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DABIGATRAN ETEXILATE: THE FIRST FDA-APPROVED ORALLY AVAILABLE DIRECT THROMBIN INHIBITOR

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Patients with atrial fibrillation (A.Fib) often require anticoagulation therapy to reduce their risk of stroke, transient ischemic attack, or thromboembolic complications. The 2008 American College of Chest Physicians' guidelines support anticoagulation with a vitamin K antagonist (VKA) such as warfarin for patients with A.Fib at intermediate or high risk of thromboembolic events based on a stratified risk assessment.¹ However, warfarin is associated with substantial costs, including the cost of therapeutic monitoring and the cost of rare, but serious, adverse bleeding events.² Warfarin therapy can be challenging for many patients due to dietary and lifestyle restrictions, and warfarin's drug interaction profile is a perennial medication safety problem.

Because of the challenges associated with warfarin therapy, researchers have sought to develop additional oral anticoagulants. Dabigatran etexilate is a new oral anticoagulant FDA approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.³ Dabigatran etexilate was approved for marketing in the U.S. in October 2010 under the trade name Pradaxa® and is manufactured by Boehringer-Ingelheim Pharmaceuticals. Although dabigatran etexilate is the first commercially available oral direct thrombin inhibitor (DTI), another oral DTI, ximelagatran, has been studied and was approved in Europe for short-term anticoagulation after orthopedic surgery.⁴ Ximelagatran was also evaluated for the prevention of thromboembolic complications

in A.Fib, but it was removed from the international market in 2006 by AstraZeneca due to concerns over severe liver damage reported after treatment lasting longer than 35 days.⁵

Dabigatran's recent approval provides clinicians with an additional oral anticoagulant to reduce the risk of thromboembolic events in A.Fib patients. This article will review dabigatran's pharmacology and pharmacokinetics, outline dabigatran's efficacy and safety data, and summarize dabigatran's dosing and expected cost.

PHARMACOLOGY

DTIs antagonize the catalytic site of thrombin. Within the clotting cascade, prothrombin is converted to thrombin, which promotes clot stability by converting soluble fibrinogen to insoluble fibrin.³ The anti-thrombotic effects of DTIs are not mediated by anti-thrombin, distinguishing DTIs from unfractionated heparin, low molecular weight heparin, and factor Xa inhibitors.⁵ Of note, dabigatran does not have an antidote to its effect in overdose. Dabigatran's antithrombotic effects are similar to the parenterally available DTIs (desirudin, lipirudin, bivalirudin, and argatroban), but these agents differ slightly in terms of their *in vivo* activity and mechanism of action.^{2,5} Univalent DTIs (dabigatran and argatroban) bind exclusively to

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Table 1 | Pharmacokinetic properties of dabigatran etexilate.³

Property	Normal Renal Function (80 mL/min)	Mild Dysfunction (50 mL/min)	Moderate Dysfunction (30 mL/min)
Absorption	Poor	–	–
Bioavailability	3 to 7%	–	–
Time to Peak	1 h	–	–
Increase in AUC	0%	50%	320%
Increase in C _{max}	0%	10%	70%
Terminal Half-Life	13 h	15 h	18 h

the active site of thrombin, whereas bivalent DTIs (desirudin, lipirudin, and bivalirudin) also attach to the fibrin-binding domain (exosite 1) of thrombin.⁶ Compared to univalent DTIs, bivalent DTIs have reduced activity against fibrin-bound thrombin due to their affinity for exosite 1. Univalent DTIs like dabigatran have been shown to effectively inhibit both free and fibrin-bound thrombin, and dabigatran has been shown to reduce thrombin-induced platelet aggregation.³

PHARMACOKINETICS

Dabigatran etexilate is an ester pro-drug that requires an acidic environment for its absorption and has an oral bioavailability between 3 and 7 percent.^{2,3} Once absorbed, dabigatran etexilate undergoes ester hydrolysis to produce the active drug. A summary of dabigatran's pharmacokinetic profile is provided in **Table 1**.

