Anticoagulation Update: Focus on Dabigatran And Its Impact on Current Practice

by Whitney White, PharmD

Upon successful completion of this article, the pharmacist should be able to:
1. Explain the standard knowledge parameters for dabigatran, including mechanism of action, pharmacokinetics, drug interactions, adverse effects, and route of administration.
2. Discuss recent clinical trials and subsequent guideline updates regarding the use of dabigatran.
3. Describe important patient counseling information surrounding dabigatran use.
4. Identify special storage and dispensing requirements for dabigatran.
5. Recognize the potential impact dabigatran may have on the traditional method of thromboprophylaxis with warfarin therapy.

Upon successful completion of this article, the pharmacy technician should be able to:
1. List the medical conditions for which dabigatran is commonly prescribed.
2. Identify special storage and dispensing requirements for dabigatran.
3. Describe scenarios when intervention by the pharmacist is needed for patient safety

INTRODUCTION
Warfarin, a vitamin K antagonist, has been available in the United States for more than 50 years and has been the standard of care for many disease states which require chronic anticoagulation, including atrial fibrillation, venous thromboembolism, prosthetic valve replacement, and various hypercoagulable disorders. Warfarin’s efficacy is well documented in the literature, and in atrial fibrillation patients specifically, warfarin was shown to prevent up to 64 percent of strokes. Although we have much experience with warfarin, its use is not without many important considerations, including pharmacokinetics, regular international normalized ratio (INR) monitoring, restricted diet, numerous OTC and prescription drug interactions, herbal interactions, and adherence. Extensive patient education is required with initiation of warfarin therapy and must be reinforced at regular intervals, while patients continue therapy in order to promote safe and effective anticoagulation.

To ensure optimal anticoagulant therapy, a tremendous burden is placed upon practitioners and patients alike. With the introduction of The Joint Commission National Patient Safety Goals (NPSG) related to anticoagulation and the Centers for Medicare and Medicaid Services (CMS) Hospital-Acquired Conditions (HACs), health systems have felt the pressure to evaluate safe medication practices and increase accountability which achieve optimal therapy and prevent unwanted patient outcomes. As part of NPSG 03.05.01, The Joint Commission requires that health systems maintain an anticoagulation management program, have approved protocols for the initiation and maintenance of anticoagulant therapy, check a baseline INR, have a written policy that addresses baseline and ongoing laboratory monitoring, and provide education regarding anticoagulant

Useful Websites
- www.theheart.org Is a resource for practitioners regarding the most recent updates in anticoagulation therapy (owned and produced by Medscape, LLC).
- www.cardiosource.org Is a treatment guideline source for practitioners (American College of Cardiology).
- www.pradaxa.com Site contains prescribing information and patient information (Boehringer Ingelheim).
therapy to prescribers, staff, patients, and family, which includes dietary counseling. Furthermore, CMS considers deep vein thrombosis or pulmonary embolism following total hip or knee replacement to be one of several HACs for which hospitals will not receive reimbursement. Community practitioners also share this burden, extending the continuum of care when a patient transitions from the hospital to the outpatient setting with anticoagulants. An effort on the part of community pharmacists to reinforce the need for regular INR monitoring, screen for drug interactions with warfarin, and continually educate patients on the safe use of warfarin is vitally important.

For chronic anticoagulation, warfarin has faced few challengers in its time on the market, but recent drug approvals provide practitioners with the first new oral anticoagulants since warfarin’s debut in 1954. Dabigatran (Pradaxa®) was the first new oral anticoagulant to be approved and marketed in the United States for long-term thromboprophylaxis. Recently, rivaroxaban (Xarelto®), an oral Factor Xa inhibitor, also won approval by the Food and Drug Administration (FDA) for post-operative thromboprophylaxis following total hip and knee replacement and stroke prevention in patients with atrial fibrillation. The details of the new agent dabigatran, including how its introduction may change current practice, are discussed as follows:

**DABIGATRAN: STANDARD KNOWLEDGE PARAMETERS**

Dabigatran exetilate is an oral, direct thrombin inhibitor (similar to parenteral argatroban) which reversibly binds to thrombin’s active site and inhibits coagulation by preventing thrombin-mediated effects, including inhibition of platelet aggregation. Following a few years of experience in Europe and Canada, dabigatran received its first approval from the FDA in October 2010 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. This approval was based on evidence from the Randomized Evaluation of Long-term Anticoagulation Therapy study (RE-LY). This trial compared dabigatran 110 mg or 150 mg twice daily to adjusted-dose warfarin (target INR of 2-3). Dabigatran is prescribed off-label for postoperative thromboprophylaxis in total hip and knee replacement following evidence of noninferiority compared to enoxaparin 40 mg daily in clinical trials. Dabigatran is currently available in 75 mg and 150 mg capsules for oral administration. The standard treatment dose in patients with normal kidney function for prevention of stroke in atrial fibrillation is 150 mg twice daily.

