New Drugs and Technologies

Dabigatran Etexilate
A New Oral Thrombin Inhibitor

Graeme J. Hankey, MD, FRACP, FRCP; John W. Eikelboom, MBBS, FRACP, FRCPA

Long-term oral anticoagulation is indicated for several cardiovascular diseases, including the prevention of cardiac thromboembolism in patients with atrial fibrillation (AF), mechanical heart valves, and acute myocardial infarction (MI), as well as the secondary prevention of venous thromboembolism (VTE).

For the past 60 years, oral vitamin K antagonists (eg, warfarin, acenocoumarol, phenprocoumon, fluindione) have been widely prescribed. However, their impact in preventing thromboembolism has been hampered by several limitations that compromise their effectiveness and safety and make them difficult to use (Table 1). Vitamin K antagonists have a delayed onset and offset of action that often prolong hospitalization, and thus increase healthcare costs. Their large interindividual variability in dose response and narrow therapeutic window demand regular monitoring of the international normalized ratio (INR) and result in complex individualized dosing. Despite careful dose adjustment, the INR is frequently outside the target therapeutic range, which increases the risk of thromboembolism and bleeding. Patients treated with a vitamin K antagonist require counseling about drug and food interactions, the need for routine monitoring, and the inherent risk of bleeding. To reduce some of the dose variability, an algorithm based on clinical and genetic data has been developed and validated for estimating the appropriate dose of warfarin, but evidence of the cost-effectiveness of pharmacogenetic testing to optimize warfarin dosing in routine clinical practice is lacking.

As a consequence of the limitations of vitamin K antagonists, the quality of anticoagulant control is frequently suboptimal among those who receive the treatment, and many patients at risk of thromboembolism do not receive treatment; only 50% to 70% of patients with AF at risk of stroke who are eligible for anticoagulant therapy are treated with a vitamin K antagonist.

This very large unmet need has prompted the development and evaluation of new oral anticoagulants that target the inhibition of specific coagulation factors, most commonly activated factor X (Xa) and thrombin (Figure 1). This first evidence supporting thrombin as a suitable target for new oral anticoagulants came from studies with the oral direct thrombin inhibitor ximelagatran. Ximelagatran underwent extensive evaluation in phase III randomized, controlled trials for the prevention and treatment of VTE, stroke prevention in patients with AF, and treatment of MI. For all of these indications, fixed-dose, unmonitored ximelagatran was noninferior to conventional anticoagulant therapy or superior to placebo in the prevention of thromboembolic events, but its further development was precluded by unacceptable liver toxicity.

Pharmacology of Dabigatran

Mechanism of Action
Dabigatran etexilate is a low-molecular-weight prodrug that exhibits no pharmacological activity. After oral administration, dabigatran etexilate is converted to its active form, dabigatran, a potent, competitive, and reversible direct inhibitor of the active site of thrombin, the final effector in blood coagulation (Figure 1).

Thrombin has an active site and 2 secondary binding 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. Dabigatran is a univalent direct thrombin inhibitor that binds to the active site, thereby inactivating both fibrin-bound and unbound (ie, free) thrombin. Indirect thrombin inhibitors such as unfractionated heparin and low-molecular-weight heparin cannot inhibit fibrin-bound thrombin. The ability to inhibit fibrin-bound thrombin is an important theoretical advantage of dabigatran over the heparins because bound thrombin can continue to trigger thrombus expansion. By inhibiting thrombin, dabigatran prevents the conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation, and inhibition of fibrinolysis (Figure 1).

