New Drug Review

Dabigatran Etexilate: An Oral Direct Thrombin Inhibitor for the Management of Thromboembolic Disorders

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ABSTRACT

Background: Until recently, warfarin was the only oral anticoagulant available in the United States. Its narrow therapeutic index, interpatient variability in dose response, and drug and food interactions make it difficult to use. Dabigatran etexilate (DE) is a new oral direct thrombin inhibitor that was approved in the US and in Canada for the prevention of thromboembolic events in patients with atrial fibrillation (AF), as well as in Europe and Canada for the prevention of venous thromboembolism (VTE).

Objective: To discuss the role of DE for the prevention and treatment of VTE, as well as for the prevention of stroke in patients with AF.

Methods: Peer-reviewed clinical trials, review articles, and treatment guidelines were identified from MEDLINE and the Current Contents database (both 1966–February 15, 2012) using the search terms *dabigatran, VTE, Afib, pharmacokinetics, pharmacodynamics, pharmacoeconomics,* and *cost-effectiveness*. Citations from available articles were also reviewed for additional references.

Results: For VTE prophylaxis, DE 150 or 220 mg orally daily has demonstrated either superiority or noninferiority to subcutaneous enoxaparin once daily in most studies. However, one study failed to demonstrate noninferiority to subcutaneous enoxaparin dosed BID in the composite end point of VTE, and all-cause mortality. For VTE treatment, DE 150 mg BID orally was shown to be noninferior to warfarin in preventing recurrent events. For AF, DE 150 mg BID orally is superior to warfarin in the prevention of thromboembolism, whereas 110 mg BID is noninferior to warfarin. Pharmacoeconomic analyses performed in the United Kingdom and Ireland found that DE can be cost-saving compared with enoxaparin in the prevention of VTE. Adverse effects of DE reported in clinical studies include dyspepsia (12%–13%) and bleeding (minor bleeding: 6%–22%).

Conclusions: DE exhibited a safety profile and efficacy comparable to enoxaparin for VTE prophylaxis; comparable safety profile and efficacy to warfarin for VTE treatment; and superiority (150 mg BID orally) in the prevention of stroke and systemic embolism compared with warfarin in patients with AF. The relative ease of oral administration, no need for routine monitoring, and lack of significant drug interactions, may favor use of DE over other anticoagulants. However, there is no antidote for DE currently available. (*Clin Ther*. 2012;34:766–787)

Key words: dabigatran etexilate, venous thromboembolism, atrial fibrillation.

INTRODUCTION

Anticoagulant agents play an important role in the management of different thromboembolic diseases. Until recently, warfarin was the only oral anticoagulant option available in the United States. Warfarin's narrow therapeutic index, interpatient variability in dose response, slow onset and offset of action, and extensive drug and food interactions remain a concern regarding its use.[1,2] Other options of anticoagulant agents include unfractionated heparin, low- molecular-weight heparin, all of which are currently available only in parenteral forms in the United States.[3,4] Direct thrombin inhibitors (DTIs) represent another newer class of anticoagulants. There are 3 intravenous DTIs available in the United States, and they are primarily used in the treatment of heparin-induced thrombocytopenia (lepirudin and argatroban) and during percutaneous coronary interventions (bivaliru-

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din).[5,6] Ximelagatran was a previously developed oral DTI that was approved and available for use in venous thromboembolism (VTE) treatment and prevention in selected European countries for a brief period in 2005. The manufacturer subsequently withdrew the medication from the market and withheld further applications for marketing the drug in other countries, including the United States, because of the risk of liver toxicity and possible increase in acute coronary syndrome (ACS) events.[7] Dabigatran etexilate is another oral DTI that has recently been approved by the US Food and Drug Administration (FDA; October 19, 2010) and in Canada for the prevention of thromboembolic events in patients with atrial fibrillation (AF).[8] Dabigatran etexilate was approved in Europe and Canada in 2008 for the prevention (but not treatment) of VTE in patients undergoing hip and knee replacement.[7]

VTE and AF are both highly prevalent diseases. VTE is the third most common cause of cardiovascular mortality, after coronary heart disease and stroke, in the United States.[9] The annual incidence of VTE is reportedly 100 to 192 per 100,000 person-years in the United States.[9,10] Because only ~33% of VTE cases are diagnosed, the actual incidence of VTE is probably substantially higher.[11] Incidence of VTE among in-hospital medical patients is 10% to 20% and can be as high as 80% in patients with spinal cord injury, major trauma, or those who are critically ill.[10] VTE is idiopathic 25% to 50% of the time.[12] It is reportedly the second most common cause of extended hospital length of stay and the third most common cause of hospital mortality.[13] AF is a common arrhythmia associated with increased cardiovascular mortality, stroke, and hospitalization in the United States.[14] Approximately 2.2 million patients have AF. Risk of AF increases with age, with an incidence up to 26.0% for men and 23.0% for women by age 40 years.[14] Due to the growing proportion of elderly patients, the number of patients with AF is expected to increase by 2.5-fold over the next 50 years.[15] AF is the most common cause of stroke in the United States. It independently increases stroke risk by ~5-fold throughout all age groups. The percentage of stroke increases steeply from 1.5% at age 50 to 59 years to 23.5% at age 80 to 89 years in patients with AF.[14]

Currently, in the United States, the 9th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy (published in 2012) recommends use of all anticoagulant agents as therapeutic options for the treatment of VTE and prevention of VTE in patients undergoing orthopedic surgery.[9,10] The same guideline, as well as the American Heart Association's 2010 guidelines for the management of AF, recommends the use of warfarin or dabigatran for stroke prevention in AF patients with CHADS2 scores ≥2 (Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke: each risk factor scores 1 point, stroke scores 2); aspirin, warfarin or dabigatran in patients with CHADS2 scores of 1; and aspirin in those with CHADS2 scores of 0.[16,17] Unfractionated or low-molecular-weight heparin can be used as an anticoagulant for bridging if necessary, such as in patients undergoing invasive surgical procedures or patients whose international normalized ratio (INR) is subtherapeutic. In addition, in the 2010 edition of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines, it was recommended that when an oral anticoagulant is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin.[18] Possible exceptions would include patients who are prone to dyspepsia or gastrointestinal bleeding and those at substantial risk of coronary events. Similarly, the 2010 European Society of Cardiology Atrial Fibrillation guidelines stated that dabigatran can be considered an alternative to warfarin.[19]

This article discusses the role of dabigatran etexilate as a therapeutic alternative for the prevention and treatment of VTE, as well as for prevention of stroke in patients with AF.

METHODS

Peer-reviewed clinical trials, review articles, and relevant treatment guidelines were identified from MEDLINE and the Current Contents database (both 1966–February 15, 2012) using the search terms *dabigatran, venous thromboembolism, atrial fibrillation, pharmacokinetics, pharmacodynamics, pharmacoeconomics,* and *cost-effectiveness*. Citations from available articles were also reviewed for additional references.

RESULTS

Clinical Pharmacology of Dabigatran

Mechanism of Action

Dabigatran etexilate is a prodrug that is converted into its active metabolite, dabigatran, in the liver by esterase-catalyzed hydrolysis.[20] A prodrug is necessary because dabigatran is highly hydrophilic and not orally bioavailable. Dabigatran is a selective thrombin inhibitor, and has low affinity and inhibitory activity to

other human enzymes involved in the coagulation cascade such as factor Xa, trypsin, plasmin, tissue plasminogen activator, and activated protein C.[21] By inhibiting thrombin directly, dabigatran prevents the conversion of fibrinogen into fibrin and prevents thrombus formation. Thrombin has 3 structural domains: 1 active site and 2 exosites. Exosite 1 acts as a dock for substrates such as fibrin to promote orientation for active site binding. Exosite 2 is the heparin-binding domain. The *N*-methyl group of dabigatran binds to the proximal pocket of the thrombin-active site directly (not the exosite). Through this binding, both free and clot-bound thrombin are reversibly inhibited by dabigatran.[20]

Pharmacokinetics

Normal Volunteers

The oral bioavailability of dabigatran etexilate was evaluated in 10 healthy volunteers.[22] Subjects were randomized to receive 1 dose of oral dabigatran etexilate 200 mg or an intravenous infusion of dabigatran 5 mg. Dabigatran etexilate was rapidly converted to dabigatran, with dabigatran C_{max} values achieved after ~1.5 hours. The oral bioavailability of dabigatran etexilate was found to be 7.2%. Approximately 20% of dabigatran is conjugated by glucuronosyltransferases to active glucuronide conjugates. Unabsorbed dabigatran etexilate is eliminated in the feces after oral administration. Dabigatran absorbed into the bloodstream is eliminated by the kidneys. The mean $t_{½}$ of dabigatran was determined to be ~8 hours.[22]

Another open-label, 3-way crossover pharmacokinetics study was performed with dabigatran etexilate. Dabigatran etexilate 150 mg, as a single oral dose, was administered to 18 male volunteers in the fasted state, after administration of food and coadministration of pantoprazole. The extent of absorption of dabigatran etexilate was similar with and without food. A decrease in the mean dabigatran $AUC_{0-\infty}$ (from 904 to 705 ng · h/mL; geometric mean value ratio of $AUC_{0-\infty}$ after and before pantoprazole administration, 0.68; 90% CI, 0.53–0.86) occurred with coadministration of pantoprazole, indicating a reduction in drug absorption.[23] Whether this interaction is clinically significant (in terms of affecting coagulation parameters) is not known.

In another pharmacokinetics study, dabigatran etexilate or placebo was administered orally at single doses of 10 to 400 mg to 40 healthy volunteers or at multiple doses of 50 to 400 mg 3 TID for 6 days to a different group of 40 healthy individuals.[24] Absorption of dabigatran etexilate was rapid, and C_{max} was achieved within 2 hours of administration. The $t_{½}$ was reported to be 8 to 10 hours and 14 to 17 hours with single- and multiple-dose administrations, respectively. Steady-state dabigatran concentration was reached within 3 days with continuous multiple daily dosing. The mean apparent volume of distribution (V_d/F) during the terminal phase was calculated to be 1860 L (range, 1430–2400 L), and mean CL/F was 2031 mL/min (range, 1480–2430 L).