Dabigatran’s oral bioavailability is approximately 6.5 percent, and its elimination half-life is 12–17 hours. The dosage form is prepared using a tartaric acid core to increase oral bioavailability. Therefore, the capsules should be swallowed whole, with or without food; they should not be chewed, broken, or opened. Dabigatran exetilate is a pro-drug. Unlike warfarin, it does not undergo metabolism via the cytochrome P450 system, a recognizable benefit with regard to drug interactions. However, the drug is a substrate of P-glycoprotein, resulting in decreased or increased metabolism when administered with P-glycoprotein inhibitors (ketoconazole, verapamil, amiodarone, dronedarone) or inducers (rifampin), respectively. The package insert was updated to give dosing guidelines for patients with interacting medications: if prescribed dabigatran and on concomitant dronedarone or ketoconazole with a creatinine clearance between 30-50 mL/min, reduce dabigatran dose to 75 mg twice daily; if the patient is on any P-glycoprotein inhibitor with a creatinine clearance between 15-30 mL/min, do not use dabigatran. Patients on these interacting medications should also be monitored carefully for signs and symptoms of bleeding. Use of other anticoagulants, antiplatelet or thrombolytic agents may increase the risk of bleeding in patients taking dabigatran. Dabigatran is 80 percent renally excreted. Therefore, dosing adjustments are required for patients with renal impairment. Indicated dose adjustment for patients with creatinine clearance (CrCl) 15–30 mL/minute is 75 mg twice daily. Dabigatran is not indicated for patients with CrCl than 15 mL/minute. No dosing adjustments are required in hepatic impairment, which provides an additional advantage in comparison to warfarin.

The most anticipated adverse effect with dabigatran is bleeding. The rate of major bleeding in the RE-LY trial was 3.36 percent per year for warfarin versus 3.11 percent per year for dabigatran 150 mg twice daily, which was not a statistically significant difference. However, the
incidence of gastrointestinal bleeding was significantly higher with dabigatran 150 mg twice daily compared to warfarin (1.51 percent per year versus 1.02 percent per year; p<0.001). Hemorrhagic stroke was significantly higher in the warfarin group when compared to patients taking dabigatran 150 mg (0.38 percent per year versus 0.1 percent per year; p<0.001). The acidic formulation of the drug explains another common adverse effect. Dyspepsia, which included abdominal discomfort or pain, and epigastric discomfort occurred in approximately 11 percent of subjects taking dabigatran, versus 6 percent with warfarin. The RE-LY study data showed an increase in the incidence of myocardial infarction (MI) with dabigatran, and this adverse event has been re-evaluated in subsequent analyses with conflicting results.

A report published by Hohnloser and colleagues evaluated the risk of myocardial ischemic events in patients receiving dabigatran or warfarin from the RE-LY trial. The findings suggested a nonsignificant increase in MI infarction with dabigatran compared to warfarin in patients with atrial fibrillation. A meta-analysis of trials investigating dabigatran for various indications reported an increased risk of MI and acute coronary syndrome with use of dabigatran, and suggested that practitioners consider this a valid harmful cardiovascular effect when using the drug. Dabigatran is contraindicated in patients with an active pathological bleed and is classified as pregnancy category C.

EFFICACY
The RE-LY trial, as previously discussed, compared two doses of dabigatran (110 mg twice daily and 150 mg twice daily) to optimized warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation. Patients were included in the analysis if atrial fibrillation was documented on electrocardiogram within six months of study enrollment and at least one of the following criteria was present: previous stroke or transient ischemic attack, left ventricular ejection fraction less than 40 percent, New York Heart Association Class II or higher heart failure, age of at least 75 years or age 65 to 74 years with diabetes mellitus, hypertension or coronary artery disease. In this non-inferiority study of more than 18,000 patients, the average CHADS2 score was 2.1 (moderate risk for stroke), and average patient age was 71 years. Those patients with severe valve disease, stroke occurring within 14 days or severe stroke within six months, increased risk of hemorrhage, CrCl less than 30 mL/min, active liver disease and pregnancy were excluded from the study. Concomitant aspirin therapy was permitted. The mean duration for follow-up was two years. A therapeutic INR of 2–3 was seen in 64 percent of patients in the warfarin group.

