continuing education for pharmacists

Volume XXIX, No. 12

Overview of Anticoagulants and the Role of New Oral Agents

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Dr. Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide an overview of the anticoagulant agents that are commonly prescribed for the prevention and treatment of thrombotic events and to discuss two new oral anticoagulant agents.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. demonstrate an understanding of the role that anticoagulants play in the prevention and treatment of thrombotic events;
2. identify the clotting cascade site of action where each anticoagulant exerts activity;
3. list the key prescribing points, safety concerns, and monitoring parameters for each anticoagulant discussed; and
4. recognize the treatment advantages and/or disadvantages for dabigatran and rivaroxaban.

Anticoagulants and Thrombosis

Thrombosis is hypothesized to occur in the cumulative presence of stasis of blood, hypercoagulability of the blood, and damage to the vascular endothelium. Anticoagulants are a class of medications used to treat and prevent thrombotic events that can occur in blood vessels and may lead to myocardial infarction or ischemic stroke. Anticoagulants prevent coagulation or inhibit the blood from clotting. New products have recently been developed and therapy recommendations are continuously changing. It is important for pharmacists to keep up-to-date in this area. The following reflects information current at the time of writing this lesson.

Venous thromboembolism (VTE) may manifest as deep vein thrombosis (DVT), pulmonary embolism (PE), or thrombotic/ischemic stroke. DVT and PE affect an estimated 300,000 to 600,000 people each year in the United States and lead to mortality in 60,000 to 100,000 of these cases. In addition, approximately 33 percent of people with a DVT/PE will have a recurrence within 10 years. Each year, an estimated 700,000 people experience a new or recurrent stroke and 88 percent are ischemic.

Risk factors for the development of VTE include general surgery, major orthopedic surgery, trauma, acute medical illness, advanced age, malignancy, immobility, obesity, and pregnancy. Atrial fibrillation, the most common type of arrhythmia, increases a person's risk of ischemic stroke by five times. An estimated 2.66 million people had atrial fibrillation in 2010 and as many as 12 million will be diagnosed with the condition by 2050.

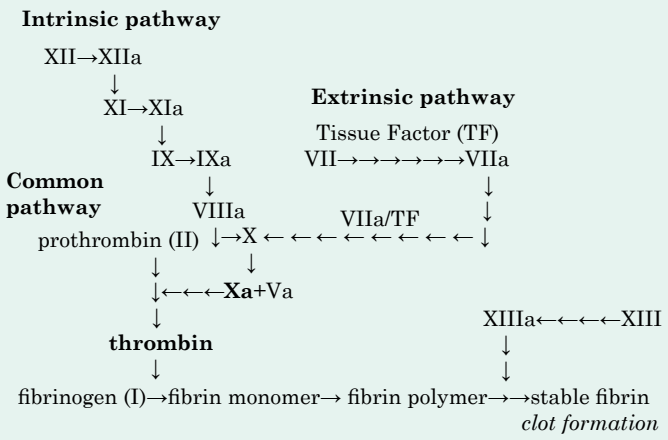
Anticoagulants are a vital tool in preventing disability and mortality in affected patients. However, they are not prescribed without risk and can lead to minor or life-threatening bleeding. Most traditional anticoagulants are generally dosed according to weight, are administered by injection and require routine coagulation monitoring. For these reasons, the Institute for Safe Medication Practices (ISMP) has collectively classified anticoagulants as "high alert medications" which means that these medications, when used in error, bear a heightened risk of causing patient harm.

Unfractionated heparin (UFH), low molecular weight heparins (LMWH), fondaparinux, and warfarin are currently in use for the prevention of the thrombotic events discussed in this lesson. Following a brief review of these agents, the focus of this lesson will be on two new oral anticoagulant agents, which have been approved for marketing, and may offer some treatment and monitoring advantages. The review of each agent may not be comprehensive and, therefore, readers are encouraged to read each product's Prescribing Information leaflet and other published references for full details, as well as review the clinical trials that have been summarized in this lesson.