Protein-binding studies with radiolabeled dabigatran were performed and found that 35% of dabigatran is bound to plasma protein.[25] Because of the low percentage of protein binding, displacement interactions are unlikely. Dabigatran etexilate, but not dabigatran, is a substrate of P-glycoprotein.[26] Neither dabigatran etexilate nor dabigatran is metabolized by the cytochrome P450 system. In addition, dabigatran does not seem to inhibit or induce cytochrome P450 enzyme activity.

Elderly

An open-label, parallel-group study was designed to evaluate the pharmacokinetic profile of dabigatran etexilate in 36 otherwise healthy volunteers aged >65 years.[27] Subjects were randomized to receive oral dabigatran etexilate 150 mg BID for 7 days with or without the coadministration of oral pantoprazole. Pantoprazole was administered at 40 mg BID, starting 2 days before dabigatran etexilate administration and ending on the morning of day 7. With BID administration of dabigatran etexilate, plasma concentrations of dabigatran reached steady state within 2 to 3 days. C_{max} was reached after a median of 3 hours. Coadministration with pantoprazole decreased the AUC_{ss} by 24%, similar to that observed in younger subjects.[27] Half-life of dabigatran etexilate in this patient population was 12 to 14 hours, which is slightly longer than that reported in the younger population (no direct comparison made), and likely reflected the age-related decrease in renal function, thus leading to a reduction in the clearance of dabigatran etexilate. Specific dosing adjustments based on age alone have not been made. However, elderly patients receiving dabigatran should be monitored carefully because they are more

likely to have reduced renal function and decreased clearance of the medication.

Gender

A meta-analysis on data from Phase I and II studies revealed a gender effect, with female subjects having an ~31% to 46% higher exposure (*P* value not reported) than males after the same dabigatran etexilate dose.[26] The effect is most likely caused by the average 29.5% lower (*P* value not reported) creatinine clearance (CrCl) in female subjects observed in these studies. From the RE-LY population (the AF study population to be discussed in greater detail in the Clinical Studies section) pharmacokinetics analysis, after adjustment for other factors such as CrCl, age, and weight, female patients with AF were found to have an 8.3% decreased clearance compared with male patients (*P* value not reported).[26] The slight effect on exposure was not associated with any increase in bleeding rates. To date, these observations have not led to any specific recommendations regarding dabigatran dosing on the basis of gender.[28]

Hepatic Dysfunction

The impact of moderate hepatic impairment on the pharmacokinetics of dabigatran etexilate has been evaluated in an open-label, parallel-group study.[29] Twelve healthy volunteers and 12 patients with hepatic impairment (Child-Pugh classification B) were each given a single oral dose of dabigatran etexilate 150 mg. The mean values for AUC, $t_{½}$, and renal clearance of dabigatran were comparable between patients with hepatic impairment and healthy volunteers. Conversion of dabigatran etexilate to active dabigatran was slower in patients with hepatic impairment, indicating that the liver is partly responsible for the conversion of dabigatran etexilate to its metabolites. However, total drug exposure was comparable between groups. The extent of dabigatran glucuronidation, as well as protein binding, was unchanged by liver disease.

Renal Impairment

The pharmacokinetic profile of dabigatran etexilate in patients with renal impairment was evaluated and compared with that of normal volunteers in an open-label, parallel-group study.[30] Six healthy volunteers and 23 patients with mild, moderate, or severe renal impairment (CrCl >50 to <80, >30 to <50, and <30 mL/min, respectively) were given a single oral dose of dabigatran etexilate 150 mg. Six patients with end-stage renal disease (ESRD) were given an oral dose of 50 mg. The AUC values were 1.5-, 3.2-, and 6.3-fold higher than normal volunteers in subjects with mild, moderate, and severe renal impairment, respectively ($P < 0.05$). T_{max} was unchanged. In patients with severe renal impairment, the mean $t_{½}$ was doubled (28 vs 14 hours in healthy volunteers; $P < 0.05$). In patients with ESRD, the dose-normalized AUC was approximately twice the value in the control group. Hemodialysis removed 62% to 68% of the dabigatran dose. The investigators concluded that dabigatran exposure is increased by renal impairment and correlates with the severity of renal dysfunction. In patients with ESRD, dabigatran can be partly removed from the plasma by using hemodialysis. Dosing of dabigatran is based on renal function, which will be discussed in greater detail in the Dosage, Handling, and Administration section.

Patients Undergoing Hip Replacement

Fifty-nine patients who underwent total hip replacement were given a single dose of oral dabigatran etexilate 150 mg, which was administered 1 to 3 hours after their surgical procedure.[23] Immediate onset of absorption was seen, with C_{max} of dabigatran observed after 6 hours. Other pharmacokinetic parameters were similar to those reported in healthy volunteers from other studies. Compared with healthy volunteers, the pharmacokinetic postoperative profile demonstrated a delay to peak concentrations.

Overall, oral dabigatran etexilate is ~7.2% absorbed and achieves its C_{max} within 2 hours after administration in healthy volunteers. Its half-life is ~12 hours. Steady state is attained in 2 to 3 days of treatment with BID dosing. Total and peak exposure have been shown to increase linearly and are dose proportional after single and multiple oral dosing of dabigatran etexilate. Dabigatran is mainly (80%–85%) eliminated in the unchanged form via glomerular filtration. Increasing age and decreasing CrCl can increase dabigatran accumulation. Dabigatran and dabigatran etexilate are neither substrates nor inhibitors or inducers of cytochrome P450 enzymes. Dabigatran etexilate is a substrate but not an inducer or inhibitor of P-glycoprotein. Dabigatran, the active metabolite, is not a substrate, inducer, or inhibitor of the efflux transporter P-glycoprotein.

Pharmacodynamics

The pharmacodynamics of dabigatran were evaluated in 80 healthy volunteers in doses ranging from 10 to 400 mg as a single oral dose and 50 to 400 mg TID.[17] Blood coagulation parameters, including activated partial thromboplastin time (aPTT), INR, thrombin time (TT), and ecarin clotting time (ECT), were measured. Time curves for aPTT, INR, TT, and ECT paralleled plasma concentration–time curves in a dose-dependent manner. At the highest dose of 400 mg TID, maximum prolongations over baseline for aPTT, INR, TT, and ECT were 3.1-, 3.5-, 29-, and 9.5-fold times, respectively. Of the 4 assays, TT and ECT exhibited the greatest sensitivity and correlation with the doses.

Pharmacodynamics of dabigatran have also been evaluated in elderly subjects. Thirty-six healthy elderly subjects aged ≥65 years were randomly assigned to receive oral dabigatran etexilate 150 mg BID for 7 days with or without coadministration of oral pantoprazole.[22] Pantoprazole was administered at 40 mg BID, starting 2 days before dabigatran etexilate administration and ending on the morning of day 7. Prolongation of ECT and aPTT correlated with and paralleled the plasma concentration–time profile of dabigatran. ECT increased in direct proportion to the plasma concentration, and aPTT displayed a linear relationship with the square root of the plasma concentration. Pantoprazole has no effect on pharmacodynamic parameters. The authors concluded that age did not affect the pharmacodynamic profile of dabigatran in terms of blood coagulation parameters.

The impact of moderate hepatic impairment on the pharmacodynamics of dabigatran etexilate has also been evaluated in an open-label, parallel-group study.[23] Healthy volunteers (n = 12) and patients with hepatic impairment (Child-Pugh classification B; n = 12) received a single oral dose of dabigatran etexilate 150 mg. The aPTT, ECP, and TT relationships were essentially identical in both groups.

Similarly, the impact of renal function on the pharmacodynamic profile of dabigatran etexilate was evaluated in an open-label, parallel-group, single-center study.[24] Six healthy volunteers and 23 subjects with mid, moderate, or severe renal impairment (CrCl >50 to ≤80, >30 to ≤50, and ≤30 mL/min, respectively) were given a single oral dose of dabigatran etexilate 150 mg. Six patients with ESRD were given an oral dose of 50 mg. The AUC for prolongation of pharmacodynamic parameters (aPTT and ECT) increased in correlation with the pharmacokinetic changes (ie, increase in dabigatran half-life as renal function worsened).

Overall, prolongation of ECT, aPTT, INR, and TT correlated with and paralleled the plasma concentration–time profile of dabigatran. Age, hepatic impairment, and renal dysfunction did not affect the pharmacodynamic response of dabigatran.

Drug Interactions

Table I summarizes pertinent drug interaction with dabigatran.[26] Few drug-interaction studies of dabigatran etexilate have been published. However, according to the briefing materials submitted to the FDA, the manufacturer has performed 13 pharmacokinetic or

Table I. Pertinent drug interactions with dabigatran.[26]

Interacting Agent	Outcome of Interaction	Dosage Adjustment Recommendation
Pantoprazole	Decrease bioavailability by ~13%	Not needed
Clopidogrel (300 mg and 600 mg loading dose only)	Increase AUC by 30% and decrease C_{max} by 40%	Not needed
Ketoconazole	Increase bioavailability by 150%	Not needed
Verapamil	Increase bioavailability by 50%–60%	Not needed
Amiodarone	Increase bioavailability by 50%–60%	Not needed
Quinidine	Increase bioavailability by 50%–60%	Not needed
Rifampin	Decrease AUC by 66% and decrease C_{max} by 67%	Avoided

pharmacodynamic drug-interaction studies with dabigatran (including interaction with atorvastatin, diclofenac, clopidogrel, proton pump inhibitors, histamine$_2$-antagonists, digoxin, and P-glycoprotein inhibitors [eg, verapamil, quinidine, clarithromycin, ketoconazole, amiodarone, P-glycoprotein inducer rifampin]). They reported no significant effect of dabigatran etexilate on the pharmacokinetic profile of either atorvastatin and diclofenac, and vice versa. Because dabigatran etexilate requires an acidic environment to be absorbed, the bioavailability of dabigatran was reduced by ~30% in a Phase I study by the concomitant administration of the proton pump inhibitor pantoprazole, whereas the histamine$_2$-receptor antagonist ranitidine did not reduce the bioavailability of dabigatran etexilate. The clinical significance of this interaction in terms of whether it affects the anticoagulant property of dabigatran is, however, unknown. In a Phase I study, coadministration of oral dabigatran and clopidogrel had no effects on the pharmacokinetic or pharmacodynamic profile of either compound. However, if a loading dose of clopidogrel (300 or 600 mg) was given, dabigatran AUC_{ss} and C_{max} at steady state increased by ~30% to 40%. Because clopidogrel is a substrate of P-glycoprotein, a high loading dose may have competitively inhibited the ability of intestinal P-glycoprotein to bind to dabigatran, thus allowing more dabigatran etexilate to be absorbed. The steady-state pharmacokinetics of digoxin (a P-glycoprotein substrate) and dabigatran were not altered with coadministration.