Results showed dabigatran 110 mg twice daily to be non-inferior to warfarin in preventing stroke with lower major bleeding rates. Dabigatran 150 mg twice daily was found to be superior to warfarin with similar rates of bleeding overall. The higher dose of dabigatran did lead to an increase in gastrointestinal bleeding, as previously mentioned. The results from this study influenced the subsequent guideline update in February 2011 from the American College of Cardiology Foundation and the American Heart Association. This guideline states that "dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF 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 <15 ml/min), or advanced liver disease (Class I/Level B evidence)." The February 2012 update to the CHEST guidelines modified the recommendation for use of dabigatran to state it should be used in place of vitamin K antagonists (warfarin) when oral anticoagulation is indicated for stroke prevention in atrial fibrillation.

Although not an FDA-labeled indication, dabigatran has also been evaluated for thromboprophylaxis following total hip and knee replacement. The RE-MOBILZE and RE-MODEL studies compared dabigatran 220 mg twice daily and 150 mg twice daily to standard enoxaparin therapy in total knee replacement. The primary endpoint for both trials was a composite of venous thromboembolism (VTE) and all-cause mortality. In the RE-MOBILZE study, dabigatran failed to meet the prospectively set criteria for non-inferiority compared to enoxaparin 30 mg twice daily. In RE-MODEL, dabigatran was found non-inferior to enoxaparin 40 mg daily. The RE-NOVATE trial compared
dabigatran 220 mg twice daily and 150 mg twice daily to enoxaparin 40 mg daily following hip replacement, and showed dabigatran to be noninferior to enoxaparin.

In the treatment of VTE, dabigatran 150 mg twice daily was compared to dose-adjusted warfarin (INR 2–3) in the RE-COVER trial. Investigators assessed six-month recurrence of VTE and death and found dabigatran was non-inferior to warfarin. They concluded fixed-dose dabigatran could be an alternative to warfarin with a similar safety profile and less monitoring. This indication is also not FDA-approved at this time.

INTRODUCTION TO PRACTICE

Since dabigatran’s approval in the fall of 2010, many physicians have begun prescribing it as initiation of therapy for atrial fibrillation or as a switch from warfarin therapy. According to a prescription tracking system, approximately 128,000 dabigatran prescriptions were dispensed from October 2010 to January 2011. When initiating anticoagulation with dabigatran, practitioners should be aware of its single FDA-approved indication for stroke and systemic embolism risk reduction in non-valvular atrial fibrillation. Additionally, it is not advised that physicians try to customize the prescribed dose in the general population simply because two strengths (75 and 150 mg) are available; the lower dose of 75 mg twice daily should only be used in patients with renal impairment. Before initiating dabigatran, renal function should be assessed using creatinine clearance to verify no dosing adjustments are required. Furthermore, a baseline complete blood count (CBC) may be necessary in the event bleeding should occur with dabigatran.

After the FDA’s approval of dabigatran, some debate arose as to why the higher dose of 150 mg twice daily was approved, as it carries a higher risk of some major bleeding. The FDA Advisory Committee considering the drug’s approval stated their discussion on the appropriate treatment dose focused on elderly patients, patients with renal impairment, and patients with previous bleeding episodes. For the 40 percent of patients in the RE-LY study more than 75 years old, the rate of stroke or systemic embolism was lower with dabigatran 150 mg twice daily but the rate of major bleeding was higher. Though an outcome of stroke or major bleeding is undesirable, the review team felt the irreversible effects of stroke have a greater clinical significance for patients and that a potentially safer option of dabigatran 110 mg twice daily (the lower dose studied in RE-LY) is not an acceptable reason for using a less effective regimen.