Formulation
Dabigatran etexilate is available in capsule form. It is formulated together with tartaric acid to reduce the variability of dabigatran etexilate absorption, which is dependent on an acid environment. A dabigatran etexilate coating is applied onto a tartaric acid core to form tiny pellets (∼1-mm diameter). A single capsule contains hundreds of these pellets, the exact number depending on the dose strength of the capsule. In this way, dabigatran etexilate absorption is
independent of gastrointestinal tract acidity and is not materially affected by coadministration of a proton pump inhibitor.\textsuperscript{23}

Absorption
After oral administration, dabigatran etexilate is rapidly absorbed and quickly and completely hydrolyzed to its active moiety, dabigatran, by nonspecific ubiquitous esterases in the gut, plasma, and liver.\textsuperscript{24,25} Because bioconversion of dabigatran etexilate begins in the gut, the drug enters the portal vein as a combination of prodrug and active compound. The absolute bioavailability after oral administration of dabigatran etexilate is only $\approx 6.5\%$, so relatively high doses must be given to ensure that adequate plasma concentrations are achieved.\textsuperscript{24,26}

Dabigatran plasma concentrations and anticoagulant effects are dose dependent and predictable, and peak within 0.5 to 2 hours (average, 1.5 hours) of oral administration.\textsuperscript{23–25} Steady-state dabigatran concentrations are achieved $\approx 3$ days after multiple-dose administration in healthy volunteers.\textsuperscript{24} At steady state, plasma concentrations in patients with AF taking 150 mg twice daily (BID) are $\approx 180$ ng/mL at peak and 90 ng/mL at trough (11.5 hours after ingestion).\textsuperscript{19} There is no unexpected accumulation of dabigatran after multiple dosing.

Metabolism
Bioconversion of dabigatran etexilate to dabigatran is completed in the liver, and $\approx 20\%$ is conjugated with glucuronic acid (to acyl glucuronides) and excreted via the biliary system.\textsuperscript{27} Dabigatran etexilate is not metabolized by the cytochrome P450 enzymes or other oxidoreductases, but is a substrate for p-glycoprotein (see below).

In patients with mild hepatic impairment, the area under the curve after a single oral dose of dabigatran etexilate was comparable to that in healthy control subjects, and the bioconversion of the prodrug was only slightly reduced.\textsuperscript{24,28}

Half-Life
The mean terminal half-life of dabigatran after oral administration is $\approx 8$ hours after a single dose, and ranges from 12 to 14 hours after multiple doses (Table 2).\textsuperscript{23–25,29–31} In older healthy volunteers, more typical of the patient population for which dabigatran may be indicated, the half-life is about 13 hours.\textsuperscript{23,32} The half-life is increased to $\approx 24$ hours in patients with a creatinine clearance of $<30$ mL/min.\textsuperscript{32}

Excretion
Renal excretion is the dominant elimination pathway. Up to 80% of circulating unchanged dabigatran and small amounts

Table 1. Limitations of Warfarin and Other Oral Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset and offset of action</td>
<td>Need for bridging with a rapidly acting anticoagulant</td>
</tr>
<tr>
<td>Interindividual variability in anticoagulant effect</td>
<td>Variability in dosing requirements</td>
</tr>
<tr>
<td>Narrow therapeutic index</td>
<td>Need for routine coagulation monitoring</td>
</tr>
<tr>
<td>Food and drug interactions</td>
<td>Dietary precautions; need for routine coagulation monitoring</td>
</tr>
<tr>
<td>Reduced synthesis of all vitamin K–dependent proteins</td>
<td>Risk of skin necrosis in patients with protein C or S deficiency; potential for osteoporosis*</td>
</tr>
</tbody>
</table>

*Vitamin K antagonists appears to inhibit production of vitamin K–dependent proteins found in bone (osteocalcin synthesized by osteoblasts, matrix Gla protein found in bone cartilage and soft tissue, and protein S synthesized by osteoblasts).