Clotting Cascade

Before discussing each agent, it is pertinent to review the series of events that occur in response to tissue injury initiating coagulation or clot formation. Each agent or class of agents will target different sites within the clotting cascade (Figure 1). In the first step, also called *initiation*, the physiologic initiator of clotting, tissue factor (TF), is released in response to tissue damage. TF forms a complex with factor VIIa (FVIIa) via the extrinsic

Figure 1
Simplified clotting cascade



pathway and creates a TF-FVIIa complex. The intrinsic pathway is notable for the conversion of factor XII to factor XIIa, leading to the conversion of factor XI to factor XIa which ultimately results in activated factor IX. The TF-FVIIa complex activates factor X (FX), either directly or indirectly, via activation of factor IX. The activation of FX is the point in the cascade where the extrinsic and intrinsic pathways join as the common pathway. Factor Xa, in the presence of cofactor factor Va and phospholipids, forms a prothrombinase complex which converts prothrombin to thrombin. This is noteworthy as following the activation of factor Xa, thrombin, the final enzyme in the clotting cascade, is created.

In the next step, thrombin activates platelets and cofactors V and VII. Coagulation factors and cofactors assemble on the surface of activated platelets. This second major step is appropriately called *amplification* as through multiple feedback loops, the process is amplified and more thrombin and activated platelets are created.

In the third and final step, termed *propagation*, thrombin converts fibrinogen to fibrin followed by clot stabilization.

Traditional Anticoagulants

Unfractionated heparin (UFH), derived from pork, was discovered in the early 1900s, and is a large molecule with a molecular weight ranging from 5,000 to 30,000 daltons. Heparin is indicated for the prophylaxis and treatment of thromboembolic disorders, but also has an anticoagulant role in various cardiovascular conditions. It exerts its action by binding strongly to the protein, antithrombin III, which potentiates its activation. This results in the inactivation of thrombin and other factors involved in clotting, including factor X.

Because heparin is a large molecule, it possesses a variable dose response and also interacts with platelets. Its action is unpredictable and its use requires routine coagulation and frequent dosing adjustments. Heparin may be administered by either the subcutaneous or intravenous route, depending on the prescribed dose and indication for its use. Favorable pharmacodynamics of UFH include an almost immediate anticoagulation effect within 20 to 30 minutes, and a short half-life of one to two hours.

Protamine sulfate is an effective antidote for heparin. It acts by binding to heparin sodium and creating a stable salt complex neutralizing the anticoagulant effect. Routine monitoring consists of hemoglobin, hematocrit, signs of bleeding, and activated partial thromboplastin time (aPTT) or antifactor Xa activity levels. Thrombocytopenia has been reported to occur at an incidence of up to 30 percent, but may occur without clinical significance. However, immunologically mediated heparin-induced thrombocytopenia (HIT) may occur in 1 to 2 percent of patients. Immune mediated HIT should be suspected when the platelet counts falls >50 percent from baseline, even if the absolute count remains greater than 150,000. This complication generally occurs four to 10 days after initiation of therapy, and is a life-threatening complication. Therefore, platelet count monitoring is also recommended for patients in several instances: (1) those receiving therapeutic doses of heparin; (2) postoperative antithrombotic prophylaxis; (3) if the patient has received heparin within the past 100 days; (4) if pre-exposure is uncertain; or (5) if anaphylactoid reaction to heparin occurs. Dosing adjustments for hepatic and renal impairment are not necessary, as the dose is adjusted according to aPTT or anti-Xa activity.

Over the past 20 years, **low molecular weight heparins** (LMWHs) were added to the arsenal of anticoagulants and offered a safe and effective alternative to UFH. LMWHs on the market in the U.S. at the time of writing this lesson include: dalteparin (Fragmin®), enoxaparin (Lovenox®), and tinzaparin (Innohep®). They are all administered subcutaneously. These agents are derived from heparin with either chemical or enzymatic depolymerization resulting in a molecule of only 1,000-10,000 daltons. They have the same mechanism of action as UFH, but inhibit thrombin to a lesser degree, and inhibit factor Xa to a greater degree. In addition, low molecular weight heparins bind less strongly to proteins, have enhanced bioavailability, and interact less with platelets. Hence, these "leaner" anticoagulants offer predictable blood levels, less frequent dosing, and lower likelihood of bleeding.

All three agents are contraindicated in patients with a history of hypersensitivity to heparin. Tinzaparin is contraindicated in any patient with current or history of HIT. Enoxaparin and dalteparin are contraindicated in patients with thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in the presence

Table 1
Warning: spinal or epidural hematoma

Epidural or spinal hematomas may occur in patients who are anticoagulated with any of the agents discussed in this lesson and are receiving neuraxial anesthesia (spinal, epidural, or caudal blocks) or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery

Providers must consider the benefits and risks before initiating neuraxial intervention in patients' anticoagulated or to be anticoagulated for thromboprophylaxis.