With dabigatran’s increase in use over the past year and gained experience with the new medication, case reports and anecdotal evidence are indicating the higher dose could be dangerous in the elderly population. In one case report from France, an 84-year-old female, weighing only 40 kg (88 pounds) with a creatinine clearance of 32 mL/min, who was taking dabigatran 75 mg twice daily with concomitant amiodarone for atrial fibrillation, had a massive rectal bleed, cardiac arrest, and then died. In another report from France, an 89-year-old female weighing 45 kg (99 pounds) with a creatinine clearance of 29 mL/min was taking 110 mg twice daily for atrial fibrillation and experienced recurrent nosebleeds. Prior to a planned surgery, she was found to have increased bleeding times and an elevated plasma level of dabigatran (although not routinely monitored). The surgery was cancelled and the dabigatran was discontinued.

Considering the ongoing debate regarding the most suitable dabigatran dose, a post-hoc analysis of the RE-LY study compared the risk of bleeding with dabigatran in older and younger patients in an attempt to identify sub-groups for which dabigatran use is more appropriate. The analysis showed that both dabigatran doses evaluated in the parent study (150 mg and 110 mg twice daily) were associated with lower risks of both intra- and extracranial bleeds in patients less than 75 years of age in comparison to warfarin. For patients over the age of 75, the risk of intracranial bleeding is lower compared to warfarin, but the risk of extracranial bleeding, specifically gastrointestinal bleeding, is higher. Of those patients receiving dabigatran who experienced a GI bleed, 53 percent had bleeding from the upper GI tract. No definitive explanation was found for dabigatran’s selectivity for increased GI bleeds. Its metabolism by esterases results in higher concentrations of the active drug in the GI tract; therefore, it was suggested that patients with pathology such as diverticulosis could have
an increased bleeding risk from exposure to dabigatran. Further analysis revealed a greater than two-fold increase in risk of major bleeding in patients with a creatinine clearance less than 50 mL/min whether they received dabigatran or warfarin. Dabigatran’s predominant renal excretion could explain this finding, but warfarin is not excreted renally. Thus, investigators could not find a significant interaction between treatment group and creatinine clearance for resultant major bleeding, which suggests other age-related factors more strongly determine bleeding risk in the elderly. Additional analysis showed that concomitant aspirin use resulted in a higher risk of bleeding overall, and that the combination of aspirin and anticoagulant therapy should be used with caution. Dabigatran’s presumed benefit over warfarin related to the absence of regular monitoring may in fact be a risk, with the potential for life-threatening bleeds to perhaps go undetected. Therefore, increased vigilance and reporting of adverse effects, especially in the elderly and in those patients with renal impairment, is imperative in the post-marketing period.

When practitioners choose to change patients from warfarin to dabigatran or initiate therapy with dabigatran, certain assessment criteria should be considered based on clinical guidelines and manufacturer recommendations. Patients with atrial fibrillation and at least one additional risk factor for stroke should be evaluated based on individual clinical features, including ability to adhere to a twice-daily dosing regimen with dabigatran, access to regular anticoagulation (INR) monitoring, cost of medication and monitoring, renal function, history of GERD or GI bleeds, stroke risk, potential drugs interactions, and patient preferences, among others (Table 1). Patients who are well-controlled on warfarin may have little to gain by switching to dabigatran. If the choice is made to switch to dabigatran, the patient should stop warfarin and start dabigatran when the INR is < 2.0. Conversely, dosing guidelines are also available when switching from dabigatran to warfarin (Table 2).

| Table 1. Assessment Criteria With Initiation of Dabigatran |
|----------------|---------------------------------|
| Criteria | Comments |
| Creatinine clearance | > 30 mL/min: 150 mg twice daily 15–30 mL/min: 75 mg twice daily < 15 mL/min: do not use |
| History of GERD | Evaluate control of GERD symptoms, medications |
| Chronic use of PPI’s, antacids | Separate dabigatran by at least 2 hours |
| History of GI bleeds | Do not use dabigatran |
| Mechanical valve | Do not use dabigatran |
| General medication adherence | Dabigatran require twice daily dosing |
| INR history | Historically therapeutic INR: may not need to switch |
| Stroke risk (CHADS2 score) | Dabigatran is more appropriate for moderate-severe risk patients |
| Drug interactions | P-glycoprotein inhibitors/inducers |
| Insurance coverage/cost to patient | Consider coverage; patient assistance available |

**SPECIAL DISPENSING/STORAGE CONSIDERATIONS**

Due to dabigatran’s special product formulation and the potential for breakdown and loss of potency, special requirements for storage and handling are included on the label and in the medication guide dispensed with a prescription. If dabigatran is exposed to moisture or humidity, the capsules could hydrolyze and become less effective. Therefore, dabigatran is packaged in a bottle containing a 30-day supply of medication with a drying agent in the cap. It is also available in a blister pack. Pharmacists should not open the bottle when dispensing (dispense in original bottle) and should instruct patients to open only one bottle at time if more than one bottle is dispensed. Also, pharmacists can number the bottles when dispensing multiple bottles to remind patients which bottle is in use.