Peak serum concentrations of dabigatran occur within 1 to 2 hours of administration, and the terminal half-life of the drug ranges from 12 to 17 hours in healthy individuals.^{3,5} Administration of dabigatran etexilate after a high fat meal can delay the time to

maximal serum drug concentration by up to 2 hours without changing the extent of absorption. The manufacturer recommends against opening or chewing capsules of dabigatran etexilate since that can increase absorption of the drug and potentially increase the risk of bleeding.³

Dabigatran undergoes hepatic glucuronidation to active conjugates and is not metabolized by cytochrome P450 (CYP) enzymes. However, dabigatran etexilate is a substrate of p-glycoprotein (P-gp) transporters, and a list of P-gp and other drug-drug interactions can be found in **Table 2**. Of note, concomitant administration of clopidogrel and dabigatran did not increase bleeding times compared to clopidogrel monotherapy.³ Up to 80% of dabigatran is renally cleared from the body, and this reliance on renal clearance affects the level of drug accumulation as well as the terminal half-life of the drug (**Table 1**).³

CLINICAL TRIALS

The RE-VOLUTION series of clinical trials compared the safety and efficacy of dabigatran etexilate to the clinical standard of care for a variety of thromboembolic conditions in over 38,000 patients. Two

Table 2 | Drug interactions with dabigatran etexilate.^{3,7,8}

Interacting Drug	Interaction Mechanism	Effect of Interaction on Dabigatran	Recommendation
Rifampin	P-gp induction	↓AUC 66%, ↓C _{max} 67%	Avoid combination
Verapamil IR	P-gp inhibition	↑AUC 240% (if given within 1 hour) ^a	Separate by 2 hours
Ketoconazole	P-gp inhibition	↑AUC 138%, ↑C _{max} 135%	No adjustment
Amiodarone	P-gp inhibition	↑AUC 58%, ↑C _{max} 50%, ↑Clearance 65%	No adjustment
Quinidine	P-gp inhibition	↑AUC 53%, ↑C _{max} 56%	No adjustment
Digoxin	P-gp substrate	No clinically significant changes seen for either drug	No adjustment
Atorvastatin	P-gp substrate/inhibitor	↓AUC 18% when drugs were co-administered	No adjustment
Clopidogrel	Potential of bleeding	↑AUC 30%, ↑C _{max} 30%, no change in bleeding time	No adjustment
Pantoprazole	Reduced absorption	↓AUC 22%, ↓C _{max} 33%, ↓Bioavailability 20-24%	No adjustment

AUC = area under the curve; C_{max} = maximum serum concentration; IR = immediate release; P-gp = p-glycoprotein.

^aEffect is dependent on the dosage form of verapamil, with the largest effect seen with IR-verapamil given within 1 hour of dabigatran administration.³

Table 3 | Summary of dabigatran etexilate clinical trials in patients with nonvalvular atrial fibrillation.^{9,10}

Study	Design	Outcomes	Interventions	Results
PETRO⁹ (2007)	<ul style="list-style-type: none"> Duration: 12 to 14 weeks N = 502 PROBE, OL ASA and Warfarin, DB DD DGE, DR 	<p><u>Incidence of bleeding events:</u></p> <ul style="list-style-type: none"> Total Events Major Events Clinically Significant Events 	<ul style="list-style-type: none"> Warfarin DA to INR 2-3 (n=70; 2 d/c'd) DGE 50 mg BID ± ASA (n=105; 5 d/c'd) DGE 150 mg BID ± ASA (n=166; 11 d/c'd) DGE 300 mg BID ± ASA (n=161; 20 d/c'd) 	<p>Warfarin: No TEE</p> <ul style="list-style-type: none"> 12/70 clinically relevant bleeds Average TTR 57.2% overall <p>DGE 50 mg: 2 TEE</p> <ul style="list-style-type: none"> 7/107 clinically relevant bleeds^a <p>DGE 150 mg: No TEE</p> <ul style="list-style-type: none"> 30/169 clinically relevant bleeds^a <p>DGE 300 mg: No TEE</p> <ul style="list-style-type: none"> 39/169 clinically relevant bleeds^a 4/169 major bleeding episodes^a
RE-LY¹⁰ (2009)	<ul style="list-style-type: none"> Duration: 2 years median follow-up N = 18113 ITT PROBE, OL Warfarin, DB DGE 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> Incidence of stroke or systemic embolism <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> Incidence of major bleeding events 	<ul style="list-style-type: none"> Warfarin DA to INR 2-3 (n=6022 ITT; 902 d/c'd) DGE 110 mg BID (n=6015 ITT; 1161 d/c'd) DGE 150 mg BID (n=6076 ITT; 1211 d/c'd) 	<p><u>Primary efficacy outcome:</u></p> <p>Warfarin (adjusted to INR of 2.0-3.0)</p> <ul style="list-style-type: none"> 3.4% with outcome (199/6022) Average TTR 64% overall <p>DGE 110 mg (RR v. warfarin)</p> <ul style="list-style-type: none"> 3.1% with outcome (182/6015) RR (95% CI): 0.91 (0.74-1.11)^b <p>DGE 150 mg (RR v. warfarin)</p> <ul style="list-style-type: none"> 2.2% with outcome (134/6076) RR (95% CI): 0.66 (0.53-0.82)^{b,c} <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> DGE 110mg BID had fewer major bleeds v. warfarin (5.4% v. 6.6%)^d DGE 150mg BID similar to warfarin for major bleeding (6.2% v. 6.6%) DGE 150mg BID had more GI bleeds v. warfarin (3% v. 2%)^c Warfarin had more ICH than either dose of DGE (1.48% v. 0.46% for DGE 110mg and 0.6% for 150mg)^c

