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DUR Capsules

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New Oral Anticoagulants in the Management of Atrial Fibrillation
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Introduction
Since the 1950's, the only orally available anticoagulant has been the vitamin K antagonist warfarin. While it remains an effective oral anticoagulant, its use in clinical practice presents many challenges. These include a narrow therapeutic index, high inter- and intra-patient variability, slow onset and offset of action, drug and dietary interactions, and the need for routine monitoring.[1,2] However, in October 2010 a new anticoagulant, dabigatran (Pradaxa®), was approved by the Food and Drug Administration and it was followed in July 2011 by rivaroxaban (Xarelto®). This newsletter will review pertinent information about these agents as it relates to their use in clinical practice in the management of nonvalvular atrial fibrillation (AF).

Mechanism of Action
Dabigatran is an oral, reversible direct thrombin inhibitor that is currently indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[3] Because dabigatran is not orally absorbed, it is commercially available as a prodrug, dabigatran etexilate mesylate, which is quickly converted *in vivo* to the active form dabigatran.[1] Dabigatran works by binding to the active site of thrombin and inhibits both free and clot-bound thrombin.[1,3] Additionally, it inhibits other thrombin-mediating effects, such as the activation of factors V, VIII, XI, and XIII; the cleavage of fibrinogen; and thrombin-induced platelet aggregation.[1-3] After oral administration the maximum plasma concentration is attained within 0.5-2.0 hours, although it is 6 hours if administered after surgery.[1] This delay is thought to be a result of gastrointestinal paresis, surgery, and effects from anesthesia.

Rivaroxaban is an oral factor Xa inhibitor which was initially approved for the prophylaxis of deep vein thrombosis in patients undergoing knee or hip replacement surgery. In November 2011 it received the additional indication to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.[4] It selectively and competitively blocks the active site of factor Xa and does not require a cofactor, such as anti-thrombin III, for activity.[2,4] It also inhibits free and clot-bound factor Xa.[2,4,5] Maximum concentrations of rivaroxaban are reached in approximately 2 to 4 hours after oral administration; however, inhibition of factor Xa is highly dependent on drug concentration.[2,4]

Clinical Efficacy
Dabigatran was compared to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF in the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial.[6] It was a multi-national, non-inferiority, active-control, parallel-group, blinded study which randomized 18,113 patients with AF at risk for stroke (mean $CHADS_2$ score of 2.1) to either dabigatran etexilate 110 mg twice daily or dabigatran etexilate 150 mg twice daily (in a blinded fashion) or dose-adjusted warfarin with an INR goal of 2-3 (in an unblinded fashion). The primary outcome was any stroke (including hemorrhagic) or systemic embolism. Both doses of dabigatran were found to be noninferior to warfarin ($p < 0.001$) for any stroke or systemic embolism. However, the 150 mg dose of dabigatran was found to be superior to warfarin, with a relative risk (RR) of stroke or systemic embolism (combined) of 0.66 (95% CI, 0.53-0.82; $p<0.001$). It should be noted that the mean percentage of the study period during which the INR was within the therapeutic range for the patients on warfarin was 64%. With regards to bleeds, the rates of life-threatening bleeds, intracranial, and major or minor bleeds were significantly lower with each of the dabigatran doses compared to warfarin.

However the rate of gastrointestinal bleeding was significantly higher in the dabigatran 150 mg group (1.51% per year) compared to the warfarin group (1.02% per year) (95% CI, 1.19-1.89; p<0.001).[6] Another concerning adverse event seen was an increased rate of myocardial infarction (MI). It was seen with both doses of dabigatran (110 mg, 150 mg groups) compared to warfarin (0.72% per year, 0.74% per year vs. 0.53% per year). This was a significant relative increase in MI of 38% (RR 1.38; 95% CI, 1.00-1.91; p=0.048) for the dabigatran 150 mg group as compared to warfarin.

