are the foundation for prevention and treatment of venous and arterial thromboembolic diseases. Heparins and vitamin K antagonists were discovered more than 60 years ago and have proven effectiveness.

Although the direct thrombin inhibitors, low molecular weight heparins (LMWH), and fondaparinux are newer anticoagulants with some beneficial characteristics, they are not ideal. Three direct thrombin inhibitors currently available are bivalirudin (Angiomax), argatroban (Argatroban), and lepirudin (Refludan). These agents require parenteral administration, and their use is restricted to hospitalized patients. LMWH and fondaparinux (Arixtra) can be used in ambulatory patients. Three LMWH products, dalteparin (Fragmin), enoxaparin (Lovenox), and tinzaparin (Innohep), are available in the United States. LMWH offers important advantages over UFH, including 1) more activity against Factor Xa than thrombin, 2) several pharmacokinetic advantages over UFH, which contribute to greater convenience, and 3) better bioavailability and a more predictable anticoagulant response, which minimizes the need for aPTT monitoring and dose adjustment. The newest anticoagulant is fondaparinux, which is another selective FXa inhibitor. The higher cost associated with these agents and need for parenteral administration are important limitations. Table 1 (pages 41-42) lists current anticoagulation therapies available for outpatient use.

Past attempts to develop and market a novel orally administered anticoagulant have resulted in failure. For example, the oral direct thrombin inhibitor ximelagatran and FXa inhibitor razaxaban have been burdened with hepatotoxicity and increased bleeding risk, respectively. Factor Xa is a potential target for effective anticoagulation because it is the point where the intrinsic and extrinsic coagulation pathways converge, and its only known functions are the promotion of coagulation and inflammation. One FXa molecule catalyzes the formation of approximately 1,000 thrombin molecules. Therefore, inhibitors of FXa can reduce thrombin-mediated platelet and coagulation activation. Factor Xa has also been shown to activate clotting over a wider concentration range, so the likely therapeutic window may be larger than currently available agents. This article describes the clinical data on two oral, direct FXa inhibitors, rivaroxaban and apixaban, currently in clinical development.

**RIVAROXABAN**

**Pharmacology**

Rivaroxaban is an oral, direct FXa inhibitor undergoing phase III clinical evaluation. It is a competitive, selective and reversible FXa inhibitor, and it has greater than 10,000-fold selectivity for FXa than other biologically relevant serine proteases. Rivaroxaban inhibits free and clot-associated FXa and it demonstrates antithrombotic effect in vivo in healthy subjects.

**Pharmacokinetics**

Preclinical trials have evaluated the pharmacokinetics of rivaroxaban. Orally administered rivaroxaban is rapidly absorbed within a half hour to two hours, and its bioavailability is approximately 60-80 percent. It exhibits dose-dependent pharmacokinetic characteristics. Maximum concentration is reached in approximately three to four hours after administration. Rivaroxaban is approximately 90 percent bound to plasma proteins. In one study, food moderately increased and delayed the absorption of rivaroxaban. Both the area under the curve and peak plasma concentration increased significantly with concurrent ingestion with food, and the half-life was shorter.
in the fed state. To take advantage of this effect, patients were instructed to take rivaroxaban with food or within two hours of food in clinical trials.

Rivaroxaban is eliminated by various routes. Rivaroxaban is metabolized by the liver via CYP3A4, is eliminated in the feces, and approximately 30 percent is excreted unchanged in the urine. The half-life of rivaroxaban ranges from five to nine hours in healthy young patients, and 11–12 hours in elderly subjects. There are no recommendations at this time for adjusting dosages of rivaroxaban in patients with renal insufficiency. The effect of hepatic insufficiency on rivaroxaban PK has not been well studied. In one study of patients with mild hepatic impairment, rivaroxaban PK was clinically similar compared with healthy subjects. Total body clearance, however, was moderately decreased in patients with moderate hepatic impairment. Rivaroxaban use in patients with severe hepatic impairment has not been studied, and these patients were excluded from clinical trials. Neither body weight nor gender significantly affects rivaroxaban pharmacokinetics, and the need for dose adjustment based on body weight or gender will be unlikely.

**Pharmacodynamics**

Phase I and II studies have assessed the pharmacodynamic effects of rivaroxaban. Rivaroxaban prolonged clotting assays such as the prothrombin time/International Normalized Ratio (PT/INR), activated partial thromboplastin