For drug interactions with P-glycoprotein inducers and inhibitors, the maximum increase in dabigatran bioavailability was observed with ketoconazole (increased by ~150%). After multiple dosing of verapamil (120 mg BID or 4 times daily), there was a 50% to 60% increase in dabigatran bioavailability. Amiodarone and quinidine exerted similar effects (50%–60% increased bioavailability of dabigatran) as steady-state verapamil. Clarithromycin did not significantly affect the pharmacokinetics of dabigatran. Consistent with all P-glycoprotein interactions between dabigatran etexilate and P-glycoprotein inhibitors, which should only occur primarily in the gut, when verapamil was administered 2 hours before dabigatran etexilate intake, there was only a marginal (<20%) increase in dabigatran bioavailability. Even with this increase in bioavailability due to the drug interaction, the manufacturer did not recommend any dosage adjustment when dabigatran was administered with any of these medications.[28]

However, after 7 days' pretreatment with rifampin (600 mg daily), dabigatran AUC and C_{max} were reportedly reduced by 66% and 67%, respectively.[28] These parameters returned to baseline (similar to when dabigatran etexilate was administered alone) 7 days after cessation of rifampin treatment. The manufacturer recommends that concurrent administration of dabigatran and rifampin should be avoided.

Clinical Studies

Table II[31–39] summarizes all pertinent clinical studies of dabigatran use in VTE prophylaxis and treatment, as well as stroke prevention in AF.

Prophylaxis of VTE

The Boehringer Ingelheim Study in Thrombosis I (BISTRO I) was the first study designed to determine a therapeutic dosage range for dabigatran etexilate for VTE in patients after total hip replacement.[31] A total of 314 patients aged ≥18 years were recruited between October 2000 and June 2001. They received oral dabigatran doses of 12.5, 25, 50, 100, 150, 200, and 300 mg BID or 150 and 300 mg once a day in an open-label, dose-escalating manner. The medication was administered 4 to 8 hours after surgery for 6 to 10 days. Follow-up duration was 4 to 6 weeks. The primary safety outcome was major bleeding, and the primary efficacy outcomes were venographic DVT, symptomatic DVT, and pulmonary embolism (PE) during the treatment period. The study, however, was not powered to detect differences in efficacy among different doses. The overall DVT rate was reported to be 12.4%, with the highest rates occurring in the 12.5-mg group (20.8%). The lowest rates were observed with the highest dosing groups (300 mg once daily or BID [0%]), but a dose-response relationship was not determined. There were no major bleeding events reported in this trial. Patients from multiple sites in the 300-mg BID group had to be discontinued from the study prematurely due to observed bleeding episodes within a few days of treatment. Results from this study suggest that a dose of 12.5 to 300 mg BID will likely be effective at preventing VTE in patients undergoing total hip replacement but 300 mg BID may cause more bleeding.

The BISTRO II trial was a randomized, double-blind, parallel-group, active-controlled study designed to determine the dose-response relationship of dabigatran etexilate (both safety profile and efficacy) for the prevention of VTE after total hip and total knee re-

Table II. Pertinent clinical studies on the use of dabigatran.

Reference	Patient (N)	Treatment	Follow-Up	Primary Efficacy Endpoint	Safety Endpoint
BISTRO I[31]	314 total hip replacement	DE 12.5, 25, 50, 100, 150, 200, and 300 mg BID and 150 or 300 mg once daily for 6–10 days	4–6 weeks	DVT or PE (not powered to look at differences among groups) 12.5 mg BID, 12.4% 12.5 mg BID, 12.4% 25 mg BID, 20.8% 50 mg BID, 9.5% 100 mg BID, 14.8% 150 mg BID, 9.5% 200 mg BID, 19% 300 mg BID, 0% 150 mg QD, 9.1% 300 mg QD, 6.1%	Major bleed: 0% Minor bleed: 12.5 mg BID, 7.4% 25 mg BID, 32.1% 50 mg BID, 60% 100 mg BID, 82.5% 150 mg BID, 89.7% 200 mg BID, 78.6% 300 mg BID, 80% 150 mg QD, 95.1% 300 mg QD, 89.1%
BISTRO II[32]	1464 total hip or knee replacement	DE 50, 150, or 225 mg BID or 300 mg once daily or enoxaparin 40 mg SC once daily for 6–8 days	4–6 weeks	DVT and PE DE Total population: 20% 50 mg BID: 28.5% 150 mg BID: 17.5%* 225 mg BID: 13.1%* 300 mg QD: 16.6%* Enoxaparin: 24%	Major/minor bleed: DE 50 mg BID: 0.3%/4.6% 150 mg BID: 4.1%/7.9% 225 mg BID: 3.8%/9.7% 300 mg QD: 4.7%/9.6% Enoxaparin: 2%/6.4%
RE-NOVATE[33]	3494 total hip replacement	DE 150 or 220 mg QD or enoxaparin 40 mg SC once daily for 28–35 days	3 months	VTE and all-cause mortality: 150 mg QD: 8.6%,† 220 mg QD: 6%† Enoxaparin: 6.7% *P value indicates DE to be noninferior to enoxaparin	Major/minor bleed: DE: 150 mg QD: 1.3%/6.2% 220 mg QD: 2%/6.1% Enoxaparin: 1.6%/6.4%
RE-MODEL[34]	2076 total knee replacement	DE 150 or 220 mg QD or enoxaparin 40 mg SC once daily for 6–10 days	3 months	VTE and all-cause mortality: 150 mg QD: 40.5%,† 220 mg QD: 36.4%† Enoxaparin: 37.7%	Major/minor bleed DE: 150 mg QD: 1.3%/8.4% 220 mg QD: 1.5%/8.8% Enoxaparin: 1.3%/9.9%

(continued)

Table II (continued).

Reference	Patient (N)	Treatment	Follow-Up	Primary Efficacy Endpoint	Safety Endpoint
RE-MOBLIZE[36]	Total knee replacement	DE 150 or 220 mg QD or enoxaparin 30 mg SC BID for 12–15 days	12–15 days	VTE and all-cause mortality: 150 mg QD: 33.7%, 220 mg QD: 31.1% Enoxaparin: 25.3% DE did not demonstrate noninferiority to enoxaparin	Major/minor bleed DE: 150 mg QD: 0.6%/22% 220 mg QD: 0.6%/23% Enoxaparin: 1.4%/21%
RE-COVER[37]	2339 with acute VTE	DE 150 mg BID or warfarin (dose to INR 2–3) for 6 months	6 months	Recurrent VTE symptoms, confirmed VTE, and related death DE: 2.4%‡ Warfarin: 2.1%	Major/minor bleed DE: 1.6%/16.1% Warfarin: 1.9%/21.9% HR of DE to warfarin: 0.71 (95% CI, 0.59–0.85)§
PETRO[38]	502 with AF	DE 50 or 150 or 300 mg BID or warfarin (dose to INR 2–3)	12 weeks	Thromboembolic events: 2% in 50 mg BID group. 0% in others	Major/minor bleed DE 50 mg BID: 0/4.6% 150 mg BID: 0/10% 300 mg BID: 6.3%/21.8% Warfarin: 0/4.2%
RE-LY[39]	18,113 with AF	DE 110 or 150 mg BID or warfarin (dose to INR 2–3)	2 years	Stroke and systemic embolism: DE 110 mg BID: 1.53% per year‖ DE 150 mg BID: 1.11% per year¶ Warfarin: 1.69% per year	Major/minor bleed DE 110 mg BID: 2.71§/13.16%§ per year 150 mg BID: 3.11§/14.84% § per year Warfarin: 3.6/16.37% per year

BISTRO I = Boehringer Ingelheim Study in Thrombosis I; DE = dabigatran etexilate; DVT = deep vein thrombosis; PE = pulmonary embolism; QD = daily; RE-NOVATE = Prevention of Venous Thromboembolism After Total Hip Replacement; VTE = venous thromboembolism; RE-MODEL = Thromboembolism Prevention After Knee Surgery; RE-MOBILIZE = Dabigatran Versus Enoxaparin in Preventing Venous Thromboembolism Following Total Knee Arthroplasty; RE-COVER = Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism; INR = international normalized ratio; PETRO = Prevention of Embolic and Thrombotic Events in Patients With Persistent Atrial Fibrillation; AF = atrial fibrillation; RE-LY = Randomized Evaluation of Long-term Anticoagulation Therapy; Postop = postoperation.

*$P < 0.05$ for enoxaparin.

†$P < 0.05$ indicating non-inferior to enoxoparin.

‡$P < 0.0001$ indicating non-inferior to warfarin.

§$P < 0.05$ significantly different from warfarin.

‖$P < 0.001$ indicating non-inferior to warfarin.