Efficacy for rivaroxaban in the treatment of nonvalvular AF was demonstrated in the ROCKET AF trial.[7] It was a multi-center, randomized, double blind, double dummy, noninferiority trial in which 14,264 patients with AF at moderate to high risk for stroke (mean $CHAD_2$ score of 3.5) were randomized to either rivaroxaban 20 mg daily or dose-adjusted warfarin (INR goal 2-3) daily. Like the RE-LY trial, the primary outcome was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. In this study, rivaroxaban was found to be noninferior to warfarin for any stroke or systemic embolism with a RR of 0.79 (95% CI, 0.66-0.96; p<0.001). The mean time within the therapeutic range for the warfarin group was 55%.[7] Major and clinically relevant non-major bleeds by themselves and combined did not significantly differ from warfarin (p=0.44). However the rate of intracranial hemorrhage was significantly lower in the rivaroxaban group as compared to warfarin group (0.5% per year vs. 0.7% per year, HR 0.67; 95% CI, 0.47-0.93; p=0.02).

Adverse Effects

The most common adverse effect with both of these drugs is bleeding, and both agents are contraindicated in patients with active pathological bleeding.[3,4] Additional risk factors identified that can increase the risk of bleeding with dabigatran include, dose, use of other drugs that can increase risk of bleeding (e.g., antiplatelet agents, heparin, chronic NSAID use, fibrinolytic therapy), renal impairment, and age $\geq$ 75 years. Gastrointestinal effects (e.g., dyspepsia, gastritis-like symptoms) are the most common non-hemorrhagic adverse effects reported with dabigatran.[1,3] In the RE-LY trial, 11.3% of the 150 mg group verses 5.8% of the warfarin group reported dyspepsia.[6]

Like all of the other factor Xa inhibitors (e.g., low molecular weight heparins), rivaroxaban carries a black box warning regarding the risk of spinal and epidural hematomas that can occur in patients who are receiving neuraxial anesthesia or undergoing spinal puncture.[4] It also has an additional black box warning for an increased risk of thrombotic events when therapy is discontinued in patients with nonvalvular AF.[4] This is a result of the increased rate of stroke observed in the clinical trials following the transition from rivaroxaban to warfarin in patients with AF.[4] As a result, it is recommended that if anticoagulation with rivaroxaban must be discontinued for a reason other than pathological bleeding, administration of another anticoagulant should be considered.[4]

Reversal of Anticoagulant Effect

Unlike warfarin, there is no antidote for reversal of the anticoagulant effect for either dabigatran or rivaroxaban. In the event of hemorrhagic complications, treatment should be discontinued with these agents and appropriate supportive measures should be initiated.[2,3] Because dabigatran is primarily excreted in the urine and shows low plasma protein binding, it can be dialyzed with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited.[2,3] Additionally, measurement of the aPTT or ECT may help guide the therapy approach.[3]

Unlike dabigatran, rivaroxaban is highly protein bound (92-95%); therefore, it is not expected to be dialyzable.[2,4] Current product labeling for rivaroxaban states that the use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered in patients with hemorrhagic events; however, this approach has not been specifically evaluated in human trials.[4] In the event of a rivaroxaban overdose, activated charcoal may be used to reduce its absorption.[2,4]

Dosing

There are several factors that should be taken into consideration with the dosing and administration of these drugs. These include the specific indication being treated, the patient's renal and hepatic function, concomitant medications, and the dose of the drug being used, especially in the case of rivaroxaban since its bioavailability is dose-dependent. Because dabigatran is eliminated primarily unchanged in the urine, it must be dose adjusted in patients with renal dysfunction (Table 1).[3] Rivaroxaban is metabolized by the

cytochrome (CYP) 3A4 and CYP2J2 pathways, as well as excreted unchanged in the urine (36%) and feces (7%).[2,4] In addition to dose adjustments in patients with renal dysfunction, rivaroxaban is not recommended for use in patients with moderate to severe hepatic dysfunction (Table 1).[4]

Bioavailability for the 10 mg dose of rivaroxaban is estimated at 80-100% and is not affected by food, while the 20 mg dose is about 66% in a fasting state.[4] When administered with food, the bioavailability of the 20 mg dose increases (mean AUC and C_{max} increasing by 39% and 76%).[4] As a result, it is recommended that both the 15 and 20 mg dose be administered with an evening meal.[4]