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Mechanism of Action</th>
<th>Advantages</th>
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</table>
| Warfarin sodium     | Prophylaxis and/or treatment of VTE, for the prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement, and to reduce the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization after MI. | Interferes with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide); inhibits the production of functional vitamin K dependent coagulation factors II, VII, IX, and X. | - Orally available  
- Gold standard for chronic therapy  
- Inexpensive | - Unpredictable patient response  
- Monitoring and dose adjustments necessary  
- Slow onset and offset of action  
- Narrow therapeutic window  
- Numerous drug, food interactions  
- Risk of bleeding |
| Unfractionated Heparin | Treatment of thrombosis and embolism.  
- Coagulopathies.  
- Prophylaxis of VTE.  
- Clotting prevention. | Binds to antithrombin producing a conformational change that converts antithrombin from a slow, progressive thrombin inhibitor to a rapid inhibitor; heparin/antithrombin complex inactivates thrombin (factor IIa) and factors Xa, IXa, X, and Xa. | - Fast acting  
- Good efficacy  
- Inexpensive | - Parenteral administration  
- Requires monitoring  
- Potential for severe heparin-induced thrombocytopenia  
- Unpredictable response  
- Risk of osteoporosis  
- Variable bioavailability  
- Bleeding |
| Dalteparin Fragmin  | - Unstable angina/Non-Q-wave MI.  
- DVT prophylaxis | Binds to antithrombin producing a conformational change that converts antithrombin from a slow, progressive thrombin inhibitor to a rapid inhibitor; heparin/antithrombin complex inactivates factor Xa more than thrombin (factor IIa). | - Once- or twice-daily dosing  
- No need for coagulation monitoring  
- Good efficacy | - SQ administration  
- Bleeding complications with renal insufficiency  
- Risk of thrombocytopenia and osteoporosis (less than regular heparin)  
- High cost |
time (aPTT) and HepTest in a dose-dependent manner; maximal prolongations were reached within one to four hours. Plasma concentrations correlated linearly to inhibition of FXa activity and PT. FXa activity was inhibited with rivaroxaban in a dose-dependent manner. the inhibitory effect lasted for about eight to 12 hours. Observations suggest that thrombin generation is inhibited up to 24 hours, making once-daily dosing possible. Although rivaroxaban affects the PT, aPTT and anti-Xa activity, monitoring of these parameters to determine effective levels does not appear to be necessary at this time. PT may be more sensitive to rivaroxaban and could be used for assessing rivaroxaban exposure, if coagulation monitoring is necessary.

The availability of an antidote is important for anticoagulants, especially in case of overdose situations. Although there are no known antidotes for rivaroxaban at this time, preliminary in vitro studies suggest that recombinant Factor VIIa can partially reverse the effects of rivaroxaban in platelet-rich plasma obtained from healthy subjects.

**Drug Interactions**

Only a few studies have examined the potential for drug interactions with rivaroxaban. Rivaroxaban absorption after a single 30-mg dose was evaluated in one study. Neither antacids (10 mL) nor ranitidine (150 mg twice daily for three days) affected the plasma concentration-time profile. Aspirin and naproxen did not appear to affect rivaroxaban pharmacokinetics or pharmacodynamics in a clinically significant manner. Bleeding time, compared with either naproxen or aspirin alone, was significantly prolonged with combined naproxen-rivaroxaban therapy ($p=0.017$), and slightly prolonged with concurrent aspirin-rivaroxaban. The administration of rivaroxaban with clopidogrel in 27 healthy male subjects did not affect the tolerability or pharmacokinetics of rivaroxaban, inhibition of FXa activity, prolongation of PT, or platelet aggregation. However, similar to combination therapy with naproxen, bleeding time was significantly prolonged in four subjects receiving rivaroxaban with clopidogrel. Rivaroxaban did not significantly interact with digoxin in one study.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Indication</th>
<th>Mechanism of Action</th>
<th>Advantages</th>
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<tbody>
<tr>
<td>Enoxaparin</td>
<td>- DVT/PE prophylaxis.</td>
<td>- Synthetic analog of the antithrombin-binding pentasaccharide found in heparins; specific anti-Xa activity.</td>
<td>- Once daily dosing</td>
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<td>Lovenox</td>
<td>- DVT/PE treatment in conjunction with warfarin sodium for inpatient treatment of acute DVT/PE or for outpatient treatment of acute DVT without PE.</td>
<td>- Unstable angina/Non-Q-wave MI.</td>
<td>- No need for coagulation monitoring</td>
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<tr>
<td>Tinzaparin</td>
<td>- Treatment of acute DVT (PE when administered in conjunction with warfarin sodium.</td>
<td></td>
<td>- Good efficacy</td>
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<tr>
<td>Innohep</td>
<td></td>
<td></td>
<td>- No evidence of thrombo-cytopenia</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>- DVT/PE prophylaxis.</td>
<td>- Synthetic analog of the antithrombin-binding pentasaccharide found in heparins; specific anti-Xa activity.</td>
<td>- Once daily dosing</td>
</tr>
<tr>
<td>Arixtra</td>
<td>- DVT/PE treatment in conjunction with warfarin sodium for inpatient treatment of acute DVT/PE or for outpatient treatment of acute DVT without PE.</td>
<td>- Unstable angina/Non-Q-wave MI.</td>
<td>- No need for coagulation monitoring</td>
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</tbody>
</table>

AF=atrial fibrillation; DVT=deep vein thrombosis; MI=myocardial infarction; PE=pulmonary embolism; SQ=subcutaneous; VTE=venous thromboembolism;
As mentioned earlier, rivaroxaban is metabolized by CYP3A4. Observations suggest that co-administration of rivaroxaban with strong CYP3A4 inhibitors such as systemic azole antifungal agents or protease inhibitors significantly increase rivaroxaban’s pharmacodynamic effects. Many phase II and III trials have excluded patients on strong CYP3A4 inhibitors or who had exposure to these agents within four days prior to randomization.

In general, there appears to be few drug interactions with rivaroxaban at this time. There is the possibility that the combined use of rivaroxaban and other antithrombotic agents such as clopidogrel and aspirin may increase bleeding events. There are no data on the effects of rivaroxaban on other drugs.

**CLINICAL TRIALS**

**Thromboprophylaxis After Major Orthopedic Surgery**

Major orthopedic surgery is associated with a significant risk for thromboembolism. Venographic DVT seven to 14 days following major orthopedic surgery occurs in approximately 40-60 percent of patients if thromboprophylaxis is not used. When evaluating new antithrombotic agents, elective major orthopedic surgery is a useful model to assess safety and efficacy. Once efficacy and safety has been established in this setting, further studies are performed for other indications requiring long-term anticoagulation.