Dabigatran etexilate

<table>
<thead>
<tr>
<th>Steps in coagulation</th>
<th>Coagulation pathway</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>TF/VIIa</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edoxaban</td>
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<td></td>
<td></td>
<td>YM150</td>
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<tr>
<td></td>
<td></td>
<td>Betrixaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAK-442</td>
</tr>
<tr>
<td>Propagation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VIIIa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IXa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Va</td>
<td></td>
</tr>
<tr>
<td>Fibrin formation</td>
<td>II</td>
<td>Dabigatran etexilate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZD0837</td>
</tr>
</tbody>
</table>

Figure 1. Illustration showing the sites of action of new anticoagulants in the coagulation cascade. Vessel injury exposes tissue factor (TF), which interacts with activated coagulant (F) VII to initiate coagulation. Cleavage of prothrombin (factor II) by the prothrombinase complex (factor Xa and its cofactor, factor Va) leads to the generation of thrombin (factor IIa). Thrombin converts fibrinogen to fibrin and provides positive feedback through activation of factors V, VIII, and XI in the coagulation cascade. Factors Va, VIIIa, and Xa promote the production of additional thrombin, which leads to cross-linkage of fibrin strands and the formation of a hemostatic plug. Thrombin also activates platelets through cleavage of the platelet membrane–bound protease-activated receptors 1, 3, and 4. Factor Xa inhibitors block the conversion of prothrombin (factor II) to thrombin (factor IIa) by factor Xa incorporated within the prothrombinase complex (the complex of factor Xa and factor Va bound to the activated platelet surface). Thrombin inhibitors block thrombin-mediated conversion of fibrin. These drugs also block thrombin-mediated feedback activation of factors V and VIII. Modified from Eriksson et al.\textsuperscript{13}
of dabigatran glucuronides are excreted via the kidneys. Consequently, reduced kidney function results in elevated dabigatran plasma concentrations and a prolonged drug half-life. For patients taking dabigatran who have or are at risk of developing renal impairment, it would seem prudent to monitor renal function every 6 to 12 months during long-term therapy.

**Interactions**

Dabigatran etexilate (not dabigatran) is a substrate of the efflux permeability glycoprotein transporter, which is highly expressed in the intestine and kidneys and transports various molecules across extracellular and intracellular membranes. Coadministration of potent permeability glycoprotein inhibitors such as quinidine, ketoconazole, amiodarone, and verapamil can increase plasma concentrations of dabigatran by decreasing its reabsorption via permeability glycoprotein into the gastrointestinal tract. Potent inducers such as rifampicin can reduce plasma concentrations of dabigatran by increasing its reabsorption via permeability glycoprotein into the gut.

The extent of the rise in dabigatran concentration with coadministration of verapamil depends on the formulation and timing of administration of verapamil. If verapamil is present in the gut when dabigatran is taken, it will increase exposure to dabigatran. The greatest increase in dabigatran concentrations is observed when a single dose of immediate-release verapamil is given 1 hour before dabigatran (area under the curve is increased by a factor of 2.4) without significantly affecting the blood concentrations of verapamil. If verapamil is given 2 hours after dabigatran, the increase in the area under the curve is negligible. Quinidine, ketoconazole, and rifampicin are contraindicated in patients receiving dabigatran etexilate after orthopedic surgery.

Coadministration of dabigatran etexilate with other anticoagulants, and antiplatelet agents should be approached with caution because of an increased risk of bleeding. Coadministration of a proton pump inhibitor such as pantoprazole slightly reduces the mean area under the curve and peak concentration of dabigatran, but does not materially affect efficacy and safety. Dabigatran etexilate is not known to interact with any other drugs, and its absorption is not affected by food. Administration of dabigatran with atorvastatin 80 mg/d (CYP3A4), diclofenac 50 mg/d (CYP2C9), or digoxin 0.25 mg/d (p-glycoprotein) was safe and well tolerated without affecting routine coagulation assays.