Table 1. Dosing for Nonvalvular Atrial Fibrillation[3,4]

	Dosing	Renal Function	Hepatic Function
Dabigatran	**Nonvalvular AF** CrCl >30 ml/min: 150 mg po BID	**Nonvalvular AF** CrCl >30 ml/min: 150 mg po BID CrCl 15-29 ml/min: 75 mg po BID CrCl <15 ml/min: Not recommended	No issues
Rivaroxaban	**Nonvalvular AF** CrCl >50 ml/min: 20 mg po daily* * With an evening meal	**Nonvalvular AF** CrCl >50 ml/min: 20 mg po daily* CrCl 15-50 ml/min: 15 mg po daily* CrCl <15 ml/min: Not recommended	Avoid in moderate or severe liver impairment or with any degree of hepatic disease associated with coagulopathy

Table 2. Transitions between Oral Anticoagulants and Warfarin[3,4]

	Converting to warfarin*	Converting from warfarin
Dabigatran	CrCl ≥50 ml/min: start warfarin 3 days before stopping dabigatran CrCl >30-50 ml/min: start warfarin 2 days before stopping dabigatran CrCl 15-30 ml/min: start warfarin 1 day before stopping dabigatran CrCl <15 ml/min: no recommendations can be made	Discontinue warfarin and initiate dabigatran when INR is < 2
Rivaroxaban	No information from clinical trials is available to guide transition	No information from clinical trials is available to guide transition

* Because dabigatran can influence the INR, the INR will better reflect warfarin's effect after dabigatran has been discontinued for at least 2 days.

Drug Interactions

Since these drugs are anticoagulants, their use with other antithrombotic or antiplatelet agents will increase the risk of bleeding. Additionally, both drugs are P-glycoprotein (P-gp) efflux transporter substrates and rivaroxaban is a CYP3A4 inhibitor; therefore, drug interactions involving inhibitors or inducers of these enzymes/transporters may occur and require dosage adjustments (Table 3).[3,4] In addition caution should be used with other drugs that are known CYP3A4 (rivaroxaban) or P-gp inducers (both agents) and inhibitors [1-3]

Table 3. Drug Interaction Dosing Recommendations[3,4]

	Dabigatran (P-gp substrate)	Rivaroxaban (P-gp and CYP3A4 substrate)
P-gp inhibitors	CrCl 30-50 ml/min: decrease dose to 75 mg BID with systemic ketoconazole or dronedarone CrCl 15-30 ml/min: AVOID use	Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir-containing products, conivaptan)
P-gp inducers	AVOID concomitant use with rifampin	Avoid concomitant use with COMBINED P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, phenobarbital, St. John's wort)

Only drugs interactions that have prompted dosage adjustments are listed above. Other drug interactions have been identified with these agents, however no formal dose adjustments have been recommended at this time.

Discontinuation

If possible, dabigatran should be discontinued 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding.[3] Longer times should be considered for patients undergoing major surgery, spinal puncture, or placement of a spinal epidural catheter or port, in whom complete hemostasis is required.[3] Rivaroxaban should be stopped at least 24 hours before any procedures if anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures.[4]

Monitoring
Unlike warfarin, routine monitoring is not required with these new drugs. It is unlikely that routine monitoring would have clinical benefit in most patients, but there are scenarios in which monitoring drug concentrations could be valuable. These include situations of overdose, bleeding or thrombotic event, evaluation of drug interactions, monitoring in patients with renal or hepatic dysfunction, assessment of medication adherence, or the need for an invasive procedure.[2,8] Coagulant tests that are affected by dabigatran and rivaroxaban have been identified, but no therapeutic ranges have been established and no laboratory assays can be recommended for monitoring at this time. [1,2,4,6,8]