The following guidance is available for the select agents to minimize the associated risks:

Warfarin (Coumadin®)*: In general, therapy should be stopped 4-5 days before surgery and INR must be measured prior to initiating neuraxial anesthesia.
Rivaroxaban (Xarelto®)**: Epidural catheter should not be removed earlier than 18 hours after the last administration of Xarelto. The next Xarelto dose is not to be administered earlier than 6 hours after the removal of the catheter. If spinal puncture occurs, the administration of Xarelto is to be delayed by 24 hours.
Dabigatran (Pradaxa®)**: Discontinue Pradaxa 1-2 days (CrCl >50ml/min) or 3-5 days (CrCl< 50ml/min) before invasive or surgical procedures. Consider longer times for patients undergoing major surgery, spinal puncture or placement of a spinal or epidural catheter port in whom complete hemostasis may be required.

*Recommendations per American Society of Regional Anesthesia and Pain Medicine (ASRA) and may differ from European guidelines
**Recommendations per product Prescribing Information

of these agents.

LMWHs, as well as other anticoagulants, carry a warning box regarding spinal or epidural hematoma when used in conjunction with neuraxial anesthesia (spinal, epidural, or caudal blocks) or spinal puncture (Table 1).

Per the American College of Chest Physicians (CHEST) practice guidelines, routine coagulation monitoring in patients treated with LMWHs is not recommended except for pregnant women treated with therapeutic doses (versus prophylaxis doses). Patient monitoring should still consist of CBC with platelet count, presence of occult blood, and serum creatinine, as the dose of LMWHs must be adjusted in patients with severe renal impairment (creatinine clearance [CrCl] <30ml/min). The CHEST guidelines also suggest the use of UFH over LMWHs for patients with creatinine CrCl <30ml/min who require therapeutic anticoagulation. Protamine sulfate may be utilized to partially reverse the effects of LMWHs, but antifactor Xa activity is never completely neutralized.

Fondaparinux (Arixtra®) is an injectable factor Xa inhibitor that is also prescribed for the prevention and treatment of VTE. It differs from LMWHs in that it is not derived from porcine UFH and is a synthetic pentasaccharide that causes an antithrombin III-mediated selective inhibition of factor Xa. It may be used off-label for the prophylaxis of DVT in patients with a history of HIT, but is contraindicated in thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in its presence. Fondaparinux is administered subcutaneously, and is contraindicated in patients with severe renal impairment (CrCl < 30ml/min). Prophylaxis dosing in patients weighing less than 50kg is also contraindicated. As with other anticoagulants, bleeding is the major adverse event. Monitoring parameters includes CBC, serum creatinine, and occult blood testing of stools. There is no specific antidote for fondaparinux.

Warfarin (vitamin K antagonist, Coumadin®) is an oral anticoagulant that acts primarily by inhibiting the vitamin K dependent synthesis of biologically active forms of the clotting factors II, VII, IX, and X. For the prophylaxis and treatment of thromboembolic events and embolic complications arising from atrial fibrillation, it is prescribed in conjunction with either UFH or LMWH. Because warfarin's full therapeutic effect is dependent on the depletion of vitamin K stores, it has a delayed peak effect of five to seven days which is measured by the International Normalized Ratio (INR). Once the patient reaches the desired INR, the UFH or LMWH may be discontinued.

Warfarin possesses a narrow therapeutic window with wide dosing variability. Vitamin K intake from the diet, hepatic function, age, and nutritional status are all factors that contribute to dosing inconsistencies.

In addition, warfarin is a substrate and inhibitor of the CYP transport system and is involved in numerous drug interactions. Thus, its use requires continuous outpatient clinical monitoring. This leads not only to increases in the utilization of healthcare resources, but also places an additional burden on the patient that may compromise compliance. Monitoring consists of prothrombin time, hematocrit, and INR. Although there are no specific recommendations for dose adjustments in renal and hepatic disease, the effects at usual doses may be enhanced in obstructive jaundice due to reduced vitamin K absorption. Also, patients with hepatitis or cirrhosis have decreased production of vitamin K dependent clotting factors and should be monitored closely. Vitamin K may be

Table 2
Storage and handling requirements for dabigatran (Pradaxa®) capsules**

Due to the potential for product breakdown from moisture and loss of potency, **Pradaxa® capsules should only be dispensed and stored in the original bottle or blister package and patients should be aware of the specific handling requirements.** New data indicates that once a bottle of Pradaxa® is opened, it may be used for up to **4 months**. Only one bottle should be opened at a time.

