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Evidence Overview and Clinical Role of Dabigatran (Pradaxa®)

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The FDA recently approved the oral direct thrombin inhibitor (DTI), dabigatran (Pradaxa ®) to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). This is the first oral anticoagulant approved in over 50 years. The lack of laboratory monitoring and minimal food and drug interactions make dabigatran therapy less complicated than currently available treatments.[1] This article will focus on a review of the current evidence to help guide the clinical use of dabigatran.

Background

The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation therapy. A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[2] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[3] However, it is widely known that warfarin use can be complicated and inconvenient for patients, due to frequent laboratory monitoring, multiple drug and food interactions and unpredictable pharmacokinetics.[4] Consequently, warfarin is often underutilized, with only 64% of eligible patients taking warfarin therapy.[5]

Anticoagulants are a key component to managing patients with AF who are at an increased risk of stroke from cardioembolic events. Current American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (CHEST) on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with VKA for patients with one or more risk factors or in secondary prevention patients.[6] The guidelines also recommend VKA therapy for patients with a $CHADS_2$ score (scheme for stroke prediction) of ≥2 (Table 1).

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[7]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Clinical Efficacy

FDA approval of dabigatran was based on a large, phase III trial in patients with AF called the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study.[8] Although not currently FDA approved for additional indications, dabigatran has also been studied for the use in acute treatment of venous thromboembolism (VTE) and prevention of VTE after total knee replacement (TKR) and total hip replacement (THR) in the RE-COVER, RE-NOVATE, RE-MODEL and RE-MOBILIZE studies.[9,10,11,12]

RE-LY[8]

The RE-LY study was a non-inferiority trial of over 18,000 patients with AF and an additional risk factor for stroke. Patients were randomized to receive dabigatran 110mg or 150mg twice daily, in a blinded manner, or warfarin dose-adjusted to an INR goal of 2.0-3.0, in an open-label design. Patients were followed for a median of 2 years. The primary outcome was stroke or systemic embolism. Secondary outcome measures were stroke, systemic embolism and death. Other outcomes included myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary safety outcome measure was major hemorrhage. Patients had similar baseline characteristics, with a mean age of 71, an average $CHAD_2$ score of 2.1 and 64% were male. Over half of the enrolled patients had been on previous long-term VKA therapy and the other half were naïve to VKA treatment.

Both doses of dabigatran were found to be non-inferior to warfarin (Relative Risk [RR] 0.90; 95% Confidence Interval [CI], 0.74 to 1.10; p<0.001 for noninferiority for dabigatran 110mg) and the dabigatran 150mg group was shown to be superior to warfarin for the primary outcome (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001). The absolute risk reduction for the primary outcome associated with dabigatran 150mg over warfarin was 0.60%, resulting in a number needed to treat of 178.[13] Rates of hemorrhagic stroke were significantly decreased in both groups of dabigatran and all cause mortality was similar across all treatment groups. Of concern was an increased incidence of myocardial infarctions (MI) in both dabigatran groups (RR 1.29; 95% CI, 0.96 to 1.75; p=0.09 for dabigatran 110mg and RR 1.27; 95% CI, 0.94 to 1.71; p=0.12 for dabigatran 150mg) (Table 2).[13]

Table 2. RE-LY Trial Efficacy Outcomes[8,13]

Event	Dabigatran 110mg (n=6015)	Dabigatran 150mg (n=6076)	Warfarin (n=6022)
Stroke or Systemic Embolism	1.54%	1.11%*	1.71%
Hemorrhagic Stroke	0.12%*	0.10%*	0.38%
Myocardial Infarction	0.82%	0.81%	0.64%
All Cause Mortality	3.75%	3.64%	4.13%

* Indicates statistically significant findings compared to warfarin.

Dabigatran therapy was associated with gastrointestinal (GI) side effects (e.g., dyspepsia, GI hemorrhage, nausea) leading to higher discontinuation rates than warfarin, 21% and 16% respectively.[8] In the RE-LY trial, the dabigatran 110mg group was found to have less major bleeds than warfarin (RR 0.80; 95% CI, 0.69 to 0.93; p=0.003).[8] Both doses of dabigatran were associated with fewer intracranial bleeds compared to warfarin (RR 0.31; 95% CI, 0.20 to 0.47; p<0.001 for dabigatran 110mg and RR 0.40; 95% CI, 0.27 to 0.60; p<0.001 for dabigatran 150mg). GI bleeds were higher in both dabigatran groups compared to warfarin (Table 3). Initially, liver function tests were performed monthly, due to concerns raised about serious hepatotoxicity attributed to another direct thrombin inhibitor, ximelagatran. At six months the safety monitoring board deemed this frequency of testing to be unnecessary as dabigatran therapy resulted in similar liver function test elevations as warfarin, 1.9% vs. 2.2%, respectively.[8]

Table 3. RE-LY Trial Safety Outcomes[8,13]