**Total Knee Replacement**

Three major clinical trials have evaluated the efficacy and safety of rivaroxaban compared with enoxaparin for thromboprophylaxis after total knee replacement (TKR) surgery. In a phase II study, patients received either rivaroxaban 2.5, 5, 10, 20, or 30 mg twice daily at meal times or within two hours of food or enoxaparin 30 mg subcutaneously (SQ) every 12 hours. Treatment was continued until mandatory bilateral venography was performed five to nine days after surgery; venography was performed sooner if symptoms of venous thromboembolism (VTE) were present. Of the 621 patients initially randomized, 366 were included in the per protocol analysis (n=70 enoxaparin, n=296 rivaroxaban). The primary efficacy endpoint—a composite of the incidence of proximal and/or distal DVT at screening or confirmed symptomatic events, confirmed non-fatal PE, and all-cause mortal-

<table>
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<th>Table 2. Results of RECORD* Phase III Trials</th>
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<td><strong>Setting</strong></td>
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<td>Record 1</td>
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<td>Record 4</td>
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**DVb=deep vein thrombosis; ENX=enoxaparin; PE=pulmonary embolism; RIV=rivaroxaban**

*Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of Deep Vein Thrombosis and Pulmonary embolism.

†=RRR=relative risk reduction
‡=Not statistically significant
ity during the treatment period—was observed in 23.3 percent to 40.4 percent of patients treated with rivaroxaban, compared with 44.3 percent of patients treated with enoxaparin. There was a lower incidence of the primary endpoint in the rivaroxaban 10 mg and 30 mg bid dose groups compared with enoxaparin. Major bleeding was observed in 1 percent, 0 percent, 1.9 percent, 3.1 percent, and 7.5 percent of patients treated with rivaroxaban 2.5, 5, 10, 20, and 30 mg twice daily, respectively, compared with 1.9 percent of patients treated with enoxaparin. There was a significant dose-response relationship with bleeding, but not efficacy.

The RECORD 3 Trial (REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE) compared the efficacy of rivaroxaban with enoxaparin for thromboprophylaxis after TKR surgery. In this phase III, double-blind trial, patients were randomized to treatment with rivaroxaban 10 mg daily (n=1220) or enoxaparin 40 mg subcutaneously (SQ) daily (n=1239) for a total of 10 to 14 days. The primary outcome was the composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days after surgery. Mandatory bilateral venography was performed on all patients between days 11–15 of therapy. The results of this study and other Phase III trials are summarized in Table 2 (page 43). The primary efficacy outcome was significantly lower with rivaroxaban use (9.6 percent versus 18.9 percent; p<0.001). There was a 9.2 percent absolute risk reduction and a 49 percent relative risk reduction (RRR) in the primary outcome with rivaroxaban (p<0.001). Major VTE, defined as proximal DVT, PE, or VTE-related death, occurred 1 and 2.6 percent of patients in the rivaroxaban and enoxaparin groups, respectively (absolute risk reduction, 1.6 percent; P=0.01). Symptomatic VTE occurred in 0.7 and 2 percent of patients in the rivaroxaban and enoxaparin groups, respectively (absolute risk reduction, 1.6 percent; P=0.01). The authors concluded that rivaroxaban showed superior efficacy for the primary endpoint and similar safety profile to enoxaparin.

**Total Hip Replacement**

Three phase II studies have examined the efficacy and safety of rivaroxaban after total hip replacement surgery (THR). In these trials, rivaroxaban was started six to eight hours after surgery, while enoxaparin 40 mg SQ daily was started the evening before surgery; both drugs were continued for five to nine days. Routine bilateral venography was performed the day after the last dose of study drug or sooner if symptoms were present. The primary efficacy endpoint was the incidence of any DVT, nonfatal PE, and all-cause mortality within a period of up to nine days after surgery. The RECORD 3 investigators concluded that rivaroxaban was superior to enoxaparin for thromboprophylaxis after TKR, with similar rates of bleeding.

RECORD 4 also compared rivaroxaban with SQ enoxaparin for thromboprophylaxis after total knee replacement. Although this study has yet to be published, the results were presented at the European Federation of National Associations of Orthopaedics and Traumatology (EFORT) May 29, 2008, meeting. Patients received either rivaroxaban 10 mg daily or enoxaparin 30 mg SQ twice daily until the day before venography. Mandatory bilateral venography was performed on all patients between day 11 and day 15 of therapy. The primary efficacy endpoint was any DVT, nonfatal PE, and all-cause mortality up to day 13±4. The primary efficacy endpoint occurred in 6.9 percent (67/965) of rivaroxaban-treated patients and 10.1 percent (97/959) of enoxaparin-treated patients (p=0.012). There was no statistical difference in rates of major VTE or symptomatic VTE. Rates of major bleeding were similar (0.7 percent rivaroxaban versus 0.3 percent enoxaparin; p=0.110). The authors concluded that rivaroxaban showed superior efficacy for the primary endpoint and similar safety profile to enoxaparin.
to 14.9 percent rivaroxaban daily, compared with 25.2 percent of patients who received enoxaparin. Although there was a trend toward lower incidence in primary efficacy endpoint with increasing doses of rivaroxaban, this difference in dose-response relationship did not reach statistical significance (p=0.0852). Major bleeding occurred in 0.7 to 5.1 percent of patients receiving rivaroxaban, compared with 1.9 percent of patients receiving enoxaparin. While these phase II trials showed no significant dose response for efficacy, there was a significant dose-response relationship for bleeding. Moreover, these phase II trials provided evidence to pursue further investigations.

Three phase II studies have examined the efficacy and safety of rivaroxaban after total hip replacement surgery (THR).

