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Dabigatran: An Alternative to Warfarin

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Introduction: Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, estimated to affect nearly 2.3 million people in the United States.[1] It is characterized by rapid, uncoordinated atrial depolarization which can lead to blood stasis and the subsequent formation and embolization of thrombi. Consequently, the rate of ischemic stroke among patients with non-valvular AF averages 5% per year, which is 2 to 7 times higher than the general population.[1] Thus, prevention of ischemic stroke is an essential component in the management of AF. Until recently, aspirin and warfarin (Coumadin®) were the only oral antithrombotic therapies routinely used for stroke prevention in patients with AF.[2] Warfarin, a vitamin K antagonist, has been the only oral anticoagulant available in the United States for the past 50 years.[3,4] However, attainment of optimal anticoagulation with warfarin can be problematic and therefore, requires intensive monitoring of the international normalized ratio (INR). Evidence suggests that patients on long-term warfarin therapy are outside the therapeutic range more than one-third of the time. One recent meta-analysis revealed that 44% of bleeding complications were associated with INRs above the therapeutic range and 48% of thromboembolic events occurred with INRs below it.[5] Difficulties in achieving optimal anticoagulation with warfarin can be attributed to its slow onset of action (~5 days), unpredictable and variable pharmacological effects, narrow therapeutic index, as well as numerous food and drug interactions.[3,4] Consequently, a variety of new oral anticoagulant therapies are being developed to overcome the limitations of warfarin. Dabigatran etexilate (Pradaxa®; Boehringer Ingelheim Pharmaceuticals, Inc.), an orally administered anticoagulant, has been recently approved by the Food and Drug Administration (FDA) for the reduction of stroke and systemic embolism in patients with non-valvular AF.[2-4] It is not currently FDA-approved for primary or secondary prevention of venous thromboembolism.[3,4] With no recommended routine monitoring, a faster onset of action, and less food and drug interactions, dabigatran offers some important clinical advantages over warfarin therapy.[2-5]

Mechanism of Action: Dabigatran, an oral direct thrombin inhibitor (DTI), is a synthetic, univalent nonpeptide that competitively and reversibly blocks both free and fibrin-bound thrombin. Thrombin (Factor IIa), a plasma serine protease, is the most potent and final agonist in the blood coagulation cascade.[2-6] Major functions of thrombin include the conversion of soluble fibrinogen into insoluble fibrin along with the activation of platelets and Factors V, VIII, and X. Thus, the use of dabigatran in AF can play a significant role in reducing thrombus formation, resulting in a subsequent reduction in the risk of ischemic stroke.[2-5]

Pharmacokinetics: Dabigatran etexilate meslyate, the orally administered prodrug of dabigatran, has a bioavailability of 3 to 7% which is independent of dose and coadministration with food. Since the drug requires an acidic environment for adequate absorption, its capsule formulation contains tartaric acid to help maintain a low gastric pH.[3] After oral administration, dabigatran etexilate is hydrolyzed by microsomal carboxylesterases into the active moiety, dabigatran. Due to its rapid absorption, dabigatran's peak plasma levels occur within 1 to 2 hours following administration. Approximately 20% of dabigatran undergoes further transformation into active glucuronide metabolites.[3] Plasma levels decline in a biphasic manner characterized by a rapid distribution phase followed by a prolonged elimination phase, resulting in a mean half-life of 12 to 14 hours. As would be expected, steady state levels are achieved within 3 days of therapy. Dabigatran is only 35% protein bound. Approximately 80% of dabigatran and a small amount of its active metabolites undergo renal elimination.[6]