¶$P < 0.001$ indicating superior to warfarin.

placement compared with enoxaparin.[32] Dabigatran etexilate dosing regimens were 50, 150, and 225 mg BID and 300 mg once daily given orally; they were compared with enoxaparin 40 mg SC once daily. Dabigatran etexilate was administered 1 to 4 hours after surgery, and enoxaparin was given subcutaneously the evening before surgery according to product labeling. Treatment was continued for 6 to 10 days, and patients were followed up for 4 to 6 weeks after surgery. Patient inclusion criteria and exclusion criteria were similar to those in BISTRO I. A total of 1464 patients were included in the efficacy analysis (total hip replacement [68%] or total knee replacement [32%]). The primary efficacy outcome was the occurrence of VTE (ie, composite occurrence of venographically documented DVT and symptomatic DVT or PE) during the treatment period. Administration of dabigatran etexilate 150 mg BID, 300 mg once daily, and 225 mg BID resulted in significantly fewer VTEs compared with enoxaparin (17.4% [150 mg BID] vs 16.6% [300 mg BID] vs 13.1% [225 mg BID] vs 24% [enoxaparin]; $P < 0.05$ for comparison of each dose with enoxaparin). These differences are regardless of the type of surgery (knee or hip). However, no significant difference was noted in the frequency of VTE in patients receiving dabigatran etexilate 50 mg BID versus those receiving enoxaparin. Regarding timing of initial dose, post-hoc analysis indicated that the frequency of VTE was significantly lower in patients receiving their first dose of dabigatran etexilate within 2 hours after surgery compared with those receiving the drug after 2 hours (14.1% vs 22.4%; $P = 0.0005$). The primary safety outcome was frequency of major bleeding. Compared with enoxaparin, there was a higher, although nonsignificant, rate of major bleeding with doses of dabigatran 150 mg BID and higher. There was no correlation noted between the timing of the first dose and bleeding event. This study was able to demonstrate a dose-response relationship for safety profile and efficacy. At these doses, dabigatran etexilate (150 or 225 mg BID or 300 mg once daily given orally) seemed to be more effective than or as effective as enoxaparin (50 mg SC BID). Larger studies are needed to further assess the risk of bleeding with longer-term use.

The Prevention of Venous Thromboembolism After Total Hip Replacement (RE-NOVATE) trial is a randomized, double-blind, noninferiority study designed to compare the safety profile and efficacy of dabigatran etexilate with enoxaparin when given for VTE prevention in 3494 patients after total hip replacement.[33] Treatment groups were administered either dabigatran etexilate 220 or 150 mg orally once daily, with the first dose given as one half of the dose 1 to 4 hours after surgery or enoxaparin 40 mg SC once daily starting the evening before surgery. Treatment was continued for 28 to 35 days in accordance with current VTE prevention recommendations (longer duration than the previous 2 studies [6–10 days]). The noninferiority margin was set at 7.7% based on an enoxaparin VTE absolute reduction of 32.8% compared with no treatment. The primary efficacy outcome of total VTE and all-cause mortality was as follows: dabigatran etexilate 220 mg, 6%; dabigatran etexilate 150 mg, 8.6%; and enoxaparin, 6.7% ($P < 0.05$ for noninferiority). Dabigatran etexilate administered as either 150 or 220 mg orally once daily for 28 to 35 days after total hip replacement seemed to be noninferior to enoxaparin. Major bleeding events occurred in 2%, 1.3%, and 1.6% of patients receiving dabigatran etexilate 220 mg, dabigatran etexilate 150 mg, and enoxaparin, respectively. These observed differences were not statistically significant. The most frequent type of adverse event in each group was largely gastrointestinal related and included nausea, vomiting, and constipation. Alanine aminotransferase level increases >3 times the upper limit of normal were more common in the enoxaparin group (5%) than in either of the dabigatran etexilate groups (3%) ($P = 0.0081$ for dabigatran 220 mg and $P = 0.0061$ for dabigatran 150 mg). Incidence of ACS events (confirmed unstable angina, myocardial infarction, and cardiac death) were low (dabigatran etexilate 220 mg, 5 events; dabigatran etexilate 150 mg, 8 events; and enoxaparin, 9 events [*P* values not reported]). This study concluded that oral dabigatran etexilate 220 and 150 mg once daily each were noninferior to enoxaparin 40 mg SC once daily in reducing the frequency of VTE and all-cause mortality when given for VTE prophylaxis in patients undergoing total hip replacement surgery. This is the first longer period of administration to be studied, and extending the administration period did not seem to increase the frequency of liver function abnormalities or ACS events.

The Thromboembolism Prevention After Knee Surgery (RE-MODEL) study was a randomized, double-blind, multicenter, active-controlled, noninferiority trial designed to compare dabigatran etexilate 150 mg and 220 mg orally once daily versus enoxaparin 40 mg SC once daily in patients who underwent total knee

replacement.[34] The study had inclusion and exclusion criteria similar to BISTRO II.[32] The primary efficacy outcome was the same as that used in the RE-NOVATE study.[33] The first dose of dabigatran etexilate was administered 1 to 4 hours after surgery as one half of the dose. Enoxaparin was started after surgery as determined according to local practice. The treatment period was 6 to 10 days. Continuation after this time period was permitted at the discretion of the investigators. Patients were assessed up to 3 months after surgery. The primary efficacy outcome with dabigatran etexilate, using either 220 mg or 150 mg once daily, was deemed noninferior compared with enoxaparin but did not show superiority (36.4% [95% CI, 32.3%–40.6%], $P = 0.0003$; 40.5% [95% CI, 36.3%–44.7%], $P = 0.017$; and 37.7% [95% CI, 33.5%–41.9%]) respectively. The absolute difference in total VTE and all-cause mortality compared with enoxaparin was as follows: dabigatran etexilate 220 mg, −1.3% (95% CI, 7.3%–4.6%); dabigatran etexilate 150 mg, 2.8% (95% CI, 4.1%–8.7%). The rate of major bleeding was not significantly different among the groups (dabigatran etexilate 220 mg, 1.5%; dabigatran etexilate 150 mg, 1.3%; and enoxaparin, 1.3%). The frequency of alanine aminotransferase level increases >3 times the upper limit normal was similar between enoxaparin (4%), dabigatran etexilate 220 mg (2.8%), and dabigatran etexilate 150 mg (3.7%), although *P* values were not reported. All abnormal elevations returned to baseline values during follow-up after the study drugs were discontinued. Incidence of ACS events was low (dabigatran etexilate 220 mg, 0.44%; dabigatran etexilate 150 mg, 1%; and enoxaparin, 0.58% [*P* value not reported]). This study demonstrated that dabigatran etexilate 220 mg and 150 mg orally once daily were each noninferior to enoxaparin 40 mg SC once daily for the prevention of VTE in patients undergoing total knee replacement. There was no significant difference in the frequency of major bleeding or overall rate of adverse events between either dose of dabigatran etexilate and enoxaparin. It is important to note that the dosing of enoxaparin[35] (40 mg once daily) is different from what is typically used in total knee replacement (30 mg BID) and approved in the United States. Use of lower doses of enoxaparin may lead to apparently higher VTE events and a lower frequency of bleeding.

The Dabigatran Versus Enoxaparin in Preventing Venous Thromboembolism Following Total Knee Arthroplasty (RE-MOBILIZE) study was another randomized, double-blind, noninferiority trial designed to compare oral dabigatran etexilate and subcutaneous enoxaparin.[35] A total of 2615 patients were randomly assigned to receive dabigatran etexilate 150 mg or 220 mg once daily or enoxaparin 30 mg BID (the enoxaparin dose for knee replacement officially approved in the United States) for 12 to 15 days of treatment. The first dose of dabigatran etexilate was administered as a half-dose 6 to 12 hours after surgery. Enoxaparin was initiated 12 to 24 hours after surgery. The study had similar inclusion and exclusion criteria as BISTRO II.[32] In this study, when enoxaparin was given in a BID regimen, it demonstrated superiority over dabigatran for the primary efficacy outcome of proximal DVT, distal DVT, PE, and all-cause mortality (dabigatran etexilate 220 mg, 31.1%, $P = 0.02$; dabigatran etexilate 150 mg, 33.7%, $P = 0.0009$; enoxaparin, 25.3%). Both doses of dabigatran etexilate failed to demonstrate noninferiority to enoxaparin. However, the frequency of major bleeding events was higher in the enoxaparin group (dabigatran etexilate 220 mg, 0.6%; dabigatran etexilate 150 mg, 0.6%; and enoxaparin, 1.4% [*P* values not reported]). Elevated alanine aminotransferase levels >3 times the upper limit of normal occurred infrequently and similarly among the 3 groups (dabigatran etexilate 220 mg, 0.7%; dabigatran etexilate 150 mg, 1%; and enoxaparin, 0.9% [*P* values not reported]). Cardiac adverse events (exact type of event not specified) were reported in 9 patients in the dabigatran 220-mg group, 10 patients in the dabigatran 110-mg group, and 9 patients in the enoxaparin group. Findings from RE-MOBILIZE demonstrate that dabigatran etexilate was not as effective as enoxaparin in preventing total VTE and mortality. It has been postulated that differences in the study design and dosing regimen contributed to these findings. The dose of enoxaparin used was higher than previous studies (30 mg SC BID vs 40 mg SC once daily), and the starting dose of enoxaparin was given at a mean of 20 hours after surgery. The mean duration of treatment (13 days) also varied from previous studies.