Additional Information for Healthcare Professionals

- Tell patients it is important to follow the special storage and handling requirements included in the *Medication Guide* for Pradaxa® and that Pradaxa® should be stored at room temperature.
- Tell patients that Pradaxa® must be kept in the original bottle or blister package to protect from moisture. The bottle contains a dessicant in the cap, and the blister package protects unopened pills from moisture.
- Tell patients that Pradaxa® capsules must NOT be stored in pill boxes or pill organizers.
- Pharmacists should only dispense Pradaxa® in the original manufacturer bottle with the original dessicant cap. Do not repackage Pradaxa® capsules in standard amber pharmacy vials.
- Pharmacists should not open the Pradaxa® bottle when dispensing. When more than one bottle is dispensed, tell the patient to only open one bottle at a time.
- Pharmacists should place an auxiliary expiration label on the bottle and instruct the patients to date the bottle to expire 4 months after opening.

**Excerpt from FDA Drug Safety Communication dated 03/29/2011 along with PI updated November 2011

administered orally or parenterally to reverse the effects of warfarin.

Direct Thrombin Inhibitors

Direct thrombin inhibitors are a class of anticoagulants that bind directly to thrombin and block its interaction with its substrates.

Thrombin is central in the clotting cascade, as previously discussed. It is responsible for converting soluble fibrinogen to fibrin, and activating other factors that lead to the generation of more thrombin and stimulate platelets. Additionally, once fibrinogen is converted to fibrin, it favors the formation of cross-linked bonds which stabilize the clot. Recall that heparins inhibit thrombin indirectly by first catalyzing the function of antithrombin. Heparins are only able to bind to soluble thrombin via one of three available binding sites by first creating a heparin-antithrombin complex. The heparin-antithrombin complex cannot bind to fibrin-bound thrombin. This is unfavorable as fibrin-bound thrombin triggers further thrombus growth. On the other hand, direct thrombin inhibitors' activity is independent of antithrombin and can bind to both soluble thrombin and fibrin bound thrombin.

Prior to 2010, only injectable direct thrombin inhibitors were available, and primarily used for short term anticoagulation in hospitalized patients with heparin-induced thrombocytopenia, or in association with percutaneous coronary intervention (PCI). In 2010, dabigatran (Pradaxa®), an oral direct thrombin inhibitor, was approved.

Dabigatran (Pradaxa®)

Dabigatran (Pradaxa®) is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is the first new oral anticoagulant to become available for clinical use in over 50 years. Unlike warfarin, dabigatran has a rapid onset of therapeutic action, and has an established dose of 150mg twice daily (with or without food) for patients with normal renal function. Patients with an estimated CrCl of 15 to 30ml/min should only receive 75mg twice daily. There are no dosing recommendations available for patients with an estimated CrCl less than 15ml/min or on dialysis. Administration of dabigatran in patients with moderate hepatic impairment does not require dosing adjustments.

The absolute bioavailability of dabigatran is only 3 to 7 percent, and it achieves maximal plasma concentration after one to two hours which coincides with its rapid onset of action. The capsules should not be broken, chewed, or opened before administration. Doing so increases the bioavailability to 75 percent which greatly impacts the intended exposure amount. It is primarily eliminated through the urine. The capsules should only be stored and dispensed in the original bottle or blister package in order to minimize exposure to moisture and potential for breakdown. Once the bottle is opened, it may be used for up to four months. Table 2 contains important storage information.

The half-life in subjects with normal renal function is 12 to 17 hours. Dabigatran is not a substrate or inhibitor of cytochrome P (CYP) 450 enzymes. Alternatively, the concomitant use of dabigatran with P-glycoprotein (P-gp) inducers, such as rifampin, reduces exposure to dabigatran and should be avoided. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran, compared to that seen with each factor alone. Therefore, in patients with moderate renal impairment (CrCl 30-50ml/min) where concomitant use of dronedarone and systemic ketoconazole is desired, prescribers should consider reducing the dose to 75mg twice daily. The use of Pradaxa and P-gp inhibitors in patients with severe renal impairment should be avoided. Co-administration with an antacid, H2 antagonist, or proton pump inhibitor may decrease dabigatran concentration. Therefore, it is suggested to administer this

medication two hours before acid suppressors.