The RECORD 1 trial evaluated the efficacy and safety of rivaroxaban for extended thromboprophylaxis after elective THR. This phase III, randomized, double-blind trial had two treatment groups: rivaroxaban 10 mg daily, or enoxaparin 40 mg SQ daily for 35 days. Mandatory, bilateral venography was performed the day after completing drug therapy. The primary efficacy endpoint was the composite of any DVT, non-fatal PE, and all-cause mortality up to 36 days (range, 30–42). The primary endpoint occurred in 1.1 percent (18/1595) in the rivaroxaban group, and 3.7 percent (58/1558) in the enoxaparin group. There was a 70 percent relative risk reduction in the primary endpoint (P<0.001). The incidence of major bleeding was similar at 0.3 and 0.1 percent in the rivaroxaban and enoxaparin groups, respectively (p=0.18). The combined rate of major and clinically relevant non-major bleeding events was 3.2 percent in the rivaroxaban group and 2.5 percent in the enoxaparin group, not statistically significant. The authors concluded that rivaroxaban was significantly more effective for extended thromboprophylaxis after elective total hip arthroplasty than enoxaparin.

RECORD 2 compared extended duration rivaroxaban with short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty. The study design was similar to RECORD 1. In this randomized, phase III, double-blind trial, patients received enoxaparin 40 mg SQ daily for 10 to 14 days followed by placebo until day 354 (n=1257) or oral rivaroxaban 10 mg daily for 354 days (n=1252). Mandatory, bilateral venography was performed the day after completing drug therapy. The primary efficacy outcome was a composite of any DVT, non-fatal PE, and all-cause mortality up to day 30–42. The primary efficacy outcome occurred in significantly fewer patients receiving extended thromboprophylaxis with rivaroxaban (2 percent) than in those receiving short-term enoxaparin (9.3 percent; p<0.0001). There was a 79 percent relative risk reduction with rivaroxaban use. The incidence of major bleeding events was 0.1 percent in both groups, and there was no difference in non-major bleeding events. The authors concluded that extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin.

TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM

The efficacy of rivaroxaban for the treatment of DVT was evaluated in two phase II studies. The Oral Direct Factor Xa Inhibitor in Patient With Acute Symptomatic Deep Vein Thrombois (ODIXa-DVT) trial was a partially blinded, parallel-group study. Patients with a confirmed diagnosis of symptomatic proximal DVT by complete compression ultrasound (CUS) without pulmonary embolism were eligible. Patients received at least 12 weeks of anticoagulant therapy with either blinded doses of rivaroxaban (10 mg twice daily, 20 mg twice daily, 30 mg twice daily, or 40 mg once daily, with food) or standard open-label anticoagulant therapy with enoxaparin 1 mg/kg twice daily vitamin K antagonists (VKA). The primary efficacy outcome was an improvement in thrombotic burden at mean 21 days without confirmed symptomatic extension or recurrent DVT, confirmed symptomatic PE, or VTE-related death. Of 636 patients enrolled, 613 were randomized. The primary efficacy endpoint was observed in 53 (53 percent) patients who received rivaroxaban 10 mg twice daily, 58 (59.2 percent) patients who received rivaroxaban 20 mg twice daily, 62 (56.9 percent) patients who received rivaroxaban 30 mg twice daily, and 49 (43.8 percent) patients who received rivaroxaban 40 mg
once daily. In those who received traditional anticoagulation therapy, the primary endpoint was observed in 50 (45.9 percent). The primary safety outcome, the incidence of major bleeding, was observed in 1.7 percent to 3.3 percent of patients receiving rivaroxaban. No major bleeding were reported in the enoxaparin/VKA group.

The EINSTEIN-DVT study also compared rivaroxaban with standard therapy consisting of heparin/LMWH and VKA for the treatment of patients with acute, symptomatic, DVT without PE. The study design was very similar to ODIXa-DVT. Patients received once-daily dosing of rivaroxaban 20 mg, 30 mg, or 40 mg or standard therapy with heparin (5000 U bolus and 1250 U/h infusion), tinzaparin (175 U/kg SQ daily), or enoxaparin (1.5 mg/kg SQ daily or 1 mg/kg SQ twice daily) followed by vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, and fluindione). The primary efficacy outcome was the composite of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE, and asymptomatic deterioration in thrombotic burden on ultrasonography or perfusion lung scan at day 84 compared with baseline. The primary efficacy outcome was observed in 5.4 percent to 6.6 percent in the rivaroxaban group, and 9.9 percent in the standard therapy group. Symptomatic recurrent VTE ranged between 1.7 percent to 3.6 percent for the rivaroxaban-treated patients, and 6.9 percent for the standard therapy group. The principal safety outcome was the composite of major and clinically relevant, non-major bleeding up to 48 hours after treatment cessation. The incidence of the principal safety outcome was observed in 5.9 percent, 6 percent, 2.2 percent, and 8.8 percent of patients who received rivaroxaban 20 mg, 30 mg, 40 mg, and standard therapy, respectively. Major bleeding occurred in three patients (0.7 percent) receiving rivaroxaban, and in two patients (1.5 percent) receiving standard therapy. There was no statistical difference in rates of major bleeding or clinically relevant, non-major bleeding. The study did not find a dose trend for the primacy efficacy outcome in the rivaroxaban group. The authors concluded that rivaroxaban, given daily, was as effective and safe as standard therapy for the treatment of acute, symptomatic DVT.