Fuji et al[40] assessed the efficacy, safety profile, and dose response of dabigatran etexilate in the prevention of VTE in 407 Japanese patients undergoing total knee arthroplasty. Patients were randomly assigned to receive 110, 150, or 220 mg of oral dabigatran etexilate or placebo once daily for 11 to 14 days, starting the day after surgery. The primary efficacy end point was the

incidence of total VTE and all-cause mortality; the primary safety end point was incidence of major, clinically relevant, and minor bleeding events. Total VTE and all-cause mortality were lower in patients receiving dabigatran etexilate 110, 150, or 220 mg daily (39.6%, 32.7%, and 24.0%, respectively) than placebo (56.4%) ($P < 0.05$ for all comparisons). There was no difference in the incidence of major bleeding among all groups (1%, 0%, 3%, and 0.8% for dabigatran etexilate 110, 150, and 220 mg and placebo, respectively). This study concluded that dabigatran etexilate reduced the incidence of VTE in Japanese patients undergoing total knee replacement, with a safety profile comparable to placebo.

Friedman et al[41] performed a pooled analysis of the RE-MOBLIZE, RE-MODEL, and RE-NOVATE studies. In total, 8135 patients with available data for evaluation were included in this pooled analysis. These patients were randomized to receive dabigatran etexilate 220 mg or 150 mg once daily or enoxaparin (40 mg SC once daily or 30 mg SC BID depending on studies as previously discussed). Efficacy analyses were based on the modified intention-to-treat population of 6200 patients with an evaluable outcome. The composite outcome of major VTE and VTE-related mortality occurred in 3.3% of the enoxaparin group versus 3.0% of the dabigatran 220-mg group (−0.2% [95% CI, −1.3% to 0.9%]) and 3.8% in the dabigatran etexilate 150-mg group (0.5% [95% CI, −0.6% to 1.6%]). Major bleeding occurred in 1.4% of the enoxaparin group versus 1.4% of the dabigatran 220-mg group (−0.2% [95% CI, −0.8% to 0.5%]) and 1.1% of the dabigatran 150-mg group (−0.4% [95% CI, −1.0% to 0.2%]). The authors concluded that oral dabigatran etexilate in doses of 150 or 220 mg daily was as effective as enoxaparin 40 mg SC once daily or 30 mg SC BID in reducing the risk of major VTE and VTE-related mortality after hip or knee arthroplasty and that they had a similar bleeding profile. It is important to note that the combination of 2 different dosing regimen of enoxaparin into one group for analysis may have affected the results.

A similar pooled analysis performed by a group of Canadian investigators of the RE-MOBILIZE, RE-MODEL, and RE-NOVATE studies also demonstrated similar results.[42] It was reported that dabigatran and enoxaparin had a similar risk of symptomatic VTE plus all-cause mortality (0.9% vs 1.1%; odds ratio [OR] = 0.76 [95% CI, 0.44–1.31]) and bleeding (5.0% vs 5.6%; OR = 0.90 [95% CI, 0.71–1.15]). It is important to note that the results reflect 2 different dosages of dabigatran combined into one group and 2 different dosages of enoxaparin combined into one group.

A meta-analysis was also performed with data from the RE-MODEL, RE-MOBILIZE, and RE-NOVATE studies.[43] No significant differences were detected between the effect of dabigatran etexilate and enoxaparin in any of the end points analyzed, although the investigators concluded that heterogeneity between the trials could not be ruled out.

Trkulja et al[44] performed an indirect comparison of the efficacy and safety profile of the use of dabigatran versus rivaroxaban (both given orally) in the prevention of VTE by performing a separate meta-analysis of each of these agents and comparing the results. The risk difference for symptomatic VTE were reportedly as follows: rivaroxaban – enoxaparin, −0.4% (95% CI, −0.9% to 0.05%]); dabigatran – enoxaparin, −0.09% [95% CI, −1.0% to 0.8%]); and rivaroxaban – dabigatran, −0.3% [95% CI, −1.3% to 0.7%]). Risk differences for clinically relevant bleeding were reported as follows: rivaroxaban – enoxaparin, −0.99% (95% CI, 0.29% to 1.69%); dabigatran – enoxaparin, 0.02% (95% CI, −1.0% to 1.0%); and rivaroxaban – dabigatran, 0.97% (95% CI, −0.43 to 2.37). These findings suggest that dabigatran and rivaroxaban did not differ in efficacy or safety profile outcomes in the prevention of VTE. However, it is important to note that methodologic and patient population differences did not allow direct comparison of the 2 agents, and future studies designed to prospectively compare these 2 new oral anticoagulants are needed.

The Cochrane Collaboration performed a systemic review of the use of a DTI (including ximelagatran, dabigatran, and desirudin) in the prophylaxis of VTE.[45] Four studies including 10,183 patients were included (BISTRO II, RE-MOBILIZE, RE-NOVATE, and RE-MODEL). Results were reported in combination with all other DTIs. Overall, considering all DTIs, there was no difference in major VTE compared with the use of low-molecular-weight heparin in both hip or knee replacement (OR = 0.91 [95% CI, 0.69–1.19]). No difference was observed with warfarin as well (OR = 0.85 [95% CI, 0.63–1.15]). More total bleeding were observed in the DTI group (for ximelagatran and dab-

igatran but not desirudin) in patients who underwent total hip replacement (OR = 1.40 [95% CI, 1.06–1.85]) compared with low-molecular-weight heparin, but no difference was observed with warfarin in total knee replacement (OR = 1.76 [95% CI, 0.91–3.38]). This study indicated that DTIs could be potential alternatives to enoxaparin for VTE prophylaxis in hip and knee replacement surgery. Separate conclusions regarding dabigatran etexilate could not be made, however.

Overall, for the prophylaxis of VTE, initially dabigatran etexilate 12.5 to 300 mg orally BID was proposed for patients undergoing total hip replacement.[31] This amount was narrowed to a total daily dabigatran etexilate dose of 100 to 300 mg orally due to increases in bleeding risk with higher doses. This dosing range demonstrated significantly fewer VTE in patients who had undergone total hip or total knee replacement, compared with enoxaparin at a dosage of 40 mg SC daily.[32] Studies of larger populations demonstrated noninferiority of dabigatran etexilate 220 and 150 mg once daily compared with enoxaparin 40 mg SC once daily in patients undergoing total hip or total knee replacement, without significant increases in major or minor bleeding events.[33,34] In contrast, dabigatran etexilate has failed to achieve noninferiority in patients undergoing total knee replacement when enoxaparin was administered as 30 mg SC BID.[36] The authors attributed them to including the frequency of asymptomatic distal DVT and perhaps the use of higher total daily doses of enoxaparin.

Treatment of VTE

The Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER) study is the only randomized, double-blind, noninferiority trial evaluating dabigatran etexilate for VTE treatment published to-date.[37] A total of 2339 patients with a first-time episode of acute VTE and who have been treated with parenteral anticoagulation therapy for a median of 9 days were randomized to receive either dabigatran etexilate 150 mg BID orally or oral warfarin dose adjusted to achieve an INR of 2 to 3. Duration of treatment was 6 months. The primary outcome was incidence of recurrent symptomatic, objectively confirmed VTE, and related deaths at 6 months. Safety end points included bleeding events, ACS, other adverse events, and abnormal results on liver function tests. The primary outcome occurred in 30 of the 1274 (2.4%) patients receiving dabigatran compared with 27 of the 1265 (2.1%) patients randomly assigned to receive warfarin. The difference in risk was 0.4 % (95% CI, −0.8 to 1.5 [$P < 0.001$] for the prespecified noninferiority margin). Major bleeding episodes occurred in 20 patients assigned to dabigatran (1.6%) and in 24 patients assigned to warfarin (1.9%) (hazard ratio with dabigatran = 0.82 [95% CI, 0.45 to 1.48]), and episodes of any bleeding were observed in 205 patients assigned to dabigatran (16.1%) and 277 patients assigned to warfarin (21.9%) (hazard ratio with dabigatran = 0.71 [95% CI, 0.59 to 0.85]). The number of ACS was low (dabigatran, 0.4%, warfarin, 0.2% [$P = 0.73$]) and abnormal results on liver function tests (aspartate aminotransferase elevation: dabigatran, 3.1%; warfarin, 2.1% [$P = 0.14$]) were similar in the 2 groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients assigned to dabigatran and in 6.8% of patients assigned to warfarin ($P = 0.05$). This study concluded that a fixed dose of dabigatran is as effective as warfarin and has a safety profile similar to that of warfarin for VTE treatment. Future studies will continue to explore the role of dabigatran etexilate in patients with recurrent VTE who may require longer duration of treatment, especially in terms of long-term tolerance and discontinuation rate.

Stroke Prevention in AF

The Prevention of Embolic and Thrombotic Events in Patients With Persistent Atrial Fibrillation (PETRO) study was the first study designed to evaluate the use of dabigatran etexilate in stroke prevention in patients with AF.[38] The objective of this study was to identify a tolerable dosing regimen of dabigatran etexilate in patients with AF and to evaluate anticoagulant activity through aPTT changes and inhibition of D-dimer generation. A total of 502 patients with AF and coronary artery disease plus ≥1 of several risk factors were randomized to receive oral dabigatran etexilate 50, 150, or 300 mg BID in a 3 × 3 factorial design with or without aspirin 81 or 325 mg daily orally, or warfarin orally dosed to an INR of 2 to 3. The risk factors included hypertension, diabetes, symptomatic heart failure, or left ventricular ejection fraction <40%, previous stroke or transient ischemic attack (TIA), or age >75 years (ie, CHADS2 score ≥1). This trial was double-blinded in terms of dabigatran etexilate doses but

open-label for concomitant aspirin and warfarin treatment. After 4 to 7 days of treatment, all patients with glomerular filtration rates ≤50 mL/min or an aPTT ratio ≥2.5 times baseline, who were receiving dabigatran, had their doses decreased to once daily. Patients were followed up for 12 weeks. The primary outcome was the frequency of bleeding events. Major bleeding events (defined as fatal or life-threatening retroperitoneal, intracranial, intraocular, or intraspinal bleeding; bleeding requiring surgery or transfusion of ≥2 units of blood or associated with a decrease in hemoglobin of ≥2 g/L) were only observed in the group treated with dabigatran etexilate 300 mg BID plus aspirin (4 of 64). Total bleeding episodes was significantly different between the dabigatran etexilate 300 mg BID group plus aspirin compared with the dabigatran etexilate 300 mg BID group without aspirin (28 of 64 vs 14 of 105; $P = 0.03$). The total bleeding event in the dabigatran etexilate 150 mg BID without aspirin group was similar to that of the warfarin group (15 of 100 vs 12 of 70; $P > 0.05$). The frequency of bleeding in the group treated with dabigatran etexilate 50 mg BID was significantly lower than that in the warfarin group (7 of 107 vs 12 of 70; $P = 0.04$). The suppression of D-dimer in the dabigatran etexilate 150 mg BID group was similar to warfarin (3% vs –1%). The dabigatran etexilate 50 mg BID group did not demonstrate suppression of D-dimer. The only 2 systemic thromboembolic events observed in this study were both in the dabigatran etexilate 50 mg BID group. However, the number of events was too low to reach meaningful conclusions about the efficacy for this end point. Adverse events were more frequent in the dabigatran groups than in the warfarin-treated patients. The most commonly reported adverse events were gastrointestinal disorders such as diarrhea, nausea, or vomiting (26%), followed by general system disorders such as fatigue or edema (12%), dizziness and headache (12%), and infections (% not reported). The authors concluded that 150 mg BID of dabigatran etexilate was a reasonable target dose for further efficacy exploration.