ASA = aspirin; DA = dose-adjusted; DB = double blind; d/c'd = discontinued; DD = double dummy; DGE = dabigatran etexilate; DR = dose-ranging; ICH = intracranial hemorrhage; INR = international normalized ratio; ITT = intention to treat; NI = non-inferiority; OL = open label; PROBE = prospective, randomized, open blinded endpoint; RR = relative risk; TEE = thromboembolic events; TTR = time in target range; VKA = vitamin K antagonist.

^a Patients were counted more than once if they changed groups during the trial.

^b P < 0.001 for non-inferiority.

^c P < 0.001.

^d P < 0.05.

published clinical trials evaluate the safety (PETRO and RE-LY) and efficacy (RE-LY) of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation patients.^{9,10} A summary of these trials can be found in **Table 3**. Additional clinical trials have been conducted to evaluate the effectiveness of dabigatran etexilate for the treatment and prevention of venous thromboembolism (**Table 4**).¹¹⁻¹⁶

Phase II Dose-Ranging Study (PETRO)

Ezekowitz and colleagues conducted a 12-week, prospective, randomized, open-label, blinded endpoint, phase 2 clinical trial to evaluate the safety of

three different doses of dabigatran with or without concomitant aspirin (ASA) therapy compared to open-label, dose-adjusted warfarin in patients with A.Fib and at least one additional risk factor for thromboembolic complications.⁹ The PETRO study was primarily descriptive in nature, and its focus was on dabigatran's safety. Patients received open-label warfarin or dabigatran etexilate in blinded doses of 50, 150, or 300mg twice daily, with or without concomitant open-label ASA 81 or 325mg daily. A total of 502 patients were randomly assigned to one of ten treatment groups within the study. Thirty eight patients withdrew from the study, with a numerical majority

Table 4 | Summary of dabigatran etexilate clinical trials in venous thromboembolic disorders. ¹¹⁻¹⁶