Dabigatran increases the risk of bleeding and can cause significant, and sometimes fatal, bleeding. As with other anticoagulants, it is contraindicated in patients with active pathological bleeding or a history of serious hypersensitivity reactions. Caution is advised when taking dabigatran with other medications that increase the risk of bleeding such as anti-platelets, heparin, fibrinolytic therapy, and chronic use of NSAIDs. Table 1 has additional information regarding the black box warning for spinal or epidural hematomas.

There is no specific antidote for dabigatran. Supportive therapy for severe hemorrhage may include transfusions of fresh frozen plasma, packed red blood cells, or surgical intervention if appropriate. Administering activated charcoal within two hours of dosing has been suggested to reduce absorption. Although there is little experience with dialysis, data suggests that dialyzing can remove 60 percent of the drug.

Following the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, dabigatran was approved at a fixed dose of 150mg twice daily. The primary study outcome was stroke or systemic embolism, while the primary safety outcome was major hemorrhage. Stroke or systemic embolism occurred in 1.53 percent of patients per year receiving 110mg of dabigatran, 1.11 percent per year receiving 150mg of dabigatran, and 1.69 percent per year of those receiving warfarin (dose adjusted for INR 2.0 to 3.0). Both doses of dabigatran were noninferior to warfarin ($P<0.001$), while the 150mg dose was deemed superior to warfarin ($P<0.001$).

The rates of hemorrhagic stroke were also lowest with dabigatran 150mg at 0.10 percent per year compared with 0.12 percent per year in the dabigatran 110mg and 0.38 percent per year in the warfarin group. This reduction in intracranial hemorrhage, absent of a reduction in the efficacy against ischemic stroke, suggests an important advantage of dabigatran.

With respect to major bleeding, the 110mg of dabigatran was superior to warfarin, while the 150mg dose was similar to warfarin. The study did result in a significantly higher rate of major gastrointestinal bleeding at the 150mg dose of dabigatran compared to warfarin. In addition, patients on dabigatran had increased gastrointestinal adverse reactions including dyspepsia, abdominal pain or discomfort, and gastritis-like symptoms such as GERD, esophagitis, and gastrointestinal ulcer. The authors of the study suggested this increase may be associated with the formulation. The capsule contains dabigatran-coated pellets with a tartaric acid core resulting in increased acidity. The rates of myocardial infaction were higher with both groups receiving dabigatran than with warfarin. The authors are unclear as to the reason. In the RE-LY study, less than 0.1 percent of patients experienced drug hypersensitivity or anaphylaxis.

While both 110mg and 150mg would have been considered safe and effective if studied alone in comparison with warfarin, FDA decided to only approve the 150mg dose. The superiority of the 150mg dose for reducing strokes and embolic stroke was compelling, and the FDA failed to identify a group that would benefit from the lower dose when the risk-benefit assessment was applied. It was decided that even the harms of nonfatal, extracranial bleeding did not exceed the significant debilitation and mortality that may be associated with a stroke.

In 2011, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) produced a focused update for the guidelines on the management of patients with atrial fibrillation regarding the use of dabigatran. The task force published the following *Class I* recommendation: dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent atrial fibrillation and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl < 15ml/min) or advanced liver disease (impaired baseline clotting function). This *Class I* recommendation indicates that the benefit of treatment far exceeds the risk, and treatment is considered effective and useful following evidence from a single randomized trial.

The cost of Pradaxa® per month is approximately $240, while warfarin plus laboratory monitoring would cost about $80.

Table 3 includes information on switching dabigatran to or from other anticoagulants.

Rivaroxaban (Xarelto®)

Rivaroxaban (Xarelto®) is the first oral factor Xa inhibitor available in the U.S. It was approved in July 2011 for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery. In November 2011, rivaroxaban was approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

For DVT prophylaxis, the recommended dose is 10mg daily with or without food. Once hemostasis has been established, the first dose should be administered at least six to 10 hours after surgery. For patients undergoing hip replacement surgery, rivaroxaban should be continued for 35 days. Only 12 days was studied for post knee replacement surgery. For these indications, rivaroxaban use should be avoided in patients with severe renal impairment (CrCl <30ml/min). It may be used for patients with CrCl 30-50ml/min, but these patients should be monitored for signs or symptoms of blood loss.