Patients should not store the capsules in pill boxes or

| Table 2. Dose Conversions With Dabigatran |
|----------------|---------------------------------|
| Conversion | Dosing |
| Warfarin to Dabigatran | Stop warfarin & start dabigatran when INR < 2.0 |
| Dabigatran to Warfarin | • CrCl > 50 mL/min  Start warfarin 3 days before stopping dabigatran  • CrCl 31–50 mL/min  Start warfarin 2 days before stopping dabigatran  • CrCl 15–30 mL/min  Start warfarin 1 day before stopping dabigatran |
pill organizers. When opening the bottle, only one capsule should be removed at a time and the bottle should be closed tightly. The bottle or blister packs should be stored away from excessive moisture, heat, and cold. The package insert was updated in November 2011 to state that open bottles of dabigatran should be discarded after four months. It could be helpful for patients to date their bottle to expire 120 days after opening. For blister packs, patients should not open or puncture the blister earlier than the time of use. Patients are encouraged to read the medication guide for dabigatran each time their prescription is refilled. See Table 3 for more information on special dispensing and patient counseling instructions.

**COST OF DABIGATRAN VERSUS WARFARIN**

Perhaps the most controversial discussion since dabigatran’s approval has been the anticipated increase in expenditures for patients and health systems based on the higher cost of the new medication. A recent cost analysis by Shah and Gage compared the cost and quality-adjusted survival of various antithrombotic therapies, including dabigatran 110 or 150 mg twice daily, warfarin, dual therapy with aspirin and clopidogrel, and aspirin monotherapy. The analysis determined the annual cost of warfarin (with INR monitoring) to be $545 ($1.50/day). The annual cost of clopidogrel was $1,847 ($5.06/day), and the median annual cost of dabigatran was $3,240 ($9/day). Their conclusions indicated that the cost effectiveness of thromboprophylaxis in patients with an average risk of hemorrhage varied by stroke risk. Aspirin was more cost-effective for patients at a low risk for stroke (CHADS2 score of 0), and warfarin was more cost-effective for patients with a moderate stroke risk (CHADS2 score of 1 or 2). For patients at a high risk of stroke (CHADS2 score ≥ 3), dabigatran 150 mg twice daily was cost-effective regardless of hemorrhage risk. Dabigatran 150 mg twice daily was the most cost-effective option for a patient with a CHADS2 score of 2 only if patients were at a high risk of hemorrhage (>6 percent per year) or had unstable INRs with warfarin. Neither dual therapy with aspirin and clopidogrel nor dabigatran 110 mg twice daily were found to be cost-effective in this analysis. Interestingly if the annual cost of dabigatran were $1,800 or lower, dabigatran would be more cost-effective than warfarin regardless of stroke and hemorrhage risk. Shah and Gage concluded that the benefits of dabigatran with regard to stroke prevention outweigh the risks for patients at moderate to high risk of stroke and/or hemorrhage unless INR control with warfarin is exceptional (>72.6 percent time in therapeutic range).

**IMPLICATIONS TO STANDARD OF CARE WITH WARFARIN**

The new oral anticoagulants have legitimate advantages but apparent disadvantages as well. Therefore, the question still remains as to whether warfarin will become obsolete as these newer agents are introduced. As with many decisions regarding appropriate drug therapy, benefit versus risk must be evaluated. Warfarin is effective in preventing clots based on many years of experience with the medication. While regular monitoring is required and often inconvenient, the ability to check an INR gives practitioners the ability to verify efficacy and safety with warfarin. Additionally, the availability of an antidote (vitamin K) in the event of major bleeding along with well-documented guidelines for quick reversal gives warfarin an advantage over dabigatran. Likewise, the use of dabigatran does offer many advantages. It has a fixed-dose regimen with a shorter onset of action and no bridge therapy with a heparin product is required. Dabigatran has fewer drug interactions, though