Study	Design	Outcomes	Interventions	Results
BISTRO I ¹¹ (2004)	<ul style="list-style-type: none"> • TEE prevention in THR patients • 6-10 days tx (median 8) with 4-6 week follow-up • N = 289 (262 evaluated for efficacy) • P, OL DGE, DR 	<p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of major bleeding <p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Incidence of TEE (DVT and/or PE) 	<ul style="list-style-type: none"> • DGE 12.5mg BID (n=27) • DGE 25mg BID (n=28) • DGE 50mg BID (n=30) • DGE 100mg BID (n=40) • DGE 150mg daily (n=41) • DGE 150mg BID (n=29) • DGE 200mg BID (n=28) • DGE 300mg daily (n=46) • DGE 300mg BID (n=20) 	<p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • No patients met pre-defined criteria for major bleeding events • 7% had event requiring transfusion • Bleeding events (n = 19) occurred with doses of DGE over 100mg BID • No clear dose-response relationship <p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • Most TEE: DGE 12.5mg BID (5/24)^a • Least TEE: DGE 300mg BID (0/14)^a • DVT incidence was 12.4% (28/225)
BISTRO II ¹² (2005)	<ul style="list-style-type: none"> • TEE prevention in THR or TKR patients • 6-10 days tx (median 7) with 4-6 week follow-up • N = 1949 (1464 evaluated for efficacy) • P, R, DB, DR 	<p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of major bleeding <p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Incidence of TEE (DVT and/or PE) 	<ul style="list-style-type: none"> • Enoxaparin 40mg SC daily (n=392) • DGE 50mg BID (n=389) • DGE 150mg BID (n=390) • DGE 300mg daily (n=385) • DGE 225mg BID (n=393) 	<p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • 0.3% of DGE 50mg BID (1/389) • 4.1% of DGE 150mg BID (16/390) • 3.8% of DGE 225mg BID (18/385) • 4.7% of DGE 300mg daily (15/393) • 2.0% of Enoxaparin daily (8/392) • DGE 50mg BID had fewer major bleeds than Enoxaparin^b <p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • 28.5% of DGE 50mg BID (86/302) • 17.4% of DGE 150mg BID (49/282) • 16.6% of DGE 225mg BID (47/283) • 13.1% of DGE 300mg daily (39/297) • 24.0% of Enoxaparin daily (72/300)
RE-MODEL ¹³ (2007)	<ul style="list-style-type: none"> • TEE prevention in TKR patients • 6-10 days tx (median 8) with 3 month follow-up • N = 2076 (1541 evaluated for efficacy) • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Composite of TTEs and all cause mortality <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Enoxaparin 40mg SC daily (n=694; 616 completed) • DGE 150mg daily (n=703; 625 completed) • DGE 220mg daily (n=679; 608 completed) 	<p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • 37.7% of Enoxaparin (193/512) • 40.5% of DGE 150mg (213/526)^c • 36.4% of DGE 220mg (183/503)^c <p>Both doses of DGE met NI criteria against Enoxaparin</p> <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • No significant difference between either dose of DGE and Enoxaparin
RE-NOVATE ¹⁴ (2007)	<ul style="list-style-type: none"> • TEE prevention in THR patients • 28-35 day tx (median 33) with 4-5 wk follow-up • N = 3463 (2651 evaluated for efficacy) • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Composite of TTEs and all cause mortality <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Enoxaparin 40mg SC daily (n=1154; 1030 completed) • DGE 150mg daily (n=1163; 1054 completed) • DGE 220mg daily (n=1146; 1029 completed) 	<p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • 6.7% of Enoxaparin (60/897) • 8.6% of DGE 150mg (75/874)^d • 6.0% of DGE 220mg (53/880)^d <p>Both doses of DGE met NI criteria against Enoxaparin</p> <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • No significant difference between either dose of DGE and Enoxaparin
RE-MOBILIZE ¹⁵ (2008)	<ul style="list-style-type: none"> • TEE prevention in TKR patients • 12-15 day tx (median 14) with 12-15 day and 3 month follow-up • N = 2596 (1896 for efficacy) • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Composite of TTEs and all cause mortality <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Enoxaparin 30mg SC BID (n=868; 819 completed) • DGE 150mg daily (n=871; 823 completed) • DGE 220mg daily (n=857; 806 completed) 	<p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • 25.3% of Enoxaparin (163/643) • 33.7% of DGE 150mg (219/649) • 31.1% of DGE 220mg (188/604) <p>Both doses of DGE failed to meet NI criteria against Enoxaparin</p> <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • No significant difference between either dose of DGE and Enoxaparin

Table 4 (cont'd) | Summary of dabigatran etexilate clinical trials in venous thromboembolic disorders.¹¹⁻¹⁶