For nonvalvular atrial fibrillation in patients with CrCl >50ml/min, the recommended dose is 20mg once daily with the evening

Table 3
Converting anticoagulation therapy

When converting FROM warfarin therapy TO dabigatran (Pradaxa®): Discontinue warfarin and start Pradaxa when the INR is below 2.0
When converting FROM Pradaxa® TO warfarin:
For CrCl> 50ml/min, start warfarin 3 days before discontinuing Pradaxa®
For CrCl 30-50ml/min, start warfarin 2 days before discontinuing Pradaxa®
For CrCl 15-30ml/min, start warfarin 1 day before discontinuing Pradaxa®
For CrCl <15ml/min, no recommendations available
When converting FROM parenteral anticoagulant TO Pradaxa®: Start Pradaxa 0-2 hours before the time that the next dose of parenteral drug was to have been administered, or at the time of discontinuation of continually administered UFH
When converting FROM Pradaxa® TO parenteral anticoagulant: Wait 12 hours (CrCl ≥30) or 24 hours (CrCl<30ml/min) after last dose of Pradaxa® before initiating parenteral anticoagulant
When converting FROM warfarin TO rivaroxaban (Xarelto®): Discontinue warfarin and start Xarelto® as soon as INR is below 3.0
When converting FROM Xarelto® TO warfarin: Discontinue Xarelto® and begin both warfarin and a parenteral anticoagulant. (Xarelto® affects INR, therefore co-administration of Xarelto® and warfarin may lead to inaccurate INR measurements.) The parenteral anticoagulant may be discontinued when the desired INR is reached.
When converting FROM an anticoagulant other than warfarin TO Xarelto®: Start Xarelto® 0-2 hours prior to the administration of the next scheduled evening administration of the other anticoagulant and omit its dose. For UFH being administered continuously, stop the infusion and start Xarelto® at the same time.
When converting FROM Xarelto® TO an anticoagulant other than warfarin with a rapid onset: Discontinue Xarelto® and give the first dose of the other anticoagulant at the same time that the next Xarelto® dose would have been taken.

meal. For patients with CrCl 15-50ml/min, the dose should be reduced to 15mg once daily with the evening meal. This indication also carries a black box warning cautioning the discontinuation of Xarelto®. An increased rate of stroke was observed in clinical trials following treatment discontinuation in patients with atrial fibrillation. The black box warning states that if anticoagulation with Xarelto® must be discontinued for any other reason besides pathological bleeding, administering another anticoagulant should be considered. Table 3 includes information on switching rivaroxaban to and from other anticoagulants.

Clinical data in patients with moderate hepatic impairment have indicated a significant increase in rivaroxaban exposure and pharmacodynamic effect. Therefore, its use for all indications should be avoided in patients with moderate or severe hepatic impairment or any hepatic disease associated with coagulopathy.

The absolute bioavailability of rivaroxaban is dose-dependent. It is estimated to be between 80 to 100 percent for the 10mg dose and is not affected by food. On other hand, the bioavailability of the 20mg dose is only 66 percent in the fasting state, and is greatly increased when taken with food. The maximum concentration is achieved two to four hours after tablet intake. Xarelto® may be crushed and administered through a feeding tube, but it is important that the drug is released in the stomach versus the small intestine where absorption would be greatly reduced. It is highly protein bound and primarily renally excreted (66 percent) with 28 percent excreted hepatically. The terminal half-life is five to nine hours in healthy subjects aged 20 to 45 years.

Xarelto® is contraindicated in patients who have experienced a hypersensitivity reaction to the agent or have active major bleeding. As with other anticoagulants, rivaroxaban increases the risk of bleeding, and can cause serious and fatal bleeding including intracranial, epidural hematoma, retinal, and gastrointestinal bleeding. Table 1 includes additional information regarding the black box warning for spinal or epidural hematomas.

Use with other medications that affect hemostasis, such as platelet aggregation inhibitors, other antithrombotics, fibrinolytic therapy, thienopyridines, and chronic use of NSAIDs, increases the risk of bleeding. Concomitant use with other anticoagulants should be avoided. As with dabigatran, there are no recommended antidote guidelines for rivaroxaban. The administration of activated charcoal may be useful in reducing the absorption of the last dose given. Because rivaroxaban is highly protein bound, it is not expected to be dialyzable.