OTHER STUDIES AND ONGOING CLINICAL TRIALS
The ATLAS ACS TIMI 46 Trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects With Acute Coronary Syndrome) was a phase II trial that evaluated the safety and efficacy of adding rivaroxaban to aspirin or thienopyridine/aspirin in patients with acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina). The results of this study were presented as a late-breaking clinical trial at the 2008 American Heart Association Meeting in New Orleans. Patients were randomized to placebo or four different doses of rivaroxaban. The primary efficacy endpoint was a composite of death, heart attack, stroke and severe ischemia revascularization; no significant risk reduction was noted with rivaroxaban for the primary efficacy endpoint (p=0.10). For the secondary endpoint—a composite of death, heart attack or stroke—there was a significant risk reduction for rivaroxaban (p=0.028). The primary safety endpoint was a composite of major bleeding, minor bleeding and any bleeding requiring mediation attention. Bleeding risk increased with increasing doses; 6.1 percent with rivaroxaban 5 mg, 15.3 percent of those receiving rivaroxaban 20 mg daily, and 3.3 percent placebo.

Numerous trials of rivaroxaban are currently ongoing. Large phase III trials designed to evaluate the efficacy of rivaroxaban for the acute treatment of VTE and for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation are underway. The results of these trials will help to define the efficacy and safety of rivaroxaban as an anticoagulant for a broad list of indications.

ADVERSE EFFECTS
The major safety issue with rivaroxaban, like other anticoagulants, is the risk of bleeding. Bleeding rates have been discussed with the individual studies; in general, the rate of major bleeding appears to be similar to currently available anticoagulants. There is particular interest in monitoring the potential for liver toxicity of rivaroxaban. This stems from the fact that the marketing and further development of another promising oral anticoagulant, the direct thrombin inhibitor ximelagatan, was halted due to hepatotoxicity. Elevations
of ALT and AST of greater than three times the upper limit of normal (ULN) have been noted in all published studies of rivaroxaban. The incidence of treatment-emergent elevations of ALT greater than three times the ULN ranged from 1.9 percent to 4.3 percent in one study, compared with 21.6 percent in the enoxaparin/VKA groups; three patients stopped rivaroxaban due to elevated liver enzymes. In another study, ALT and AST greater than three times the ULN occurred in 11.2 percent and 8.8 percent of patients in the enoxaparin group, respectively, compared with 3.9 percent minus 6.4 percent, and 3.3 percent minus 8.3 percent, respectively, in the rivaroxaban group. One patient died due to acute liver failure, but the death was deemed to be due to fatal hepatitis B infection. In other studies, elevations in liver enzymes were similar to enoxaparin. Completed Phase III trials provide information on adverse effects with rivaroxaban. In RECORD 1, rivaroxaban and enoxaparin were associated with similar number of adverse events. Elevation of ALT occurred in 2–3 percent in each group and all events resolved by the end of the follow-up period. In RECORD 3, the adverse-event profiles of each agent was similar. The most commonly reported adverse events in both groups were nausea, vomiting and constipation. One study showed no effect on the QT-c from rivaroxaban.

**DOSEING**

Based on the available data, rivaroxaban can be administered at a fixed dose either once or twice daily. The most likely dose of rivaroxaban for thromboprophylaxis after major orthopedic surgery is 10 mg daily. The optimal dose for the acute treatment of VTE has yet to be determined.

**APIXABAN**

**Pharmacology**

Apixaban is an orally active, highly selective, reversible, direct FXa inhibitor. It is currently undergoing phase II and III development for a variety of indications. Apixaban is the follow-up compound to razaxaban, another FXa inhibitor, and is believed to have superior safety. Development of razaxaban was halted due to an excess of major bleeding. Apixaban has greater than 30,000 fold selectivity for FXa over other coagulation proteases.

**Pharmacokinetics**

The pharmacokinetic properties of apixaban have been evaluated. Preclinical studies showed that apixaban has a small volume of distribution, a low systemic clearance and good oral bioavailability. Oral bioavailability is greater than 50 percent. Peak plasma levels are achieved in about three hours. The mean terminal half-life is eight to 15 hours allowing for either once or twice daily. Apixaban has multiple elimination pathways, including renal and fecal excretion. Due to its multivariate clearance and elimination, apixaban may have less accumulation in renal dysfunction; in fact, approximately 25 percent of the drug is excreted by the kidneys. This is a potential advantage over other orally available FXa inhibitors. There is also a minimal potential for drug-drug interactions.

**CLINICAL TRIALS**

**Thromboprophylaxis After Major Orthopedic Surgery**

The Apixaban PROphylaxis in Patients undergoing tOtal knee replacement Surgery (APPROPOS) was a phase IIb, randomized, eight-arm, parallel group, multi-center study that compared six oral doses of apixaban (5, 10 or 20 mg/day given as a single or twice-daily divided dose) with open-label enoxaparin 30 mg twice daily, or warfarin alone titrated to an INR of 1.8–3. Both apixaban and enoxaparin were initiated 12-24 hours after TKR surgery, and warfarin was started the evening of surgery. Venography was performed after 12 ± 2 days of prophylaxis. The primary efficacy endpoint was a composite of VTE events (including asymptomatic and symptomatic DVT, symptomatic non-fatal PE) and death from any cause. The primary efficacy endpoint was 9 percent, with apixaban 2.5 mg twice daily and 11.3 percent with apixaban 5 mg daily, compared with 15.6 percent and 26.6 percent for enoxaparin and warfarin, respectively. While there were no major bleeding events in the enoxaparin or warfarin groups, major bleeding occurred in 0 percent to 3.3 percent of patients in the apixaban groups. All major bleeding events were associated with knee surgery (hematoma and ecchymoses), with the exception of one case each
of gastrointestinal bleed and hematuria. Minor bleeding during apixaban, enoxaparin and warfarin treatment were 0.7 percent to 7.2 percent, 4 percent and 5.3 percent, respectively. This study showed that apixaban 2.5 mg twice was the most effective regimen due to comparable point estimate for efficacy and bleeding. Based on this trial, the preferred regimen for phase III evaluation is 2.5 mg BID.