Study	Design	Outcomes	Interventions	Results
RE-COVER¹⁶ (2009)	<ul style="list-style-type: none"> • TEE treatment and secondary prevention • 6 month treatment (mean 162 days) with 7 day, monthly, and 6 month follow-up • N = 2596 (1896 evaluated for efficacy) • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Time to composite event of death or TEE <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Warfarin adjusted to INR of 2.0 to 3.0 (n=1265; 183 discontinued) • DGE 150mg BID (n=1274; 204 discontinued) 	<p><u>Primary efficacy outcome:</u></p> <ul style="list-style-type: none"> • 2.1% of warfarin (27/1265) • 2.4% of DGE 150mg BID (30/1274)^d • Warfarin average TTR 60% overall • DGE met NI criteria for prevention of recurrent or fatal TEE <p><u>Primary safety outcome:</u></p> <ul style="list-style-type: none"> • No significant difference between DGE 150mg and adjusted warfarin

BID = twice daily; **DB** = double blind; **DD** = double dummy; **DGE** = dabigatran etexilate; **DR** = dose-ranging; **DVT** = deep vein thrombosis; **GI** = gastrointestinal; **INR** = international normalized ratio; **ITT** = intention to treat; **NI** = non-inferiority; **OL** = open-label; **P** = prospective; **PC** = placebo-controlled; **PE** = pulmonary embolus; **PROBE** = prospective, randomized, open blinded endpoint; **RR** = relative risk; **SC** = subcutaneous; **TEE** = thromboembolic events; **THR** = total hip replacement; **TKR** = total knee replacement; **TTR** = time in target range; **VKA** = vitamin K antagonist.

^a Analysis not reported by investigators.

^b P < 0.05.

^c P < 0.05 for non-inferiority.

^d P < 0.001 for non-inferiority.

Table 5 | Summary of ongoing dabigatran etexilate clinical trials.¹⁷⁻²⁰

Study	Design	Outcomes	Interventions
RE-NOVATE II¹⁷	<ul style="list-style-type: none"> • TEE prevention in THR patients • Duration: 28-35 day treatment (mean 32) with 4-5 week follow-up • N = 2055 • P, R, DB, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Composite of TTEs and all cause mortality <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Enoxaparin 40mg SC daily (n=1003) • DGE 220mg daily (n=1146)
RE-COVER II¹⁸	<ul style="list-style-type: none"> • TEE treatment and secondary prevention • Duration: 6 months • N = 2580 • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Composite of TTEs and TEE mortality <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of bleeding events 	<ul style="list-style-type: none"> • Warfarin adjusted to INR of 2.0 to 3.0 • DGE 150mg BID
RE-SONATE¹⁹	<ul style="list-style-type: none"> • Long-term TEE secondary prevention in previously VKA treated patients • Duration: 6 months • N = 1412 • P, R, DB, PC 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Incidence of recurrent TTE during trial <p><u>Primary safety:</u></p> <ul style="list-style-type: none"> • Incidence of major bleeding events 	<ul style="list-style-type: none"> • DGE 150mg BID • Placebo
RE-MEDY²⁰	<ul style="list-style-type: none"> • Long-term TEE treatment and secondary prevention in previously treated patients • Duration: 18 months • N = 2867 • P, R, DB, DD, NI 	<p><u>Primary efficacy:</u></p> <ul style="list-style-type: none"> • Incidence of recurrent TTE during trial 	<ul style="list-style-type: none"> • Warfarin adjusted to INR of 2.0 to 3.0 • DGE 150mg BID

BID = twice daily; **DB** = double blind; **DD** = double dummy; **DGE** = dabigatran etexilate; **DR** = dose-ranging; **DVT** = deep vein thrombosis; **GI** = gastrointestinal; **INR** = international normalized ratio; **ITT** = intention to treat; **NI** = non-inferiority; **OL** = open-label; **P** = prospective; **PC** = placebo-controlled; **PE** = pulmonary embolus; **PROBE** = prospective, randomized, open blinded endpoint; **RR** = relative risk; **SC** = subcutaneous; **TEE** = thromboembolic events; **THR** = total hip replacement; **TKR** = total knee replacement; **TTR** = time in target range; **VKA** = vitamin K antagonist.

(29/38) of patients discontinuing therapy due to adverse events.