The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study was a randomized, parallel-group, active-controlled, noninferiority trial of 2 blinded doses of oral dabigatran etexilate (100 and 150 mg BID) compared with open-label oral warfarin (dosed to INR 2–3) in patients with nonvalvular AF with 1 additional risk factor for stroke (similar to PETRO).[39] The primary end points were stroke and systemic embolism. The mean duration of follow-up was 2 years. A total of 18,113 patients were enrolled. Incidence of the primary outcome were 1.69% per year in the warfarin group versus 1.53% per year in the group receiving 110 mg of dabigatran etexilate (relative risk [RR] = 0.91 [95% CI, 0.74–1.11]; $P < 0.001$ for noninferiority) versus 1.11% per year in the group receiving 150 mg of dabigatran etexilate (RR = 0.66 [95% CI, 0.53–0.82]; $P < 0.001$ for superiority). The rate of major bleeding (defined as reduction of hemoglobin ≥2 g/L, transfusion of ≥2 units of blood, life-threatening bleeding, or symptomatic bleeding in a critical area or organ) was 3.36% per year in the warfarin group compared with 2.71% per year in the group receiving 110 mg BID of dabigatran etexilate ($P = 0.003$) and 3.11% per year in the group receiving 150 mg BID of dabigatran etexilate ($P = 0.31$). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group compared with 0.12% per year with dabigatran etexilate 110 mg BID ($P < 0.001$) and 0.10% per year with dabigatran etexilate 150 mg BID ($P < 0.001$). The only adverse effect reported to be significantly more common with dabigatran than with warfarin was dyspepsia (5.8% in the warfarin group and 11.8% and 11.3% in the dabigatran 110-mg and 150-mg groups, respectively [$P < 0.001$ for both comparisons]). The investigators concluded that dabigatran etexilate given at a dose of 110 mg BID was associated with similar rate of thromboembolic outcomes compared with warfarin but a lower rate of major hemorrhage. Dabigatran etexilate administered at a dose of 150 mg BID, compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

Results of several subanalyses of the RE-LY study have also been published. Wallentin et al[46] performed a subanalysis evaluating the relationship between comparative efficacy of dabigatran to the TTR in warfarin. The overall mean INR TTR of warfarin was 64.4% in the whole study, similar to that reported in other clinical trials.[38,47] The quartiles of TTR for patients in the warfarin group evaluated were: <57.1%, 57.1% to 65.5%, 65.5% to 72.6%, and >72.6%. There were no significant interactions between TTR and prevention of stroke and systemic embolism with either 110 mg BID of dabigatran etexilate (interaction $P = 0.89$) or 150 mg BID of dabigatran etexilate (interaction $P = 0.20$) versus warfarin. There was also no significant interactions observed with TTR with regard to intra-

cranial bleeding with dabigatran etexilate 110 mg BID (interaction $P = 0.71$) or 150 mg BID (interaction $P = 0.89$) versus warfarin. There was a significant interaction between TTR and major bleeding between the dabigatran etexilate 150 mg BID regimen with warfarin (interaction $P = 0.03$), with fewer bleeding events observed at lower TTR (major bleeding rate—dabigatran, 3.32/100 person-years; warfarin, 3.59/100 person-years) but similar events at higher TTR (major bleeding rate—dabigatran, 3.32/100 person-years; warfarin, 3.11/100 person-years), whereas rates of major bleeding were lower with dabigatran etexilate 110 mg than with warfarin irrespective of TTR (major bleeding rate—dabigatran, 2.87/100 person-years; warfarin, 3.11–4.13/100 person-years). There were significant interactions between TTR and effects of both 110 mg and 150 mg of dabigatran etexilate versus warfarin on all cardiovascular events (incidence of cardiovascular events not reported; interaction $P = 0.036$ and $P = 0.0006$, respectively) and total mortality (dabigatran etexilate 110 mg, 3.75%; dabigatran etexilate 150 mg, 3.64%; warfarin, 4.13%; interaction $P = 0.066$ and $P = 0.052$, respectively) with reduced event rates at low TTR in the dabigatran etexilate groups and similar rates at high TTR. The investigators concluded that the benefit of dabigatran etexilate 150 mg BID in reducing thromboembolic events and the benefit of dabigatran etexilate 110 mg BID in reducing bleeding were consistent regardless of the TTR achieved by warfarin therapy.

Another subgroup analysis of the RE-LY trial specifically examined the effect of dabigatran compared with warfarin in patients with history of stroke or TIA.[48] Within the subgroup of patients with previous stroke or TIA, 1195 patients were from the dabigatran etexilate 110 mg BID group, 1233 from the dabigatran etexilate 150 mg BID group, and 1195 from the warfarin group. Primary end points (stroke or systemic embolism) occurred in 65 patients (2.78% per year) with warfarin compared with 55 (2.32% per year) with dabigatran etexilate 110 mg BID (RR = 0.84 [95% CI, 0.58–1.20]) and 51 (2.07% per year) with dabigatran etexilate 150 mg BID (RR = 0.75 [95% CI, 0.52–1.08]). The rate of major bleeding was significantly lower in patients receiving dabigatran etexilate 110 mg (RR = 0.66 [95% CI, 0.48–0.90]) and similar in those receiving dabigatran etexilate 150 mg (RR = 1.01 [95% CI, 0.77–1.34]) compared with those receiving warfarin. The authors concluded that the benefits of dabigatran observed in this subgroup are similar to the whole RE-LY cohort.

Similarly, another subgroup analysis evaluated the effect of dabigatran in patients who were or were not previously warfarin naive.[49] For warfarin-naive and warfarin-experienced patients randomized to warfarin in the study, TTRs were 62% and 67%, respectively. In warfarin-naive patients, stroke and systemic embolism rates were 1.57%, 1.07%, and 1.69% per year for dabigatran etexilate 110 mg BID ($P = 0.65$ vs warfarin), dabigatran etexilate 150 mg BID ($P = 0.005$ vs warfarin), and warfarin, respectively. Major bleeding rates were 3.11%, 3.34%, and 3.57% per year (all similar to warfarin). In warfarin-experienced patients, stroke and systemic embolism rates were 1.51%, 1.15%, and 1.74% per year for dabigatran etexilate 110 mg BID ($P = 0.32$ vs warfarin), dabigatran etexilate 150 mg BID ($P = 0.007$ vs warfarin), and warfarin, respectively. Major bleeding rates were 2.66%, 3.30%, and 3.57% per year (dabigatran 110 mg BID group was lower than warfarin, $P = 0.003$). This subanalysis indicates that previous exposure to warfarin did not affect the effect of dabigatran.

Electrical Cardioversion

Cardioversion, whether electrically or pharmacologically, in patients with AF is associated with increased risk of thromboembolic events.[50] An optimal anticoagulation regimen can substantially reduce the risk.[51] Nagarakanti et al[52] performed a subanalysis on a group of patients in the RE-LY study who had undergone cardioversion. Data from before, during, and 30 days after cardioversion were analyzed. A total of 1983 cardioversions were performed in 1270 patients: 647, 672, and 664 in the dabigatran etexilate 110 mg BID, dabigatran etexilate 150 mg BID, and warfarin groups, respectively. Transesophageal echocardiography was performed before 25.5%, 24.1%, and 13.3% of cardioversions, respectively, of which 1.8%, 1.2%, and 1.1% were positive for left atrial thrombi. Continuous treatment with study drug for ≥3 weeks before cardioversion (as recommended by the American College of Chest Physician guidelines[17]) was lower in the dabigatran etexilate 110 mg BID group (76.4%) and the dabigatran etexilate 150 mg BID group (79.2%) compared with warfarin (85.5%) ($P < 0.01$ for both). Stroke and systemic embolism rates at 30 days were 0.8% for dabigatran etexilate 110 mg BID, 0.3% for dabigatran etexilate 150 mg BID, and 0.6% for war-

farin (dabigatran etexilate 110 mg vs warfarin, $P = 0.71$; dabigatran 150 mg vs warfarin, $P = 0.40$) and similar in patients with and without transesophageal echocardiography. Major bleeding rates were 1.7% for dabigatran etexilate 110 mg BID, 0.6% for dabigatran etexilate 150 mg BID, and 0.6% for warfarin (dabigatran etexilate 110 mg vs warfarin, $P = 0.06$; dabigatran etexilate 150 mg vs warfarin, $P = 0.99$). This study is the largest cardioversion experience with dabigatran reported to-date. The frequencies of stroke and major bleeding within 30 days of cardioversion with the 2 doses of dabigatran were low and comparable to those receiving warfarin with or without transesophageal echocardiography guidance. The investigators concluded that dabigatran can be a reasonable alternative to warfarin in patients requiring cardioversion.