Xarelto® is a substrate of CYP3A4, CYP3A5, CYP2J2, and P-gp transporters. Drug interaction studies have revealed that the concomitant use of rivaroxaban and drugs that are both CYP3A4 and P-gp inhibitors leads to increased factor Xa inhibition and prothrombin time (PT) prolongation. It is recommended that the combination of rivaroxaban and ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan be avoided as it may increase bleeding risk. For patients with CrCl 15-30ml/min and who are receiving concomitant combined P-gp and weak-to-moderate CYP3A4 inhibitors, Xarelto® should only be used if the potential benefit outweighs the risk. Coadministration with a combined P-pg and strong CYP3A4 inducer can decrease exposure and decrease efficacy. Therefore, avoid concomitant use of Xarelto® with drugs that are combined P-gp and strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort.

Xarelto's approval followed the conclusion of the RECORD 1, 2,

and 3 trials (Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism). The primary efficacy outcome in RECORD 3 was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to 17 days after surgery with a primary safety outcome of major bleeding. The primary outcome occurred in 9.6 percent of the patients who received rivaroxaban and 18.9 percent who received enoxaparin (absolute risk reduction 9.2 percent). Major venous thromboembolism (secondary outcome defined as proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism) occurred in 1.0 percent of patients given rivaroxaban versus 2.6 percent of patients given enoxaparin. There was no statistical difference between the two groups in regard to major bleeding. Hence, the authors concluded that rivaroxaban was the superior agent. Nausea, vomiting, and constipation were the most common adverse events reported in both groups at similar rates.

For total knee replacement, the duration of thromboprophylaxis must be determined by the prescriber. According to the current CHEST guidelines, which were published prior to approval of Xarelto®, the Grade 1A recommendation for patients undergoing total knee replacement is to receive thromboprophylaxis with one of the recommended options (LMWH, VKA, or fondaparinux) for at least 10 days. A Grade 2B recommendation is that thromboprophylaxis be extended beyond 10 days and up to 35 days. Currently, rivaroxaban has only been studied for up to 12 days of administration for post knee replacement.

For total hip replacement surgery, a Grade 1A recommendation is present in the CHEST guidelines supporting extended thromboprophylaxis of up to 35 days. The authors from the RECORD 1 study concluded that rivaroxaban was significantly more effective than enoxaparin for patients undergoing hip replacement surgery based on a 2.6 percent absolute risk reduction. They also found a significant reduction in major venous thromboembolism, while major bleeding incidence was similar at 0.3 percent in the rivaroxaban group and 0.1 percent in the enoxaparin group. At the time of writing this lesson, the cost of Xarelto® was $8 per day, compared to $25 to $50 per day for enoxaparin, or $40 per day for dalteparin for DVT prophylaxis.

In the ROCKET AF study (the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), patients were randomly assigned to receive a fixed dose rivaroxaban (20mg or 15mg based on CrCl), or adjusted dose warfarin (target INR 2.0-3.0). The primary efficacy point was the composite of stroke and systemic embolism. The principal safety endpoint was a composite of major and nonmajor clinically relevant bleeding events. In ROCKET AF, Xarelto® was concluded to demonstrate non-inferiority to warfarin for the primary composite endpoint of time to the first occurrence of stroke or embolism, but not superiority. The major and non-major bleeding rates were similar between the two groups. However, there are some concerns to note in this study such as the INR in the warfarin group was in the therapeutic range only 55 percent of the time, and there was a much higher rate of stroke or systemic embolism in the rivaroxaban group than in the warfarin group between day 2 and day 7 after discontinuation of randomized treatment. To date, there are no studies to determine whether rivaroxaban is noninferior to dabigatran.

Summary

Pradaxa® and Xarelto® are two new oral anticoagulants that offer advantages over previous standard therapy for the prevention of thromboembolic complications. While Pradaxa® is more expensive than warfarin and must be taken twice daily, the initial study indicates that it may be superior to warfarin while decreasing the risk of intracranial bleeding and it does not require routine outpatient monitoring. Pradaxa® has fewer drug interactions than warfarin, but the dosing needs to be adjusted in patients with CrCl <30ml/min, and should not be administered in patients with CrCl <15ml/min.

The cost of Xarelto® per day for DVT prophylaxis is less than two popular LMWHs, and it is administered orally once daily. For DVT prophylaxis, initial studies also indicate that it may be superior to warfarin with a similar bleeding risk. In patients with CrCl <30ml/min, rivaroxaban is not recommended for DVT prophylaxis. However, enoxaparin can be administered at an adjusted dose.