The primary outcome was the incidence of bleeding events among study patients, which was reported in a stratified manner as major, clinically significant, or as the total number of bleeding events. Major bleeding events in the study occurred statistically more often ($p < 0.02$) with twice daily dabigatran etexilate 300mg co-administered with ASA (4/64) compared to twice daily dabigatran etexilate 300mg without ASA (0/105). The incidence of total bleeding events was statistically greater ($p = 0.0002$) with 300mg twice daily dabigatran etexilate (37/169) compared to 50mg twice daily therapy (30/169), regardless of whether or not patients were also receiving ASA. Patients receiving dabigatran etexilate 150mg twice daily experienced statistically more ($p = 0.01$) total bleeding events (30/169) than patients receiving the 50mg twice daily therapy (7/107). Another outcome evaluated in this study was the incidence of thromboembolic events, which only occurred in the 50mg twice daily dabigatran etexilate group among patients not concurrently receiving aspirin therapy (2/107).

The average proportion of time spent in the target range (TTR) for warfarin was 57.2% in this study. Patients receiving warfarin did not experience major bleeding or thromboembolic events. The incidence of total bleeding events in the dose adjusted warfarin group was 17.1% (12/70), and the incidence of major bleeding events was 5.7% (4/70), which was statistically greater than the incidence of bleeding among patients receiving dabigatran etexilate 50mg twice daily (7/107, $p = 0.044$). The authors concluded that the twice daily 300mg dose of dabigatran represented the upper limit of tolerability of dabigatran for patients in the trial. Because of the low incidence of thromboembolic events during the trial, the authors could not draw any conclusions regarding dabigatran's efficacy.

Phase III Non-inferiority Trial (RE-LY)

In a 2 year, prospective, randomized, open-label, blinded end-point, phase 3 clinical trial, Connolly et al. evaluated the safety and efficacy of dabigatran etexilate in patients with A.Fib and at least one additional risk factor for thromboembolic complications.¹⁰ The RE-LY investigators compared open-label, dose-adjusted, warfarin to blinded doses of dabigatran etexilate (110 or 150mg twice daily) in a large, multicenter, non-inferiority trial. Patients were allowed to use ASA during the trial in doses less than 100mg per day. Baseline aspirin use was similar between trial groups, with approximately 40% of patients taking aspirin in each group. Aspirin was also used continuously throughout the study period by approximately

20% of patients in each group. Over the study period, a total of 18,113 patients were randomly assigned to one of the three treatment groups. Patients were analyzed according to the intention-to-treat (ITT) principle, with only 20 patients lost to follow-up.

The primary outcome was the incidence of stroke or systemic embolism among the three groups. The average proportion of TTR for warfarin was 64% over the entire study period. The incidence of the primary outcome in the warfarin group was 1.69% per year (199/6022). Dabigatran etexilate 110mg twice daily was non-inferior to warfarin (182/6015 v. 199/6022, RR: 0.91, 95% CI: 0.74-1.11). For the primary outcome, dabigatran etexilate 150mg twice daily was also non-inferior to warfarin and appeared superior to warfarin (134/6076 v. 199/6022, RR: 0.66, 95% CI: 0.53-0.82). Comparing the two doses of dabigatran etexilate used in the study, the twice daily 150mg dose was superior ($p = 0.005$) to the twice daily 110mg dose (134/6076 v. 182/6015, RR: 0.73, 95% CI: 0.58-0.91). Additionally, the incidence of hemorrhagic stroke was significantly lower with the twice daily 110mg dose (RR: 0.31, 95% CI: 0.17-0.56) and the twice daily 150mg dose (RR: 0.26, 95% CI: 0.14-0.49) compared to warfarin therapy.

Patients receiving the 150mg dose twice daily had a non-significant ($p = 0.052$) trend toward an increased risk of major bleeding compared to patients receiving the lower dose. The 150mg dose also appeared to be associated with an increased risk of gastrointestinal (GI), minor, and total bleeding compared to the 110mg dose.¹⁰ The annual incidence of major bleeding was 3.36% with warfarin, 2.71% with dabigatran etexilate 110mg, and 3.11% with dabigatran etexilate 150mg. The rates of life threatening, intracranial, and major or minor bleeding were higher with warfarin than with either dose of dabigatran etexilate. Patients discontinued treatment because of GI bleeding more often in the dabigatran etexilate 150mg group (80/6076) than in the 110mg group (58/6015) or the warfarin group (54/6022), and the 150mg twice daily dose was associated with a greater risk of major GI bleeds compared to warfarin.¹⁰ Dyspepsia occurred more frequently with both the 110mg (11.8% v. 5.8%, $p < 0.001$) and the 150mg (11.3% v. 5.8%, $p < 0.001$) doses of dabigatran etexilate therapy than with warfarin. The authors concluded that both the 110 and the 150mg dose of dabigatran etexilate twice daily were non-inferior to warfarin for the prevention of the primary outcome of stroke or systemic embolism. They also concluded that the higher dose was superior to warfarin for the primary outcome and that the lower dose was superior to warfarin for the incidence of major bleeding.