<table>
<thead>
<tr>
<th>Table 3. Patient Education When Dispensing Pradaxa®</th>
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<tr>
<td>• Store Pradaxa® in the original 30-count bottle or blister package to protect from moisture.</td>
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<tr>
<td>• Do not store or place Pradaxa® capsules in any other container, such as pill boxes or pill organizers.</td>
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<td>• For Pradaxa bottles:</td>
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<tr>
<td>- Open only one bottle of Pradaxa at a time. Once the bottle is opened, the product must be used within 120 days.</td>
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<tr>
<td>- Remove only one capsule from the bottle at the time of use. The bottle should be immediately closed tightly.</td>
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<tr>
<td>- Date the bottle to expire 120 days after opening.</td>
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<tr>
<td>• For Pradaxa blister packages:</td>
</tr>
<tr>
<td>- Open the blister package at time of use. Do not open or puncture the blister any earlier than the time of use.</td>
</tr>
<tr>
<td>• Discuss any questions or concerns about Pradaxa with your health care professional.</td>
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<tr>
<td>• Read the Medication Guide for Pradaxa each time you get your prescription refilled.</td>
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<tr>
<td>• Report any side effects you experience to the FDA MedWatch program.</td>
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some serious interactions do exist and should be considered. Dabigatran has a broader therapeutic window which requires no routine monitoring. The absence of need for routine monitoring could also be considered a disadvantage as there are no labs to confirm safe and effective therapy. Also, patients do not have to make dietary changes when taking dabigatran. Several disadvantages with dabigatran exist as well. No clinical data is available beyond two years, and post-marketing data continues to reveal potential issues with the drug. Data is also limited in patients with renal or hepatic disease. Twice-daily dosing requires increased adherence, and dyspepsia occurs in one out of ten patients taking dabigatran. Additionally, no specific antidote is available to reverse the effects of dabigatran if major bleeding occurs. The incidence of gastrointestinal bleeding is higher with dabigatran compared to warfarin, and case reports have shown this to be a significant disadvantage in some patients.

While the “perfect” anticoagulant does not currently exist, dabigatran offers a reasonable alternative for patients initiating therapy or for those patients who have been uncontrolled on warfarin therapy and will benefit from an equally effective medication with a broader therapeutic window and fewer dietary requirements. Special attention should be paid to patient-specific criteria for initiation or switch to dabigatran from warfarin, with particular focus on age of the patient, renal function, and risk of stroke. More experience is needed with dabigatran before full evaluation of its impact on the standard of care with warfarin can be determined.

FUTURE OF ANTICOAGULATION
Though the use of dabigatran has increased in popularity since its approval in 2010, other potential competitors for chronic anticoagulation have also entered the market. Rivaroxaban (Xarelto®) was approved by the FDA in July 2011 for postoperative thromboprophylaxis following elective total hip or knee replacement procedures. Results of the ROCKET-AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antago-

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**Patient Counseling Guide**

- **Dabigatran (Pradaxa®)** is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- Dabigatran is a blood thinner and can cause bleeding which can be serious, and sometimes lead to death. Patients are at higher risk of bleeding if they:
  - Are more than 75 years old
  - Have kidney problems
  - Have stomach or intestine bleeding that is recent or recurrent, or have a stomach ulcer
  - Take other medicines that increase risk of bleeding, including aspirin or aspirin-containing products, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), warfarin sodium (Coumadin®, Jantoven®), a medicine that contains heparin, clopidogrel (Plavix®), prasugrel (Effient®) or ticagrelor (Brilinta®). **Contact the prescriber if the patient is on any of these medications.**
  - Common side effects of dabigatran include bleeding, bruising, indigestion, upset stomach, and stomach pain.
  - Instruct patients to tell their doctor if they experience unusual or prolonged bleeding, blood in the urine or stool, excessive bruising, unexpected pain or swelling, headaches, dizziness, or if they vomit blood or their vomit looks like “coffee grounds.”
  - Instruct patients to take dabigatran exactly as prescribed. Patients should not stop taking it without first talking to the prescriber. Stopping dabigatran may increase risk of a stroke.
  - Patients who are pregnant or breastfeeding should not take dabigatran. Patients should not take dabigatran if they have a history of abnormal bleeding problems. Patients with kidney problems or stomach ulcers should talk to their doctor about how these conditions affect the risks of bleeding on dabigatran before taking dabigatran.
  - Instruct patients to swallow Pradaxa capsules whole. The capsules and the pellets inside should not be broken, chewed, or emptied from the capsule.
  - Instruct patients who miss a dose of dabigatran to take it as soon as they remember. If the next dose is less than six hours away, skip the missed dose. Do not take two doses at the same time.