The phase III ADVANCE-1 trial compared apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily for prevention of thrombosis-related events following knee replacement surgery. In this study, the primary efficacy outcome was a composite of symptomatic and asymptomatic DVT, PE and death by any cause after 12 days of treatment. The rate of the primary efficacy endpoint for apixaban was similar to enoxaparin (9 percent versus 8.9 percent, p=0.064), but this study failed to demonstrate the non-inferiority of apixaban compared with enoxaparin. The composite rate of clinically relevant non-major bleeding and major bleeding was significantly less in patients who received apixaban compared with enoxaparin (2.9 percent versus 4.3 percent, p=0.034).

**Treatment of Acute Venous Thromboembolism**

A phase II study evaluated apixaban for the treatment of acute venous thromboembolism. In this randomized, parallel-arm study, patients with acute symptomatic DVT were randomized to treatment with apixaban (5 mg or 10 mg twice daily or 20 mg daily) or standard therapy consisting of either LMWH or fondaparinux initially followed by open-label VKA. The VKA was dosed to achieve an INR of 2-3. Treatment was continued for 84 to 91 days in both groups. Bilateral venous compression ultrasound (CUS) of the legs and perfusion lung scan (PLS) were performed within 36 hours from randomization and at 12 weeks. The primary efficacy outcome—the composite of symptomatic recurrent VTE and deterioration of the thrombotic burden—was assessed by repeat bilateral CUS and PLS. A total of 520 patients were randomized. For apixaban 5 mg twice daily, 10 mg twice daily, 20 mg daily and VKA, the incidence of the primary efficacy endpoint was 6 percent, 0 percent, 5.6 percent, 2.6 percent, and 4.2 percent, respectively. The principle safety outcome was a composite of major and clinical relevant non-major bleeding. For the same treatment groups, the principle safety outcome rates were 8.6 percent, 4.5 percent, 7.3 percent, and 7.9 percent, respectively. Rates of symptomatic VTE were 2.6 percent, 3.2 percent, 1.7 percent, and 2.5 percent, respectively, and the rates of major bleeding were 0.8 percent, 0 percent, 0.8 percent, and 0 percent, respectively.

**Other Studies and Ongoing Clinical Trials**

A Phase II trial called APPRAISE-1 has been completed, and the results were presented at the European Society of Cardiology Congress 2008. The study has not yet been published. APPRAISE-1 studied the safety of apixaban 2.5 mg twice daily, 10 mg daily, 10 mg twice daily and 20 mg daily for six months versus placebo in patients with recent acute coronary syndrome. These patients were clinically stable and were on optimal therapy (all patients were taking aspirin). The primary outcome was major or clinically relevant non-major bleeding and the secondary outcome was death due to cardiovascular causes, myocardial infarction, severe recurrent ischemia or stroke. The apixaban 10 mg twice daily and the 20 mg daily arms were discontinued early due to excess bleeding. Both remaining doses of apixaban resulted in increased bleeding versus placebo (7.9 percent, 5.7 percent, and 3 percent for apixaban 10 mg daily, apixaban 2.5 mg BID and placebo, respectively). However, both doses trended toward a reduction in clinically important recurrent ischemic events compared to placebo (6 percent, 7.6 percent, and 8.7 percent for apixaban 10 mg daily, apixaban 2.5 mg twice daily and placebo, respectively). However the difference was not statistically significant. The efficacy and bleeding results were similar among patients taking aspirin and aspirin plus clopidogrel.

Numerous trials of apixaban are currently ongoing. Despite the results of the ADVANCE-1 trial, ADVANCE-2 will evaluate apixaban 2.5 mg twice daily against enoxaparin 40 mg SQ once daily for thromboprophylaxis after total knee replacement surgery. Other phase III trials are comparing apixaban versus enoxaparin for the prevention of VTE following hip replacement surgery, to evaluate the safety and efficacy of apixaban in acutely ill medical patients and for prevention of VTE in patients with cancer.
The results of these trials will help to define the efficacy and safety of rivaroxaban as an anticoagulant for a broad list of indications.

Adverse Effects
There is less safety data with apixaban because it has not been studied as extensively as rivaroxaban. Only a few studies have been published. In terms of bleeding risk, the rate of major bleeding appears to be similar to currently available anticoagulants. Elevations of liver enzymes (greater three times the ULN) at any time after the start of study drug were low and comparable among groups in one study. Other findings in the apixaban group were three cases of myocardial infarction, five ischemic strokes, one case of Guillain-Barre Syndrome and one possible amyotrophic lateral sclerosis. In the comparator groups, there was only one case of myocardial infarction in a patient receiving warfarin. The authors commented that these neurologic syndromes were probably not related to apixaban therapy.

DISCUSSION
The unmet need for a safe and effective oral anticoagulant has resulted in a number of potential anticoagulant compounds. More than 60 years since the first studies of warfarin as an anticoagulant emerged, several advances in the realm of anticoagulation therapy have been made. The low-molecular weight heparins have allowed for the treatment of DVT in the outpatient setting. Fondaparinux and the direct thrombin inhibitors have opened the door for new anticoagulation targets. Fondaparinux is an indirect FXa inhibitor that requires antithrombin for anticoagulant activity. Fondaparinux also treats DVT in the outpatient setting. Unfortunately, past attempts to develop and market an orally administered anticoagulant other than a vitamin K antagonist such as warfarin have resulted in failure.