Treatment Guidelines
After the RE-LY trial was published, The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) updated their most recent AF guidelines in a focused statement to include dabigatran. They recognized dabigatran as a useful 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 (creatinine clearance <15 mL/min), or advanced liver disease (impaired baseline clotting function).[9] However, they also noted that due to its twice-daily dosing and greater risk of nonhemorrhagic side effects, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran.[9]

The recently updated American College of Chest Physicians Evidenced-Based Clinical Guidelines (CHEST guidelines), also suggested using dabigatran 150 mg twice daily over dose-adjusted warfarin (goal INR 2-3) in their recommendations that favored oral anticoagulation.[10] These included patients with a $CHADS_2$ score of >=/ 1. That recommendation does not apply to those patients with AF with concomitant mitral stenosis, stable coronary artery disease, or acute coronary syndrome with/without intracoronary stent placement.[10] This is a result of those patient populations not being adequately represented in the RE-LY trial. But like the ACCF/AHA guidelines, the CHEST guidelines also state it is reasonable for warfarin-experienced patients who are well controlled (i.e., INR within therapeutic range a high proportion of the time) to continue on warfarin therapy if they are satisfied with therapy and are tolerating it well, rather than switching to dabigatran.[10]

Because rivaroxaban received FDA approval for use in AF in November 2011, it was not considered for inclusion into either of these guidelines.

Place in therapy
Both of these new oral anticoagulants offer advantages over warfarin which include: rapid onset and offset of action, fixed dose, lack of routine monitoring, low inter- and intra-patient variability, and lack of dietary interactions. Having alternatives to warfarin for the treatment of AF is important since there have been many barriers to using warfarin identified in the literature. These barriers include inconvenience of monitoring, difficulty in maintaining therapeutic INRs, physician prior experience with warfarin, lack of clinical resources, and patient-related factors (e.g., perceived embolic and hemorrhagic risk, patient age).[11] However, these newer agents still present bleeding risks. Other challenges with them include the lack of a reliable laboratory test to measure anticoagulant effect, lack of an antidote, and limited experience with their use outside the setting of clinical trials.[2,8] A recent meta-analysis conducted with seven randomized control trials with dabigatran (i.e., AF, venous thromboembolism, acute coronary syndrome [ACS]) found an increased risk of MI or ACS in patients using dabigatran compared to patients using other various control therapies (i.e., enoxaparin, dose-adjusted warfarin, placebo).[12] This also warrants further investigation.

Both dabigatran and rivaroxaban may be beneficial for those patients with poor INR control while on warfarin therapy due to drug-drug or drug-food interactions or those who find routine INR management burdensome. Overall cost of therapy, including drug cost and INR monitoring, and patient preference/lifestyle should also be taken into consideration since the cost of dabigatran and rivaroxaban is higher than warfarin, but may require fewer laboratory monitoring-related costs.

Conclusion
These new oral anticoagulants have demonstrated safety and comparable efficacy to warfarin when used in the prevention of stroke in patients with nonvalvular AF and offer several advantages for both patients and

healthcare providers. However their true place in therapy remains uncertain at this time, as well as their bleeding and dabigatran's potential cardiovascular risks. Clinical trials are currently underway to address some of these questions and will provide more data on their long-term use and use in other patient populations for which warfarin is currently utilized. Additionally, more clinical experience is needed with these drugs to help determine which patient populations would benefit most from their use.

The anticoagulant class is managed on the West Virginia Medicaid Preferred Drug List. Preferred and non-preferred agents and prior authorization criteria are listed in the following table:

ANTICOAGULANTS

Preferred	Non-Preferred	PA Criteria
PRADAXA (dabigatran) [AP] warfarin XARELTO (rivaroxaban) [AP]		Pradaxa and Xarelto will be approved for non-valvular atrial fibrillation. Xarelto will be approved for DVT prophylaxis if treatment is limited to 35 days for hip replacement surgeries or 12 days for knee replacement surgeries.
ARIXTRA (fondaparinux) [CL] FRAGMIN (dalteparin) [CL] LOVENOX(enoxaparin) [CL]		Trials of each of the preferred agents will be required before a non-preferred agent will be approved unless one of the exceptions on the PA form is present.

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