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**Adapted from the Boehringer Ingelheim Medication Guide (Pradaxa®) – revised March 2011**
nism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) were recently published in the *New England Journal of Medicine* and showed rivaroxaban to be non-inferior to warfarin with no significant difference in major bleeding rates. Rivaroxaban is an oral factor Xa inhibitor administered once daily. The FDA approved rivaroxaban for stroke prevention in atrial fibrillation in November 2011 and also for post-operative prophylaxis following hip and knee replacement in July of 2011.

The FDA has granted a priority review for rivaroxaban use in acute coronary syndrome. Apixaban, another oral Factor Xa inhibitor, is showing promise in Europe and Asia and was recently approved by the European Commission for use in the prevention of venous thromboembolism. In the ARISTOLE trial, apixaban showed a greater reduction in the composite endpoint of stroke or systemic embolism in patients with atrial fibrillation compared to warfarin, but the study was designed as a non-inferiority trial. The FDA is scheduled to rule on apixaban’s approval for stroke prevention in atrial fibrillation in June of 2012. As more options become available and experience is gained with new drug therapy, the standard of care for patients requiring thromboprophylaxis may certainly change.

**CONCLUSION**

Dabigatran is the first of many potential competitors to warfarin on the market for chronic anticoagulation. Though this new oral agent has documented advantages compared with warfarin, several disadvantages exist which could limit its global incorporation into practice. Therefore, practitioners should carefully consider patient-specific criteria before initiating therapy with dabigatran, including renal function, patient age, stroke risk, and economic impact. Because routine laboratory monitoring is not required with dabigatran, practitioners should evaluate important drug interactions and should closely monitor patients for clinical signs and symptoms of bleeding. More experience is needed with dabigatran and the other oral anticoagulants in the pipeline before the full impact of their introduction to practice is known.

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**CONTINUING EDUCATION QUIZ**

Select the correct answer.

1. What is the mechanism of action of dabigatran?
   a. Antithrombin III-mediated selective inhibition of Factor Xa
   b. It reversibly binds to active thrombin site and inhibits coagulation by preventing thrombin-mediated effects and through inhibition of platelet aggregation.
   c. It inhibits the hepatic synthesis of vitamin K-dependent clotting factors and Proteins C & S.
   d. It inhibits ADP activity, causing an accumulation of adenosine, adenine nucleotides, and cyclic AMP, thus inhibiting platelet aggregation.

2. Why do you ask E.B. if her mother-in-law has a mechanical heart valve?
   a. Dabigatran is only approved for prevention of stroke and systemic embolism in patients with mechanical valves.
   b. Dabigatran is only approved for treatment of VTE in patients with mechanical valves.
   c. The recommended dose of dabigatran is 110 mg twice daily in patients with mechanical valves.
   d. Dabigatran is not indicated for prevention of stroke and systemic embolism in patients with mechanical valves.

3. After consulting with the prescriber to confirm that M.B. does not have a mechanical valve you learn that this 76-year-old woman has a creatinine clearance of 42 mL/min. What is the proper starting dose?
   a. 150 mg BID
   b. 75 mg BID
   c. 110 mg BID
   d. Dabigatran should not be used.
4. Which of the following medications WOULD NOT interact to increase the risk of bleeding with dabigatran?
   a. Dronedarone
   b. Clopidogrel
   c. Rifampin
   d. Verapamil

5. Which of the following statements accurately describes the results of the RE-LY trial?
   a. Dabigatran 150 mg twice daily was found to be superior to warfarin in preventing stroke or systemic embolism.
   b. Dabigatran 110 mg twice daily was found to be inferior to warfarin in preventing stroke or systemic embolism.
   c. Dabigatran 150 mg twice daily was found to be superior to warfarin in reducing bleeding events.
   d. A and C.

6. Which of the following adverse effects occurred in approximately 11 percent of patients on dabigatran in the RE-LY trial?
   a. Major bleeding
   b. Dyspepsia
   c. Headache
   d. Elevated LFT’s

7. Which of the following is NOT an appropriate patient counseling point with use of dabigatran?
   a. Once the bottle is opened, the product must be used within 120 days.
   b. Only one capsule should be removed at a time and the bottle should be closed tightly.
   c. It is appropriate to store dabigatran with your other medications in a pill organizer.
   d. Dabigatran capsules should not be opened, chewed, or crushed.