Now, the oral, direct FXa inhibitors rivaroxaban and apixaban are in clinical development. Factor Xa is an attractive target for effective anticoagulation because it is the point where the intrinsic and extrinsic coagulation pathways converge, and one FXa molecule catalyzes the formation of approximately 1,000 thrombin molecules. Factor Xa has also been shown to activate clotting over a wider concentration range so the likely therapeutic window should be larger than currently available agents. These agents can be administered either once- or twice-daily as a fixed oral dose. The onset of action is rapid and routine coagulation monitoring does not appear to be necessary. The potential for drug interactions appears to be low. Direct FXa inhibitors appear to be effective in preventing and treating thromboembolism.

Rivaroxaban is further along in clinical development. Phase II trials have shown preliminary evidence of efficacy with rivaroxaban in thromboprophylaxis after major orthopedic surgery and acute treatment of DVT. In phase III trials, rivaroxaban was highly effective for thromboprophylaxis after major orthopedic surgery. In fact, rivaroxaban 10 mg daily was superior to enoxaparin 40 mg daily after total hip and knee replacement surgery. Due to the positive findings of these phase III trials, in September 2008 Health Canada granted marketing approval for rivaroxaban for the prevention of venous blood clots in adult patients undergoing elective hip or knee replacement surgery. The European Commission also granted marketing authorization a month later.

Similarly, preliminary preclinical studies showed that apixaban was effective for thromboprophylaxis after major orthopedic surgery and treatment of acute VTE. In a phase III trial, however, apixaban for the prevention of VTE in patients undergoing total knee replacement did not show non-inferiority compared with enoxaparin. Bristol-Myers Squibb Co., and Pfizer Inc. have agreed to collaborate in the development and commercialization of apixaban. Initially, submission for U.S. regulatory approval of apixaban for prevention of VTE was planned for the second half of 2009. However, Bristol-Myers Squibb and Pfizer will not submit for the indication of VTE prevention.
in 2009 due to the negative findings of the ADVANCE-1 trial. Filings for additional indications may not occur until 2010. Numerous trials are currently underway and will clarify the efficacy and safety of apixaban for the prevention and treatment of thromboembolism.

Despite the promising data, it is still too soon to predict whether these agents will replace VKAs as the oral anticoagulants of choice. The major indication for VKAs at this time is for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation. The efficacy of oral, direct FXa inhibitors for other indications, such as treatment of acute VTE and atrial fibrillation, still need to be clarified. Another important consideration is safety. Another novel, oral anticoagulant ximelagatran, showed promising efficacy; however, the risk of hepatotoxicity became evident after long-term use for indications such as stroke prevention in atrial fibrillation. Both drugs have been studied with short-term use only. The long-term safety and adverse event profiles are yet unclear. If efficacy and safety are proved, oral, direct FXa inhibitors may be an alternative to VKA.

CONCLUSIONS
Oral, direct FXa inhibitors rivaroxaban and apixaban appear to be effective new anticoagulants in clinical development. Both rivaroxaban and apixaban appear to be well-tolerated and effective in preventing VTE after major orthopedic surgery. Rivaroxaban has been approved in Canada and Europe for thromboprophylaxis after major orthopedic surgery. Additional studies are necessary to fully determine their place in the management of arterial and venous thromboses.

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CONTINUING EDUCATION QUIZ
Select the correct answer.

1. In terms of advantages with existing anticoagulants, which of the following statements is FALSE?
   a. Warfarin has been proven efficacy for arterial and venous thromboses.
   b. Unfractionated heparin is fast acting and inexpensive.
   c. Dalteparin can be administered either once or twice daily.
   d. Fondaparinux has been shown to cause heparin induced thrombocytopenia.

2. Which of the following statements is FALSE regarding unfractionated heparin?
   a. Unfractionated heparin requires parenteral administration.
   b. Unfractionated heparin requires clotting test monitoring.
   c. Unfractionated heparin may cause osteoarthritis with prolonged use.
   d. Unfractionated heparin may cause thrombocytopenia.

3. Problems with available anticoagulants include: I. variable intra-patient response to unfractionated heparin; II. multiple drug interactions with warfarin; III. need for parenteral administration with fondaparinux
   a. I only
   b. I and II only
   c. II and III only
   d. II and III

4. What are the characteristics of an “ideal” anticoagulant? I. oral administration; II. narrow therapeutic window; III. rapid onset and offset of activity
   a. I only
   b. I and II only
   c. II and III only
   d. I, II and III

5. Fondaparinux is:
   a. A direct FXa inhibitor
   b. A selective FXa inhibitor
   c. A low-molecular weight heparin
   d. A direct thrombin inhibitor.

6. Factor Xa is an optimal target for anticoagulation because:
   a. It is the point where the extrinsic pathway begins.
   b. It functions only to promote inflammation and coagulation.
   c. It increases thrombin-mediated platelet activation.
   d. It has a narrow therapeutic window.

7. Rivaroxaban: I. is a direct Factor Xa inhibitor; II. is administered orally; III. inhibits free and clot-associated Factor Xa
   a. I only
   b. I and II only
   c. II and III only
   d. I, II and III

8. Which of the following accurately describes rivaroxaban’s pharmacokinetic parameters?
   a. Rivaroxaban is rapidly absorbed within 12 hours.
   b. Maximal concentrations of rivaroxaban are reached within 3-4 days.
   c. Food decreases rivaroxaban’s absorption.
   d. Rivaroxaban is eliminated by both the liver and the kidneys.