Select Clinical Trials: The **P**revention of **E**mbolic and **Thro**mbotic Events in Patients with Persistent AF (PETRO) study was a 12-week, multi-center, Phase II clinical trial to determine the safety of dabigatran doses in patients with AF with a high risk of thromboemolic events. The study included patients with AF with coronary artery disease (CAD) plus one or more of the following: hypertension requiring medical therapy, diabetes, symptomatic heart failure or left ventricular ejection fraction (LVEF) <40%, age >75 years, or a previous stroke or transient ischemic attack (TIA). Patients (N=502) were randomized to receive either dabigatran or warfarin; those randomized to dabigatran received 50-, 150-, or 300-mg twice daily along with no aspirin or aspirin 81- or 325-mg once daily. Patients in the warfarin comparator group did not receive aspirin. The primary goal of this trial was to identify a safe and effective dose of dabigatran as determined by the occurrence of bleeding and thromboembolic events over the trial period. Irrespective of aspirin assignment, patients receiving dabigatran 300 mg twice daily experienced a higher incidence of bleeding events than those in the 150- or 50-mg twice daily groups (P=0.0002; P=0.01, respectively), while thromboembolic events were limited to those patients in the dabigatran 50 mg twice daily groups with either no aspirin or 81 mg aspirin (1.7% versus 4.8%, respectively; P=not available). Based on the results of this study, the authors concluded that the 150 mg dose of dabigatran given twice daily was relatively safe and demonstrated adequate anticoagulant activity.[7]

The FDA approved dabigatran based on the results of the **R**andomized **E**valuation of **L**ong-Term Anticoagulation Therap**y** (RE-LY) study. This randomized, Phase III, multi-center, non-inferiority trial compared the clinical efficacy of dabigatran etexilate 110- or 150-mg administered twice daily with the open-label use of warfarin in patients with non-valvular AF at increased risk of stroke. Patients (N=18,113) were eligible if they had at least one of the following risk factors: previous stroke or TIA, LVEF <40%, New York Heart Association (NYHA) class II-V heart failure within 6 months before screening, age ≥75 years, or age 65 to 74 years along with diabetes, hypertension, or CAD. Use of other antiplatelet agents and aspirin at a daily dose <100 mg was permitted during the study. The primary efficacy and safety outcomes were the incidence of stroke/systemic embolism and major hemorrhage, respectively. Requirements of major bleeding included the following: a reduction in hemoglobin of at least 20 g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. The incidence of stroke/systemic embolism was 1.53% per year for patients receiving dabigatran 110 mg twice daily, 1.11% per year for patients receiving dabigatran 150 mg twice daily, and 1.69% per year for patients receiving warfarin. Both doses of dabigatran were non-inferior to warfarin (P<0.001 for both), but the dabigatran 150 mg dosing regimen was also found to be superior to warfarin therapy (P<0.001). Major hemorrhage occurred at a rate of 2.71% per year for patients receiving dabigatran 110 mg twice daily (P=0.003), 3.11% per year for patients receiving dabigatran 150 mg twice daily (P=0.31), and 3.36% per year for patients receiving warfarin. The authors concluded that in regards to the prevention of stroke/systemic embolism, dabigatran 110 mg twice daily was non-inferior to warfarin with a lower rate of major hemorrhage, while dabigatran 150 mg twice daily was found to be superior to warfarin with a similar incidence of major hemorrhage.[8]

Adverse Events: The most common adverse events of dabigatran are bleeding and gastrointestinal (GI) disorders (e.g., dyspepsia, gastritis, esophagitis).[2,4-6] In the RE-LY trial, approximately 17% of patients taking dabigatran 150 mg twice daily experienced some type of bleeding adverse event; major bleeding was documented in about 3% of those patients. Additionally, a higher rate of major GI bleeding occurred in patients receiving the dabigatran 150 mg dosage compared to warfarin (1.6% versus 1.1%, respectively; P<0.001).[6] The incidence of GI adverse events was greater in patients treated with dabigatran 150 mg twice daily compared to those treated with warfarin (35% versus 24%, respectively; P=not available).[6] It has been hypothesized that the high incidence of GI intolerance can be attributed to the tartaric acid component of the dabigatran capsules.[3] Unlike its predecessor, ximelagatran, dabigatran has not been shown to be associated with significant hepatotoxicity.[2-4]

Drug Interactions: Dabigatran is not a substrate, inhibitor, or inducer of the cytochrome (CYP) 450 enzyme system; thus its risk of interacting with CYP 450 metabolized medications is minimal.[2,5] Furthermore, since the drug has a relatively low degree of protein binding, it is not generally associated with drug displacement interactions. However, dabigatran etexilate is a substrate of P-glycoprotein, an efflux transporter; therefore, coadministration with a P-glycoprotein inducer (e.g., rifampin) or inhibitor (e.g., amiodarone, quinidine, verapamil, ketoconazole, clarithromycin) can result in reduced or elevated dabigatran plasma concentrations, respectively. Despite these effects, the manufacturer has not recommended any changes in dosing with the concurrent use of P-glycoprotein inhibitors. However, the avoidance of concomitant therapy with P-glycoprotein inducers is recommended.[3,6] Medications that can increase gastric pH, like proton pump inhibitors, could potentially reduce the absorption of dabigatran. Although a study which evaluated the coadministration of dabigatran with pantoprazole found that the resulting decrease in dabigatran levels was not clinically significant.[2-6]