Adverse Event	Dabigatran 110mg / Dabigatran 150mg (% per yr)	Warfarin (% per year)	P-Value*
Major Bleeds	2.87 / 3.32	3.57	0.003 / 0.32
Intracranial Bleeds	0.23 / 0.30	0.74	<0.001 / <0.001
GI Bleeds	1.12 / 1.51	1.02	0.43 / <0.001

* Dabigatran 110mg vs warfarin / dabigatran 150mg vs warfarin

Conclusions on the relative efficacy of warfarin and dabigatran are uncertain based on the RE-LY trial due to the open-label study design causing threats to the validity of the data. Another direct thrombin inhibitor, ximelagatran, was compared to warfarin in an open-label fashion for stroke prevention in patients with AF (SPORTIF III) and was found to have a numerical trend toward efficacy but a second double-blind study (SPORTIF V) showed opposite results.[14] The amount of time a patient's international normalized ratios (INR) are in therapeutic range, for those taking warfarin, can have a

significant clinical impact on treatment outcomes. The mean time in therapeutic range (TTR) for warfarin treated patients in the RE-LY study was 64%. In a RE-LY trial sub-analysis of TTR the level of INR control was compared to outcomes and it was found that the rate of non-hemorrhagic stroke and systemic embolism were lower as TTR improved in the warfarin group.[15] Additionally, the FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[14] The incidence of major bleeds and gastrointestinal bleeding also decreased in the warfarin groups as TTR improved. Major bleeds were less in the dabigatran groups, compared to warfarin, only at centers in which TTR was worse than the median.[14] However, rates of intracranial bleeds were not affected by TTR, with consistently lower incidences in both dabigatran groups.[15] Also of concern is the trend toward higher rates of MI associated with both doses of dabigatran on drug as well as off-drug. The reason for the higher rate of MI with dabigatran has not yet been determined. Additional data is needed to delineate this risk. With discontinuation rates being higher in both dabigatran groups compared to warfarin, there is an added concern of adherence in this population whom often is seen infrequently for follow-up.

RE-COVER[9]

RE-COVER was a non-inferiority study in over 2500 patients comparing dabigatran to warfarin for the acute treatment of VTE. Participants were randomly assigned in a blinded manner to six months of treatment with either dabigatran 150mg twice daily or warfarin, dose-adjusted to an INR of 2.0-3.0, after initial treatment with parenteral anticoagulation (median duration of 9 days). The primary outcome measure was incidence of recurrent symptomatic, objectively confirmed VTE and related deaths. Noninferiority was determined for the hazard ratio with the predefined margin of 2.75 and the difference in risk with the predefined margin of 3.6 percentage points. Dabigatran was found to be non-inferior to warfarin with an incidence rate of recurrent VTE of 2.4% compared to 2.1% for warfarin (difference in risk 0.4%; 95% CI, -0.8 to 1.5; p=<0.001 for prespecified non-inferiority margin). Warfarin and dabigatran were similar in regards to major bleeds, deaths, and acute coronary syndromes.

The RE-COVER study showed dabigatran to be as effective as warfarin over a six month time period for acute treatment of VTE. A statistically significant number of patients discontinued treatment in the dabigatran group compared to warfarin, suggesting clinically relevant issues with tolerability over time. The question of whether dabigatran alone, without use of an injectable anticoagulant, is effective for acute VTE treatment remains unanswered.

RE-NOVATE, RE-MODEL and RE-MOBILIZE [10,11,12]

RE-NOVATE and RE-MODEL were studies that evaluated the efficacy of dabigatran for the prevention of VTE in patients undergoing TKR and THR using the European dosing recommendations for enoxaparin (40mg once daily) as the comparator drug. In these randomized, double blind studies patients received dabigatran 150mg or dabigatran 220mg once daily compared to enoxaparin 40mg subcutaneous once daily. The primary efficacy outcomes were the same for both studies, the composite of total venous thromboembolism (venographic or symptomatic) and mortality from all causes. In the RE-NOVATE trial the primary efficacy outcome occurred 6.7% in the enoxaparin group, 6.0% in the dabigatran 220mg group (absolute difference 0.7%; 95% CI, -2.9 to 1.6; p<0.0001) and 8.6% in the dabigatran 150mg group (absolute difference 1.9%; 95% CI, -0.6 to 4.4; p<0.0001) , with an average treatment duration of 32.6 days. In the RE-MODEL study the primary efficacy endpoint was experienced by 37.7% of the enoxaparin group, 36.4% of the dabigatran 220mg group (absolute difference -1.3%; 95% CI, -7.3 to 4.6; p=0.0003) and 40.5% of the dabigatran 150mg group (absolute difference 2.8%; 95% CI, -3.1 to 8.7; p=0.017), with an average treatment duration of 8.3 days. Both studies proved to be non-inferior to enoxaparin with a similar incidence of major bleeding.