8. According to the recent report in Circulation, the average daily cost of dabigatran is approximately:
   a. $5
   b. $20
   c. $1.50
   d. $9

9. According to the analysis reported in Circulation, what would be the most cost effective therapy for stroke prevention in a patient with a CHADS2 score of 2 who has maintained a therapeutic INR for the last six months while on warfarin therapy?
   a. Aspirin
   b. Warfarin
   c. Dabigatran
   d. Clopidogrel and aspirin

10. Patients can be safely converted to dabigatran from warfarin when the INR is < 2.0.
    a. True
    b. False

11. Which dosing schedule is correct when switching a patient from dabigatran to warfarin who has a CrCl of 45 mL/min?
    a. Start warfarin three days before stopping dabigatran.
    b. Start warfarin two days before stopping dabigatran.
    c. Start warfarin one day before stopping dabigatran.
    d. Start warfarin one week before stopping dabigatran.

12. Which of the following factor(s) should be considered before starting dabigatran?
    a. Appropriate indication
    b. Renal function
    c. Cost to patient
    d. All of the above

13. Patients are at a higher risk of bleeding with dabigatran if:
    a. They are more than 75 years old
    b. They have renal dysfunction
    c. They take chronic NSAIDS
    d. All of the above

14. Dabigatran is safe for use in pregnancy.
    a. True
    b. False

15. According to the ACCF/AHA guideline update in February 2011, dabigatran should be used as an alternative to warfarin, regardless of a documented history of therapeutic INRs.
    a. True
    b. False
16. You are preparing to fill and dispense a prescription for dabigatran 150 mg twice daily. Which of the following statements is CORRECT when filling or dispensing dabigatran?
   a. Pharmacists should open the manufacturer bottle and transfer the capsules to an amber vial.
   b. The filled prescription of dabigatran should be stored in the refrigerator for pickup by the patient.
   c. The FDA does not require that a medication guide be dispensed with each dabigatran prescription.
   d. Pharmacists should instruct patients to open one bottle at a time if multiple bottles are dispensed.

17. According to the analysis reported in Circulation, for patients at a high risk of stroke (CHADS2 score ≥ 3), which anticoagulant option is more cost-effective?
   a. Dabigatran
   b. Warfarin
   c. Clopidogrel and aspirin
   d. Aspirin

18. Which of the following is a disadvantage with dabigatran use?
   a. Increased risk of intracranial bleeds
   b. Increased laboratory monitoring required
   c. Fixed-dose regimen
   d. No specific antidote

19. Which of the following represents a mechanism for drug interactions with dabigatran?
   a. CYP3A4 inhibition
   b. P-glycoprotein induction
   c. CYP2D6 inhibition
   d. Binding site displacement

20. According to a post-hoc analysis, both doses of dabigatran were associated with lower risks of intra- and extracranial bleeds compared to warfarin in patients younger than 75 years old.
   a. True
   b. False

Anticoagulation Update: Focus on Dabigatran And Its Impact on Current Practice
July 2, 2012 (expires July 2, 2015) • Activity Type: Knowledge-based

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Quiz: Shade in your choice
   1. ☐ ☐ ☐ ☐ ☐ 11. ☐ ☐ ☐ ☐ ☐
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   3. ☐ ☐ ☐ ☐ ☐ 13. ☐ ☐ ☐ ☐ ☐
   5. ☐ ☐ ☐ ☐ ☐ 15. ☐ ☐ ☐ ☐ ☐
   6. ☐ ☐ ☐ ☐ ☐ 16. ☐ ☐ ☐ ☐ ☐
   7. ☐ ☐ ☐ ☐ ☐ 17. ☐ ☐ ☐ ☐ ☐
   8. ☐ ☐ ☐ ☐ ☐ 18. ☐ ☐ ☐ ☐ ☐
   9. ☐ ☐ ☐ ☐ ☐ 19. ☐ ☐ ☐ ☐ ☐
  10. ☐ ☐ ☐ ☐ ☐ 20. ☐ ☐ ☐ ☐ ☐

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   23. Age group: ☐ a. 21–30 ☐ b. 31–40 ☐ c. 41–60 ☐ d. 61–60 ☐ e. Over 60
   24. Did this article achieve its stated objectives?
      ☐ a. yes ☐ b. no
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      ☐ a. all ☐ b. some ☐ c. very little ☐ d. none

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