Special Populations: Dabigatran is classified as a pregnancy-risk category C medication due to safety concerns reported in animal studies (e.g., higher incidence of dead offspring, excess vaginal/uterine bleeding close to parturition, and a reduction in implantation); however, there are no adequate or well-controlled studies in pregnant women which directly link these findings to humans.[6] In addition, it is not known whether dabigatran is excreted in human breast milk; therefore, the manufacturer recommends that caution should be exercised when dabigatran is given to a nursing woman. The safety and effectiveness of dabigatran in pediatric patients has not been established. However, there are data to support the use of dabigatran in the geriatric population.

Dose and Administration: In patients with a creatinine clearance (CrCl) >30 mL/min, the recommended dose of dabigatran is 150 mg orally taken twice daily with or without food.[6] For patients with a CrCl 15-30 mL/min, the recommended dose is 75 mg twice daily. There are no dosing recommendations for patients with a CrCl <15 mL/min, for those on dialysis, or for patients with hepatic impairment. Dabigatran capsules should be swallowed whole since administration involving breaking, chewing, or emptying the capsule contents has been shown to significantly increase drug absorption by up to 75%. In cases of a missed dose, the dose should be taken as soon as possible on the same day; however, the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. Converting between dabigatran and other oral or injectable anticoagulants is described in Tables 1 and 2. Due to dabigatran's minor impact on the INR, it is important to note that when converting a patient from dabigatran to warfarin, the INR will not be a true reflection of warfarin's sole therapeutic effects until 2 days after discontinuation of dabigatran. Recommendations for stopping dabigatran therapy prior to a surgical procedure are dependent upon renal function and are described in Table 3. Unlike warfarin, there is not a specific agent recommended for reversing dabigatran's anticoagulant effects.[3] If a procedure cannot be delayed, the risk of bleeding can be assessed by the ecarin clotting time (ECT); if this test is not available, the activated partial thromboplastin time (aPTT) can be utilized to approximate dabigatran's activity.[6]

Table 1: Converting Between Dabigatran and Warfarin[6]

Warfarin → Dabigatran
Discontinue warfarin and initiate dabigatran when INR <2.0
Dabigatran → Warfarin
CrCl >50 mL/min → Initiate warfarin 3 days before discontinuing dabigatran
CrCl 31-50 mL/min → Initiate warfarin 2 days before discontinuing dabigatran
CrCl 15-30 mL/min → Initiate warfarin 1 day before discontinuing dabigatran
CrCl <15 mL/min → No recommendations

Table 2: Converting Between Dabigatran and Parenteral Anticoagulants[6]

Parenteral Anticoagulant → Dabigatran
Intermittent parenteral anticoagulant Initiate dabigatran 0 to 2 hours prior to the next scheduled dose of the parenteral anticoagulant Continuous parenteral anticoagulant Initiate dabigatran at the time of discontinuation of the continuous parenteral anticoagulant
Dabigatran → Parenteral Anticoagulant
CrCl ≥30 mL/min → Initiate parenteral drug 12 hours after discontinuing dabigatran
CrCl <30mL/min → Initiate parenteral drug 24 hours after discontinuing dabigatran

Table 3: Recommendations for Discontinuing Dabigatran Prior to Surgery[6]

Dabigatran → Surgery
CrCl ≥50 mL/min → Discontinue dabigatran 1 to 2 days prior to surgery*
CrCl <50 mL/min → Discontinue dabigatran 3 to 5 days prior to surgery*

*Consider longer times in patients undergoing major surgical procedures, spinal puncture, or placement of a spinal or epidural catheter or port, who require complete hemostasis