9. Rivaroxaban:
   a. Inhibits Factor Xa in a dose-dependent manner.
   b. Requires monitoring with anti-Factor Xa levels.
   c. Is administered twice weekly.
   d. Requires activated partial thromboplastin time (aPTT) monitoring.

10. Which statement is FALSE?
    a. Major orthopedic surgery is associated with a significant risk for thromboembolism.
    b. Venographic DVT seven to 14 days following major orthopedic surgery occurs in approximately 40 percent to 60 percent of patients if thromboprophylaxis is not used.
    c. Venographic DVT seven to 14 days following major orthopedic surgery occurs in approximately 20 percent to 30 percent of patients if thromboprophylaxis is not used.
    d. When evaluating new antithrombotic agents, elective major orthopedic surgery is a useful model to assess safety and efficacy.
11. In the RECORD 3 phase III clinical trial of rivaroxaban after knee replacement surgery,
   a. The primary efficacy outcome was 18.9 percent with rivaroxaban and 9.6 percent with enoxaparin.
   b. The primary efficacy outcome was 9.6 percent with rivaroxaban and 18.9 percent with enoxaparin.
   c. The primary efficacy outcome was 6.9 percent with rivaroxaban and 8.9 percent with enoxaparin.
   d. The primary efficacy outcome was 6.9 percent with rivaroxaban and 19.8 percent with enoxaparin.

12. In the RECORD 4 phase II clinical trial of rivaroxaban after knee replacement surgery,
   a. Rivaroxaban 10 mg daily was compared with enoxaparin 30 mg twice daily.
   b. The primary efficacy endpoint occurred in 6.9 percent of rivaroxaban-treated patients, and 10.1 percent of enoxaparin-treated patients.
   c. Rivaroxaban has a superior safety profile to enoxaparin.
   d. Both A and B are correct.

13. In the RECORD 2 phase III clinical trial of rivaroxaban after hip replacement surgery,
   a. There was a 33 percent relative risk reduction in the symptomatic venous thromboembolism with rivaroxaban.
   b. There was a 79 percent relative risk reduction in the symptomatic venous thromboembolism with rivaroxaban.
   c. There was a 55 percent relative risk reduction in the symptomatic venous thromboembolism with enoxaparin.
   d. There was an 80 percent relative risk reduction in the symptomatic venous thromboembolism with enoxaparin.

14. In the RECORD phase III trials,
   a. There was a higher risk of bleeding with rivaroxaban than enoxaparin.
   b. There was a lower risk of bleeding with rivaroxaban than enoxaparin.
   c. There was a similar risk of bleeding with rivaroxaban and enoxaparin.
   d. There was a higher risk of elevated liver enzymes with rivaroxaban than enoxaparin.

15. Which statement about rivaroxaban is FALSE?
   a. Rivaroxaban can be given either once or twice daily.
   b. Rivaroxaban must be taken on an empty stomach.
   c. Rivaroxaban may interact with protease inhibitors or azole antifungal agents.
   d. Rivaroxaban prolongs the prothrombin time.

16. In the phase II EINSTEIN-DVT trial of rivaroxaban for the treatment of deep vein thrombosis:
   a. The study compared rivaroxaban with standard therapy consisting of fondaparinux and VKA for the treatment of patients with acute, symptomatic, DVT without PE.
   b. The study did not find a dose trend for the primacy efficacy outcome in the rivaroxaban group.
   c. Rivaroxaban was less effective than standard therapy for the treatment of acute, symptomatic DVT.
   d. There was a statistical difference in rates of major bleeding with rivaroxaban.

17. Which statement about rivaroxaban is TRUE?
   a. The dose of rivaroxaban is determined by patient weight.
   b. Rivaroxaban is safe to use in patients with severe liver disease.
   c. The need for dose adjustment based on gender will be unlikely with rivaroxaban.
   d. The half-life of rivaroxaban is longer in young healthy patients.

18. What is the antidote for rivaroxaban?
   a. Vitamin K
   b. Vitamin E
   c. Protamine sulfate
   d. There is no known antidote for rivaroxaban.
19. The APROPOS study concluded that which of the following doses of apixaban is the most effective regimen for prophylaxis against venous thromboembolism?
   a. 2.5 mg BID
   b. 5 mg QD
   c. 5 mg BID
   d. 10 mg QD

20. Which of the following statements is TRUE about ADVANCE-1?
   a. It compared apixaban 2.5mg BID with enoxaparin 40mg SQ daily.
   b. It failed to demonstrate non-inferiority of apixaban versus enoxaparin.
   c. Bristol Myers Squibb and Pfizer will pursue a DVT prophylaxis indication in 2009 based on the results of this trial.
   d. Both the occurrence of the primary efficacy endpoint and clinically relevant non-major bleeding and major bleeding risk was higher in the apixaban group.

Oral, Direct Factor Xa Inhibitors and Thromboembolic Disorders

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Quiz: Shade in your choice
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Quiz: Circle your choice
21. Is this program used to meet your mandatory C.E. requirements?  
   a. yes  b. no
22. Type of pharmacist:  
   a. owner  b. manager  c. employee
23. Age group:  
   a. 21–30  b. 31–40  c. 41–50  d. 51–60  e. Over 60
24. Did this article achieve its stated objectives?  
   a. yes  b. no
25. How much of this program can you apply in practice?  
   a. all  b. some  c. very little  d. none

How long did it take you to complete both the reading and the quiz? ______ minutes

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