An additional analysis of the TTR of the warfarin group was undertaken by the RE-LY investigators.²¹ The individual patient TTRs were calculated into center-specific TTRs, and these values were compared between centers. Based on the analysis, the TTR for warfarin was heterogeneous across study center locations. Dabigatran therapy appeared superior to warfarin for the primary outcome at centers with TTRs below the median 67% (HR: 0.57, 95% CI: 0.42-0.76). Dabigatran therapy also appeared superior to warfarin in terms of all cause mortality (HR: 0.78, 95% CI: 0.66-0.93), and the incidence of major bleeding events (HR: 0.82, 95% CI: 0.68-0.99) at centers with lower warfarin TTRs. Dabigatran therapy did not appear superior to warfarin for the primary outcome at centers with TTRs above the median 67% (HR: 0.76, 95% CI: 0.55-1.05).³ Warfarin and dabigatran etexilate appeared no different at centers with higher TTRs for all cause mortality (HR: 1.01, 95% CI: 0.84-1.23) or for the incidence of major bleeding events (HR: 1.08, 95% CI: 0.89-1.31).³

Additional trials of dabigatran are ongoing and should further elucidate the role of this agent in various anticoagulation settings (Table 5).

ADVERSE EFFECTS

The tolerability of dabigatran etexilate therapy was lower than that of warfarin therapy in the RE-LY study, with significantly more patients discontinuing dabigatran etexilate at the 1 and 2 year follow-up.¹⁰ A summary of the most common adverse events experienced by patients receiving dabigatran can be found in

Table 6.

Compared to warfarin, patients who received dabigatran experienced a higher incidence of major gastrointestinal bleeding (1.6% v. 1.1%, HR: 1.5, 95% CI: 1.2-1.9), and dyspepsia occurred significantly more often in patients receiving dabigatran etexilate 150mg compared to dose adjusted warfarin (11.3% v. 5.8%, p<0.001).^{3,10} The overall risk of bleeding between dabigatran etexilate 150mg and warfarin was similar among most patients. However, a subgroup of patients 75 years of age or older who received dabigatran had a non-significant increase in the risk of major bleeding compared to warfarin (HR: 1.2, 95% CI: 1.0-1.4).³ Patients taking dabigatran etexilate 150mg had a higher risk of myocardial infarction at 0.74% per year compared to patients taking warfarin at 0.53% per year (RR: 1.38, 95% CI:1.00-1.38, p=0.048).¹⁰ Neither dose of dabigatran etexilate used in RE-LY significantly increased AST or ALT compared to warfarin, and the incidence of elevated transaminases was 0.9% in PETRO. Hypersensitivity reactions occurred in less than 0.1% of patients who received dabigatran etexilate during clinical trials.³

DOSAGE & ADMINISTRATION

The approved dose of dabigatran etexilate is 150mg twice daily for the prevention of stroke and systemic embolism. The dose of dabigatran etexilate does not need to be adjusted in patients with a creatinine clearance (CrCl) greater than 30mL/min. The manufacturer recommends reducing the dose to 75mg twice daily in patients with a CrCl between 15