Assessment of Dabigatran's Anticoagulant Activity: The predictable pharmacodynamic response of dabigatran is attributed to its rapid onset of action, consistent pharmacokinetic profile, and lack of clinically significant drug interactions. Because of these properties, dabigatran requires no coagulation monitoring in clinical practice.[2-6] While coagulation monitoring is not required, a number of parameters such as ECT, thrombin clotting time (TT), and aPTT can be used to determine dabigatran's anticoagulant activity. The ECT provides the strongest estimation of dabigatran's pharmacologic effects; if this test is not available, the aPTT can provide an approximation of the drug's anticoagulant action.[6] At therapeutic plasma concentrations dabigatran has only a minor impact on prothrombin time (PT) and INR; therefore, INR monitoring during dabigatran therapy is not recommended.

Reversing Dabigatran's Anticoagulant Effects: Unlike other anticoagulants, there is no specific antidote available to reverse bleeding resulting from dabigatran therapy or overdose.[3,4,6] In patients with normal renal function who experience mild bleeding, discontinuing dabigatran or delaying administration of the next scheduled dose may suffice. In those patients with moderate-to-severe or life-threatening bleeding, dabigatran therapy should be discontinued and the source of bleeding should be fully assessed. Since dabigatran is primarily renally excreted, maintaining adequate diuresis may expedite drug elimination. If necessary, dabigatran can be dialyzed with removal of approximately 60% of the drug over 2 to 3 hours. Significant dabigatran-induced bleeding episodes may necessitate the use of packed red cells or fresh-frozen plasma transfusions or surgical hemostasis. There is some experimental data supporting the use of recombinant Factor VIIa (e.g., NovoSeven®), prothrombin complex concentrates (e.g., FEIBA), or concentrates of coagulation factors II, IX, or X as dabigatran reversal agents, but the clinical effectiveness of these products in treating patients with serious bleeding secondary to dabigatran has not been fully established.[4,6] Although not evaluated in humans, *in vitro* studies have shown that dabigatran etexilate is adsorbed by activated charcoal therapy. Therefore, the administration of activated charcoal within 1 to 2 hours of dabigatran overdose may be beneficial in preventing GI absorption.[4]

Availability: Dabigatran is available as 75- and 150-mg capsules, in bottles of 60 or as a 10-by-6 blister card allowing for a 30-day supply. However, due to the potential for product breakdown from moisture and loss of potency, the capsules should only be dispensed and stored in the original bottle with the original desiccant or in the blister package. Once the bottle is opened, the capsules have a 60-day expiration date.[5,6]

Formulary Status and Cost: Dabigatran was added to the CCHS Formulary in December 2010. Average wholesale pricing information for dabigatran capsules and warfarin 5 mg tablets is located in Table 4.[9]

Table 4: Average Wholesale Price (AWP) for Dabigatran versus Warfarin[9]

Drug Name	AWP Per Unit	AWP for 30-Day Supply
Dabigatran 75 mg capsule	$ 4.40	$ 264.00
Dabigatran 150 mg capsule	$ 4.40	$ 264.00
Warfarin 5 mg tablet – Brand (Coumadin®)	$ 1.50	$ 45.00
Warfarin 5 mg tablet - Generic	$ 0.70	$21.00

Conclusion: Dabigatran is the first oral anticoagulant to be approved in the United States in over 50 years. It offers several advantages over warfarin which include no requirement for coagulation monitoring, fewer clinically relevant food and drug interactions, a fixed dosing regimen, and rapid onset of action. However, dabigatran is not without its own limitations. With no recommended coagulation monitoring, there is no way to objectively assess adherence or to easily determine if a patient is at risk for bleeding. And most importantly, there is no specific antidote to reverse the anticoagulant effects of dabigatran. With all that aside, dabigatran is currently a viable oral alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF.

References:

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Formulary Update

Please be aware of this addendum to the Formulary Update in the May/June 2011 Pharmacotherapy Newsletter:

Abiraterone (Zytiga™): Abiraterone is restricted to continuation of therapy from home. It was determined after further review that it is not necessary to include this medication in the list of Oral Chemotherapy Agents that must be ordered by a staff physician as per Pharmacy Policy #04-003 "Placing and Processing Orders for Chemotherapy and Biological Agents." Therefore, abiraterone is not required to be ordered by a staff physician.