The RE-MOBILIZE trial studied dabigatran use compared to enoxaparin, using the North American dosing regimen of 30mg twice daily, for prevention of VTE after knee arthroplasty surgery. Over 3000 patients received either dabigatran 220mg or dabigatran 150mg once daily or enoxaparin 30mg twice daily, in a randomized, double blind fashion. The primary efficacy outcome was the same as the RE-NOVATE and RE-MODEL studies, the composite of total VTE events (symptomatic or venographic) and all cause mortality. After an average of 14 days of treatment, both doses of dabigatran were deemed inferior to enoxaparin. Rates of VTE were experience by 25% in the enoxaparin group, 31% of patients in the dabigatran 220mg group (abosolute difference 5.78%; 95% CI, 0.78 to 10.77%; p=0.02 vs. enoxaparin) and 34% in the dabigatran 150mg group (absolute difference 8.39%; 95% CI, 3.44 to 13.35%; p<0.001 vs. enoxaparin). Major bleeding was similar among treatment groups.

Results from RE-NOVATE and RE-MODEL trials suggest dabigatran may have a role in the prevention of VTE. However, data from the RE-MOBILIZE trial suggest that more studies are needed to substantiate the efficacy of dabigatran compared to enoxaparin. Limitations to the data are that studies excluded or had a low incidence of patients with a history of VTE, those with severe renal or hepatic disease or those over 75 years of age. Additionally, a high number of patients were excluded because of the inability to adequately assess thromboembolism by contrast venography. The primary outcome was a composite measurement of symptomatic and venographic data, in which asymptomatic DVTs accounted for the majority of the events. The clinical importance of asymptomatic DVTs has yet to be determined and a bias in detecting events may have been present to do unilateral instead of bilateral venography. Due to the conflicting results of the use of dabigatran in VTE prevention, The Canadian Agency for Drugs and Technologies in Health (CADTH) preformed a systematic review and has recommended against the use of dabigatran for this indication.[17] The Cochrane Database for Systematic Reviews also evaluated direct thrombin inhibitors (DTI) for the prevention of VTE following TKR and THR. They concluded that no difference was found when only symptomatic VTE events were compared between groups. They caution, that the occurrence rate of symptomatic VTEs are so low, that none of the studies enrolled enough participants for them to be powered appropriately to make this determination.[18] A sensitivity analysis on the timing of anticoagulation initiation was also performed, based on evidence that this variable may impact the effectiveness of therapy as much as the actual treatment itself. The analysis found that DTI treatment started before surgery, resulted in less VTEs than treatment started after surgery, in comparison with LMWH. The Cochrane report concludes that DTIs are considered equally effective to LMWH in the prevention of VTEs in patients undergoing TKR and THR, but, overall there is insufficient evidence to support the use of dabigatran in preference to LMWH.[18] Additional studies evaluating the most effective dosing regimen along with use in a broader patient population will help to determine the role of dabigatran use as preventative therapy in patients undergoing orthopedic surgery.

Dosing

Dabigatran capsules should not be crushed or chewed and can be given without regard to food. Dabigatran is renally cleared and dosing is dependent upon renal function (table 4). Patients transitioning from warfarin to dabigatran should discontinue warfarin and start dabigatran when the INR is less than 2. If patients are switching from dabigatran to warfarin, warfarin should be started 1-3 days before stopping dabigatran, dependent on renal function (table 5). For patients on parenteral anticoagulants, dabigatran should be given 0-2 hours before the next dose of parenteral anticoagulation is due or at the time of discontinuing continuously administered parenteral medication. Patients taking dabigatran wishing to switch to parenteral anticoagulants can be started 12 hours (CrCl ≥30 ml/min) or 24 hours (CrCl <30 ml/min) after last dabigatran dose. Dabigatran should be discontinued 1-2 days (CrCl ≥50 ml/min) or 3-5 days (CrCl <50 ml/min) before invasive or surgical procedures due to risk of bleeding. Dabigatran should be stored in the bottle in which it is dispensed and discarded 60 days after opening.[1,16]

Dabigatran should be used cautiously with p-glycoprotein inhibitors (P-gp) inhibitors (e.g., amiodarone, ketoconazole and verapamil) and inducers (e.g., rifampin and St.John's wort). Currently, there is no reversal agent or antidote for dabigatran in a bleeding emergency.[1]

Table 4. Pradaxa Dosing[1]

Renal Function	Oral Dose
Normal	Dabigatran 150mg twice daily
CrCl 15-30ml/min	Dabigatran 75mg twice daily
CrCl <15ml/min or dialysis	No recommendation given
Hepatic dysfunction	No recommendation given

Table 5. Converting from Dabigatran to Warfarin[1]

Renal Function	Warfarin Initiation
CrCl >50 ml/min	3 days before stopping dabigatran
CrCl 31-50 ml/min	2 days before stopping dabigatran
CrCl 15-30 ml/min	1 day before stopping dabigatran
CrCl <15 ml/min	No recommendation can be made

Summary

The clinical efficacy data for the use of dabigatran for stroke prevention in patients with AF should be interpreted cautiously. Patients that are unable to tolerate warfarin or experience difficulty with INR regulation are potential candidates for dabigatran therapy. Post-marketing surveillance data will help determine the clinical significance of the increased risk of MI associated with dabigatran therapy as demonstrated in the RE-LY study. Off-label use of dabigatran for acute or preventative treatment of VTE appears promising but there is no evidence to suggest that it is superior to existing agents.

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