Table 6 | Adverse events in the RE-LY trial.^{3,10}

Adverse Event	Warfarin (n=6022)	Dabigatran 110 mg (n=6015)	Dabigatran 150 mg (n=6076)
Dyspepsia ^a	348 (5.8%)	707 (11.8%)	688 (11.3%)
Dizziness	568 (9.4%)	486 (8.1%)	506 (8.3%)
Dyspnea	586 (9.7%)	557 (9.3%)	580 (9.5%)
Peripheral edema	468 (7.8%)	473 (7.9%)	478 (7.9%)
Fatigue	372 (6.2%)	399 (6.6%)	401 (6.6%)
Diarrhea	346 (5.7%)	377 (6.3%)	397 (6.5%)
Chest Pain	357 (5.9%)	312 (5.2%)	377 (6.2%)
Life threatening bleed ^b	212 (3.5%)	145 (2.4%)	175 (2.9%)
Non-life threatening	208 (3.5%)	198 (3.3%)	226 (3.7%)
Gastrointestinal bleed ^c	120 (2.0%)	133 (2.2%)	182 (3.0%)
Intracranial bleed ^d	87 (1.4%)	27 (0.4%)	36 (0.6%)

^aSignificantly more dyspepsia with either dose of dabigatran compared to warfarin (p<0.001).

^bSignificantly more life threatening bleeds with warfarin compared to low dose dabigatran (p<0.001).

^cSignificantly more gastrointestinal bleeds with high dose dabigatran than with warfarin (p<0.001).

^dSignificantly more intracranial bleeds with warfarin than with either dose of dabigatran (p<0.001).

and 30mL/min. However, dabigatran etexilate is not recommended for patients with a CrCl less than 15mL/min. Dabigatran etexilate can be taken without regard to meals. Patients who miss a dose may take it as soon as they remember up to 6 hours after the missed dose. Doses delayed longer than 6 hours should be skipped, but the manufacturer cautions against taking twice the dose to make up for missed doses.³

Dabigatran etexilate therapy can be started in patients changing from warfarin once warfarin has been discontinued and the INR is less than 2.0. Because dabigatran can influence the INR, the manufacturer advises that INRs may be more accurate two days after stopping dabigatran. In patients currently using parenteral anticoagulation, dabigatran etexilate therapy should be started within 2 hours of the next dose of parenteral anticoagulant before discontinuing therapy. Patients already taking dabigatran etexilate should wait 12 to 24 hours before beginning parenteral anticoagulation based on renal function. Patients undergoing invasive surgical procedures should discontinue dabigatran etexilate at least 1 to 2 days (CrCl \geq 50mL/min) or 3 to 5 days (CrCl $<$ 50mL/min) before the procedure to reduce the risk of adverse bleeding events.

COST

The acquisition cost of branded dabigatran etexilate (Pradaxa[®]) was expected to be \$6.75 per day and the retail cost was expected to be \$7.90 per day (\$237 per month).²² An informal survey of several retail pharmacies (n=5) in Florida revealed that the average \pm SD price of a 30 days' supply of Pradaxa[®] 150mg was \$261.37 \pm \$18.30 (median: \$267.99, range: \$231.32 to \$277.99). This survey of chain, independent, grocery-store, and discount pharmacy prices indicates that Pradaxa[®] therapy may cost \$8.71 per day, on average. Practitioners and payors must weigh the expected costs and benefits of dabigatran therapy against the established costs and benefits of warfarin therapy. The cost-effectiveness of dabigatran compared to dose adjusted warfarin was evaluated in a pharmacoeconomic study.²³ The authors took a societal perspective in their analysis, which used data from RE-LY and other trials of dabigatran to estimate the improvement in quality adjusted life years and the incremental cost-effectiveness ratio for the two doses of dabigatran used in the RE-LY study. The authors concluded that if the cost of dabigatran 150mg was less than \$13.70 per day, it may be cost-effective compared to warfarin for patients 65 years or older with a CHADS₂ score of 1 or more.

SUMMARY

Prior to dabigatran's approval, clinicians did not have an alternative to warfarin for oral anticoagulation in patients at high risk for thromboembolic complications of atrial fibrillation. Dabigatran etexilate appears relatively safe and non-inferior to warfarin for the prevention of systemic embolism or stroke in patients with non-valvular atrial fibrillation. This agent is associated with fewer drug-drug interactions and requires less frequent laboratory monitoring than warfarin. However, dabigatran is associated with an increased risk of dyspepsia, gastrointestinal bleeding, and major bleeding events in certain patients. The lack of a proven antidote for dabigatran's effect should be factored in to the clinical decision making process. The role of dabigatran in daily practice remains to be seen, but its use may become routine if it gains approval for additional indications.

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