For the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, Xarelto® was non-inferior to warfarin with similar bleeding risks. Rivaroxaban may be used at a reduced dose in patients with CrCl 15-50ml/min for this indication.

Xarelto® should also be avoided in patients with moderate to severe hepatic impairment and a thorough medication history must be conducted in advance to avoid serious drug interactions.

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This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

Program 0129-0000-11-012-H01-P
Release date: 12-15-11
Expiration date: 12-15-14
CE Hours: 1.5 (0.15 CEU)

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continuing education quiz

Overview of Anticoagulants and the Role of New Oral Agents

Program 0129-0000-11-012-H01-P
0.15 CEU

1. Anticoagulants prevent thrombosis by:
   a. restoring movement of blood.
   b. inhibiting platelet aggregation.
   c. healing damage to vascular endothelium.
   d. inhibiting blood from clotting.

2. The three major steps of the clotting cascade in correct order are:
   a. initiation, extrinsic, intrinsic.
   b. initiation, amplification, propagation.
   c. extrinsic, intrinsic, common.

3. Which of the following factors is the physiologic initiator of clotting?
   a. Thrombin
   b. Factor Xa
   c. Tissue factor
   d. Fibrin

4. Which of the following is useful in reversing the effects of heparin?
   a. Vitamin K
   b. Protamine sulfate
   c. Activated Charcoal
   d. Dialysis

5. According to the CHEST guidelines, routine coagulation monitoring in patients treated with LMWHs is only recommended for:
   a. elderly patients.
   b. patients with CrCl < 30.
   c. therapeutic doses.
   d. pregnant women treated with therapeutic doses.

6. Which of the following agents is synthetic, and may be used off-label in patients with a history of heparin-induced thrombocytopenia?
   a. Fondaparinux
   b. Heparin
   c. Enoxaparin
   d. Tinzaparin

7. Dabigatran exerts its anticoagulant effect by which of the following mechanisms of action?
   a. Inhibiting vitamin K dependent clotting factors
   b. Directly inhibiting thrombin
   c. Indirectly inhibiting thrombin by first binding to antithrombin
   d. Directly inhibiting factor Xa

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]	[d]	6.	[a]	[b]	[c]	[d]	11.	[a]	[b]	[c]	[d]
2.	[a]	[b]	[c]		7.	[a]	[b]	[c]	[d]	12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	8.	[a]	[b]	[c]		13.	[a]	[b]	[c]	[d]
4.	[a]	[b]	[c]	[d]	9.	[a]	[b]	[c]	[d]	14.	[a]	[b]	[c]	[d]
5.	[a]	[b]	[c]	[d]	10.	[a]	[b]	[c]	[d]	15.	[a]	[b]	[c]	[d]

❑ **I am enclosing $5 for this month's quiz made payable to: Ohio Pharmacists Association.**

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8. Dabigatran is indicated to:
   a. treat pulmonary embolisms.
   b. prevent VTE in patients following hip surgery.
   c. reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

9. Once a Pradaxa bottle is opened, it may be used for up to:
   a. 4 months.
   b. 6 months.
   c. 8 months.
   d. 1 year.

10. Rivaroxaban exerts its anticoagulant effect by which of the following mechanisms of action?
   a. Inhibiting vitamin K dependent clotting factors
   b. Directly inhibiting thrombin
   c. Indirectly inhibiting thrombin by first binding to antithrombin
   d. Directly inhibiting factor Xa

11. What is the recommended daily dose of Xarelto for DVT prophylaxis?
   a. 25mg
   b. 20mg
   c. 15mg
   d. 10mg

12. Which of the following medications should not be administered to patients with moderate or severe hepatic impairment?
   a. Fondaparinux
   b. Enoxaparin
   c. Rivaroxaban
   d. Heparin

13. Avoid co-administration of Xarelto with all of the following EXCEPT:
   a. ketoconazole.
   b. ranitidine.
   c. phenytoin.
   d. rifampin.

14. According to the CHEST guidelines, patients who have undergone hip surgery should receive thromboprophylaxis for up to:
   a. 42 days.
   b. 35 days.
   c. 12 days.
   d. 10 days.

15. All of the following are advantages of dabigatran therapy over warfarin EXCEPT:
   a. it is less expensive.
   b. studies indicate a lower risk of intracranial bleeding.
   c. it does not require routine outpatient monitoring.
   d. it is associated with fewer drug interactions.

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