Dosing, Handling, and Administration

Dabigatran etexilate is currently approved in Europe and Canada for the prevention of VTE, and in the United States and Canada for stroke prevention in patients with AF. The drug has not yet been officially approved for the treatment of VTE. The recommended dosage of dabigatran etexilate for prevention of VTE in patients after knee replacement surgery is 220 mg once daily. Treatment should be initiated within 1 to 4 hours of completed surgery, with 110 mg and continued with 220 mg once daily thereafter for a total of 10 days.[53] For the prevention of VTE in patients after elective hip replacement surgery, the recommended dosage of dabigatran etexilate is also 220 mg orally once daily. Similarly, treatment should be initiated orally within 1 to 4 hours of completed surgery with 110 mg and continued with 220 mg once daily thereafter but for a total of 28 to 35 days. For both types of surgery, if patients are not hemodynamically stable or if hemostasis cannot be achieved within the first day after surgery, then treatment with dabigatran etexilate should be delayed. If treatment is delayed beyond the first day of surgery, then the starting dose should be 220 mg orally once daily. For stroke prevention in AF, the dose of dabigatran etexilate is 150 mg BID.[28,54] Dabigatran is not currently approved for VTE treatment; however, based on the results of RE-COVER,[37] the treatment dose for VTE would be dabigatran 150 mg BID.

According to the European dabigatran etexilate prescribing information,[53] treatment with dabigatran etexilate in patients with CrCl <30 mL/min for VTE prophylaxis is contraindicated given there are no data to support its use in this population. In addition, for patients with CrCl of 30 to 50 mL/min, the recommended dose is 75 mg given 1 to 4 hours after surgery and 150 mg daily starting the next day. According to the US prescribing information (which pertains to AF management only),[28] the dose of dabigatran etexilate in patients with CrCl 15 to 30 mL/min should be 75 mg BID (not recommended for patients with CrCl <15 mL/min), and no dosage adjustment is necessary for CrCl of 30 to 50 mL/min. According to the European and Canadian dabigatran etexilate prescribing information,[53] in patients >75 years of age, the recommended dose for VTE prevention is similar to those with CrCl of 30 to 50 mL/min (ie, 75 mg given 1–4 hours after surgery, and 150 mg daily starting the next day). According to the Canadian prescribing information,[54] for prevention of thromboembolic events in AF, patients aged ≥80 years should be treated with dabigatran etexilate 110 mg BID. This dose for AF is not approved in the United States. In addition, in patients with increased risk of bleeding (including those with moderate renal impairment; using concomitant medications that inhibit P-glycoprotein; receiving aspirin, NSAIDs, or clopidogrel; have concurrent disease; or undergoing procedures with special hemorrhagic risk), the Canadian prescribing information also recommends a dose of 110 mg BID. Furthermore, according to the European and Canadian prescribing information, dabigatran etexilate is not recommended for patients with elevated liver enzymes >2 times the upper limit of normal.[53,54] No such specific recommendation is made in the US prescribing information.

Based on drug interaction data discussed previously, the use of dabigatran etexilate with a P-glycoprotein inducer such as rifampin should be avoided. Dosage adjustment is not required when dabigatran etexilate is used with the P-glycoprotein inhibitors verapamil, amiodarone, quinidine, and clarithromycin.[26,28] However, it is recommended that in patients with moderate renal impairment (CrCl, 30–50 mL/min), the dose of dabigatran should be reduced to 75 mg BID when administered concomitantly with the P-glycoprotein inhibitors ketoconazole and dronedarone.[28] In addition, the concomitant use of dabigatran and P-glycoprotein inhibitors in patients with severe renal impairment (CrCl, 15–30 mL/min) should be avoided.

In patients undergoing major orthopedic surgery, the use of dabigatran etexilate is not recommended in patients undergoing anesthesia with postoperative indwelling epidural catheters. Administration of the first dose of dabigatran etexilate should occur at least 2 hours after the catheter is removed.[28]

If patients are to be converted from warfarin to dabigatran etexilate (in the case of AF), the US prescribing information recommends discontinuation of warfarin and initiation of dabigatran etexilate when the INR is <2.[28] When converting from dabigatran etexilate to warfarin, the starting time of warfarin should be based on patients' CrCl. For patients whose CrCl is >50 mL/min, warfarin should be used for 3 days before discontinuing dabigatran etexilate. For those with CrCl 31 to 50 mL/min, warfarin should be used for 2 days before discontinuing dabigatran etexilate. For those with CrCl 15 to 30 mL/min, warfarin should be used for 1 day before discontinuing dabigatran etexilate. No recommendation is made for patients with CrCl <15 mL/min because dabigatran etexilate is contraindicated in this situation.[28]

When dabigatran was first approved for marketing, the manufacturer recommended that the product should be discarded 30 days after the bottle was opened.[55] However, further data indicate that the product maintains its potency beyond 30 days, and the latest prescribing information indicates that the product can be kept for 4 months once the bottle is opened.[28,55] Hopefully, this change in policy will help patients minimize wastage. Patients should be advice to not store dabigatran etexilate in any other containers, such as pull boxes or pill organizers. Pharmacists should always dispense dabigatran in the original bottle.

Adverse Effects

The most common adverse effects of dabigatran demonstrated in clinical studies include bleeding and gastrointestinal adverse reactions, which include dyspepsia and gastritis-like symptoms.[28] The incidence of major bleeding was reported earlier with individual clinical studies. Subanalysis of the RE-LY trial indicated that there was a significant treatment-by-age interaction in terms of bleeding. Dabigatran 110 mg BID compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% vs 3.04%; $P < 0.001$) and a similar risk in those aged ≥75 years (4.43% vs 4.37%; $P = 0.89$; P for interaction < 0.001), whereas dabigatran 150 mg BID compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% vs 3.04%; $P < 0.001$) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% vs 4.37%; $P = 0.07$; P for interaction <0.001). The interaction with age was evident for extracranial bleeding but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.[56]

Gastrointestinal adverse effects were uncommon in clinical trials evaluating DVT prophylaxis because the treatment duration was short (6–35 days). However, in the RE-LY trial, in which patients received dabigatran for an average of 2 years, the overall incidence of dyspepsia was 12.3% in patients receiving dabigatran etexilate110 mg BID, 12.7% in patients receiving dabigatran etexilate 150 mg BID, and 3.7% in patients receiving warfarin.[39]

Reversibility of Dabigatran

Currently, there is no antidote for DTIs, including dabigatran. In certain clinical situations, such as serious bleeding into critical organs, potential overdose, and emergency surgery, clinicians will need to make an assessment of the anticoagulant status of a patient receiving dabigatran before deciding on future management strategies. Measurement of TT or ECT are recommended to evaluate the anticoagulant effect of dabigatran.[57] Because it is more clinically accessible, aPTT can also provide useful qualitative assessment of anticoagulant activity, but it may be sensitive at supratherapeutic dabigatran serum concentrations.

In patients who require temporary discontinuation of dabigatran due to surgery, the manufacturer has recommended that in patients with CrCl >50 mL/min, dabigatran etexilate should be discontinued at least 24 hours before surgery; for those with CrCl between 30 to 50 mL/min, the drug should be discontinued at least 48 hours before surgery; and for those with CrCl <30 mL/min, the drug should be discontinued 2 to 5 days before surgery.[57]

In case of overdose, because dabigatran etexilate is a lipophilic molecule, adsorption by activated charcoal is expected and has been demonstrated in in vitro but not in in vivo study.[57] In the event of bleeding compli-

cations, management should be individualized, and treatment should be discontinued. Because dabigatran predominantly undergoes renal excretion, maintenance of adequate diuresis is essential. Mechanical compression, surgical hemostasis, and transfusion of blood products if needed should be done. In patients with normal renal function, plasma concentration levels should decline relatively rapidly after drug discontinuation (~12 hours).[57] If all of these measures fail to control bleeding, the use of hemodialysis to increase the rate of dabigatran elimination can be considered because dabigatran is 62% to 68% removed by hemodialysis. However, the clinical experience is limited.[58]

Use of activated prothrombin complex concentrates or recombinant factor VIIa or concentrates of coagulation factors II, IX, or X may be considered.[26] According to the briefing document submitted to the FDA, there is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran. A recent randomized, placebo-controlled, crossover study in 6 healthy subjects, who had received dabigatran 150 mg BID for 2.5 days, indicated that the administration of a single bolus dose of 50 IU/kg of prothrombin complex did not reverse dabigatran's effect on aPTT, ECT, or TT.[59] However, these were healthy individuals who were not bleeding. Results from future clinical studies are required to evaluate whether concentrates of coagulating factors will aid in bleeding control in patients receiving dabigatran.

Cost-Effectiveness

Dabigatran etexilate offers a new oral anticoagulant alternative to warfarin. With the significant economic burden of VTE and AF, pharmacoeconomic analysis may help determine if newer anticoagulants such as dabigatran etexilate promise more convenient, well-tolerated, and cost-effective alternatives in managing these disease states.

Wolowacz et al[60] evaluated the cost-effectiveness of oral dabigatran etexilate compared with subcutaneous enoxaparin for the prevention of VTE after total knee or hip replacement from the UK National Health Service's perspective. Dabigatran etexilate (220 mg orally once daily) was compared with enoxaparin (40 mg once daily) in patients undergoing total knee replacement (duration of prophylaxis, 6–10 days) and total hip replacement (duration of prophylaxis, 28–35 days). The 10-week postsurgical phase was modeled using a decision tree. Long-term outcomes (recurrent VTE, postthrombotic syndrome, and consequences of intracranial hemorrhage) were modeled using a Markov process (1-year cycle length) for patients' remaining lifetimes. The probabilities of long-term events were estimated using data from published longitudinal studies. Rates of VTE and bleeding events did not differ significantly between dabigatran etexilate and enoxaparin. The cost of prophylaxis for patients undergoing total hip replacement, including drugs and administration costs, was estimated at £137 for dabigatran etexilate and £237 for enoxaparin for the duration of treatment. At a willingness-to-pay threshold of £20,000 per quality-adjusted life-year (QALY), the probability of cost-effectiveness for dabigatran etexilate was 75% in total knee replacement and 97% in total hip replacement. These results were robust across a range of sensitivity analyses. The authors concluded that from the perspective of the UK National Health Service, thromboprophylaxis with dabigatran etexilate was cost-saving compared with enoxaparin 40 mg once daily, with comparable efficacy and safety profile.

The same group of investigators (Wolowacz et al[58]) performed another similar pharmacoeconomic analysis of oral dabigatran etexilate 150 mg once daily, specifically in patients aged >75 years from a UK National Health Service perspective. Dabigatran etexilate was compared with enoxaparin 40 mg SC daily, using a decision model. Dabigatran etexilate was demonstrated to be less costly than enoxaparin; cost savings varied from £62 to £274 and were primarily due to differences in administration costs. Results were robust across a range of sensitivity analyses.

McCullagh et al[61] evaluated the cost-effectiveness of rivaroxaban (an oral anti–factor Xa inhibitor) and dabigatran etexilate compared with enoxaparin for the prophylaxis of VTE in patients undergoing elective total hip or knee replacement from an Irish health payers' perspective. A decision-tree model was developed with a 180-day postsurgery time horizon. Costs were valued in euros/year 2008 values. A probabilistic sensitivity analysis using second-order Monte Carlo simulation was performed to determine the probability of cost-effectiveness at €45,000 per QALY threshold. In the total hip replacement model, rivaroxaban dominated both dabigatran etexilate and enoxaparin sodium. The incremental cost-effectiveness ratios for dabigatran etexilate relative to enoxaparin were €23,934 per life-year gained and €17,835 per QALY. In the total knee

replacement base-case model, rivaroxaban dominated both dabigatran etexilate and enoxaparin sodium. Dabigatran etexilate also dominated enoxaparin sodium. At a cost-effectiveness threshold of €45,000 per QALY, the probability that rivaroxaban was the most cost-effective strategy after total hip replacement was 39%, followed by dabigatran etexilate at 32%, and enoxaparin sodium at 29%. The probability that rivaroxaban was the most cost-effective strategy after total knee replacement was 46%, followed by dabigatran etexilate at 30%, and enoxaparin sodium at 24%. This cost-effectiveness analysis demonstrates that when both rivaroxaban and dabigatran etexilate are compared with enoxaparin, rivaroxaban is the less costly and more effective option after total hip or knee replacement. Probabilistic sensitivity analysis indicates that rivaroxaban is the most cost-effective strategy at a cost-effectiveness threshold of €45,000 per QALY.

Freeman et al[62] used the RE-LY study database to estimate the quality-adjusted survival, costs, and cost-effectiveness of dabigatran compared with warfarin for preventing thromboembolic stroke in patients aged ≥65 years with nonvalvular AF based on the US societal perspective. A Markov model was used to perform a decision analysis comparing the 3 treatment strategies (dabigatran etexilate 150 mg BID vs dabigatran etexilate 110 mg BID vs warfarin). Total annual costs (expressed in 2008 US dollars) were $143,193 for warfarin, $164,576 for low-dose dabigatran, and $168,398 for high-dose dabigatran. The incremental cost-effectiveness ratios compared with warfarin were $51,229 per QALY for dabigatran etexilate 110 mg BID and $45,372 per QALY for dabigatran etexilate 150 mg BID. The model was sensitive to the cost of dabigatran. The incremental cost-effectiveness ratio increased to $50,000 per QALY at a cost of $13.70 per day for dabigatran 150 mg BID but remained <$85,000 per QALY over the full range of model inputs evaluated. The investigators concluded that dabigatran may be a cost-effective alternative to warfarin depending on its pricing. Dabigatran etexilate's average wholesale price of the 150-mg capsule in the United States is $3.83.[63]

Sorensen et al[63] performed a cost-effectiveness analysis on the RE-LY database from the Canadian payer perspective. A Markov model simulated AF patients at moderate to high risk of stroke, tracking their clinical events (primary and recurrent ischemic strokes, systemic embolism, TIA, hemorrhage [intracranial, extracranial, and minor], acute myocardial infarction, and death) and resulting functional disability. Acute event costs and resulting long-term follow-up costs incurred by disabled stroke survivors were based on a Canadian prospective study, other published literature, and national statistics. Over a lifetime, dabigatran etexilate–treated patients experienced fewer intracranial hemorrhages (0.49 dabigatran etexilate vs 1.13 warfarin vs 1.05 "real-world" prescribing) and fewer ischemic strokes (4.40 dabigatran etexilate vs 4.66 warfarin vs 5.16 real-world prescribing) per 100 patient-years. The incremental cost-effectiveness of dabigatran etexilate was $10,440/QALY versus warfarin and $3962/QALY versus real-world prescribing. This study demonstrates that dabigatran etexilate is a highly cost-effective alternative to current care for the prevention of stroke and systemic embolism among AF patients from a Canadian societal perspective.

Overall, dabigatran etexilate's cost-effectiveness depends on the structure of payment of the different health care systems as well as on the cost of the drug itself.

DISCUSSION

Before dabigatran, warfarin was the only available oral anticoagulant for many years. Dabigatran seems to offer benefits over warfarin in terms of having less interpatient variability in dose response, not requiring routine anticoagulation monitoring, fewer drug–food and drug–drug interactions, and offering a faster dose titration process in patients with normal renal function. Completed trials offer insight into the efficacy and safety profile of dabigatran etexilate for VTE prophylaxis in high-risk patients undergoing total knee or hip replacement, and treatment for patients who developed DVT and PE, as well as stroke prevention in patients with AF. For VTE prophylaxis, dabigatran etexilate has demonstrated either superiority or noninferiority to enoxaparin in most studies.[31–34] However, the RE-MOBILIZE study failed to demonstrate noninferiority to enoxaparin when a BID enoxaparin dosing regimen was used.[36] The 2 noninferiority studies have different noninferiority margins (RE-NOVATE, 7.7%; RE-MODEL, 9.2%).[33,34] This finding may introduce disparity when analyzing the results. Both of these studies also have a relatively low occurrence of primary events compared with historical studies of VTE prophylaxis in this patient population, which may also have made it more difficult to see a difference between

groups. The dosage and timing of initiation of enoxaparin in the RE-MODEL trial are also an issue.[34] Enoxaparin 40 mg once daily was not an FDA-approved regimen in the United States for knee replacement surgery. This regimen may have reduced the efficacy of enoxaparin and also the frequency of bleeding events. Additional data comparing dabigatran etexilate with the recommended dose of enoxaparin 30 mg BID in patients undergoing total knee replacement surgery are needed.

The generalizability of the completed trials to clinical practices must also be addressed. All of the VTE prophylaxis trials used enoxaparin as the comparator. Fondaparinux is another anticoagulant that is indicated for VTE prophylaxis in patients undergoing total hip or knee replacement surgery. In a previous clinical trial, fondaparinux demonstrated a 55.2 % RR reduction ($P < 0.001$) in VTE in patients undergoing total hip and knee replacement compared with enoxaparin.[64] Therefore, additional data comparing dabigatran etexilate with fondaparinux are warranted to more clearly define the role of this medication in these patient populations.

In terms of AF, the RE-LY trial demonstrated that dabigatran etexilate 150 mg BID is superior to warfarin in prevention of thromboembolic events.[39] The benefits seemed to be applicable to a wide variety of patient subgroups.[46,48,49] The dosage of dabigatran etexilate approved for use in the United States is 150 mg BID, with a dosage of 75 mg BID recommended for patients with renal dysfunction (CrCl, 10–30 mL/min).[28] However, in Canada, a dose of 150 mg BID was recommended for most patients, and 110 mg BID was recommended for those with renal impairment, age >80 years, and increased risk of bleeding.[54] The 110-mg dose is not available in the United States. The disparity in dosing recommendations in certain patient populations does raise the concern regarding the use of dabigatran etexilate in these patients who are at higher risk of bleeding, especially given that routine laboratory therapeutic monitoring will not be available or used.

Finally, when considering clinical application of new agents, pharmacoeconomics must be addressed. Pharmacoeconomic analyses performed in the United Kingdom and Ireland found that dabigatran etexilate can be cost-saving compared with enoxaparin in VTE prevention.[58–60] Pharmacoeconomic analysis performed in Canada also found that dabigatran is highly cost-effective when used for AF.[63] This finding actually led to the latest Canadian AF management guidelines recommending dabigatran etexilate over warfarin in most patients.[18] Dabigatran etexilate's average wholesale price of the 150-mg capsule in the United States is $3.83 (compared with warfarin at a cost of ~$0.40 daily).[65]

Due to past experience with ximelagatran, additional postmarketing monitoring is needed for incidence of liver dysfunction and ACS.[66] Future studies of dabigatran will likely continue to explore other indications in which it may serve as an alternative to warfarin.

CONCLUSIONS

Dabigatran etexilate is an oral DTI that has exhibited a comparable efficacy and safety profile with enoxaparin for VTE prophylaxis in patients undergoing total hip or knee replacement, and comparable efficacy and safety profile with warfarin for VTE treatment, as well as superiority (150 mg BID) and noninferiority (110 mg BID) in the prevention of stroke and systemic embolism compared with warfarin in patients with nonvalvular AF. Dabigatran etexilate's ease of oral administration, lack of routine coagulation monitoring, and lack of significant drug/food interactions, along with its rapid onset and offset of action in most patients, may favor use of dabigatran etexilate over warfarin and other parenteral anticoagulant agents. Additional data from ongoing long-term studies evaluating treatment of VTE and other indications are needed to confirm its efficacy and long-term adverse effects, especially as they relate to liver dysfunction and development of ACS events.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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