**Anticoagulant Effect**

Dabigatran prolongs the activated partial thromboplastin time (aPTT), which targets the intrinsic pathway of coagulation;
the thrombin clotting time (TT), which directly assesses the activity of thrombin in a plasma sample; and the ecarin clotting time, which is a specific assay for thrombin generation.34,35 However, at clinically relevant plasma concentrations, dabigatran has relatively little effect on the prothrombin time and INR, which targets the extrinsic coagulation pathway. The TT assay is the most sensitive to prolongation by dabigatran, followed by the ecarin clotting time and aPTT.34,35

The relationship between plasma concentrations of dabigatran and the TT, ecarin clotting time, and INR is linear (ie, dabigatran prolongs the TT, ecarin clotting time, and INR in a concentration-dependent fashion over therapeutic concentrations), whereas the aPTT concentration-response curve is curvilinear and flattens at higher concentrations (>200 ng/mL).34,35 A dilute thrombin time assay (Hemoclot test, Hyphen Biomed, France) has been certified in Europe since late 2010 for the quantitative determination of dabigatran plasma levels. It can be calibrated with dabigatran standards.

Prolongation of blood coagulation times is maximal at peak plasma concentrations of dabigatran (~2 hours). The effect declines to ~50% of the peak inhibition at 12 hours after administration, reflecting the half-life of the drug.35–37

Reversing the Anticoagulant Effect of Dabigatran

Patients Undergoing Invasive Procedures

Dabigatran etexilate should ideally be discontinued at least 24 hours before invasive procedures and at least 48 hours before procedures associated with a high risk of bleeding. The duration of discontinuation of dabigatran before procedures also depends on renal function. Table 3 provides guidance for discontinuation of dabigatran etexilate before elective invasive procedures according to renal function and risk of bleeding.34

Renal function should be assessed by measurement of the serum creatinine (so that creatinine clearance can be calculated) at least 5 days before the procedure. In patients with normal renal function, discontinuation of dabigatran 24 hours before surgery will decrease plasma levels to ~25% of steady-state trough levels. Plasma levels fall to ~12% to 15% of trough levels after 36 hours and ~5% to 10% after 48 hours.34 In patients with severe renal impairment (creatinine clearance <30 mL/min), dabigatran should be permanently discontinued (unless renal function improves) and surgery delayed for at least 5 days, if at all possible. After the procedure and recovery of renal function, dabigatran can be reinitiated as soon as clinically indicated. If oral medication is not feasible, parenteral heparinization should be considered if an immediate anticoagulant effect is required.

In patients at high risk of bleeding or undergoing major surgery in which normal hemostasis is required, dabigatran etexilate should be stopped 2 to 5 days before surgery (Table 3).34 A TT should be performed 6 to 12 hours before surgery and a normal result obtained; if the TT test is not available, the aPTT, although less precise, can be used. If the TT is elevated, consideration should be given to delaying surgery because, in the absence of heparin, other direct thrombin inhibitors (eg, lepirudin and bivalirudin), fibrin/fibrinogen degradation products, or high concentrations of serum pro-

<table>
<thead>
<tr>
<th>Renal Function (Creatinine Clearance), mL/min</th>
<th>Half-Life, h</th>
<th>Timing of Discontinuation After Last Dose of Dabigatran Before Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>High Risk</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>24 h</td>
<td>2–4 d</td>
</tr>
<tr>
<td>&gt;50~&lt;80</td>
<td>24 h</td>
<td>2–4 d</td>
</tr>
<tr>
<td>&gt;30~&lt;50</td>
<td>2 d (48 h)</td>
<td>4 d</td>
</tr>
<tr>
<td>≤30</td>
<td>2 d (48 h)</td>
<td>&gt;5 d</td>
</tr>
</tbody>
</table>

*Data are from renal impairment study in healthy volunteers.32 geometric mean (range).
†Types of surgery associated with a high risk of bleeding (or major surgery in which complete hemostasis may be required) include but are not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgery involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, comorbidities (eg, major cardiac, respiratory, or liver disease), and concomitant use of antplatelet therapy.

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teins (eg, myeloma), prolongation of the TT indicates the presence of dabigatran in the blood. The serum creatinine should also be checked in patients who have unexpectedly prolonged TT values because the clearance of dabigatran is delayed in patients with renal impairment.

Patients With Bleeding While Taking Dabigatran

Unlike warfarin and heparin, no specific antidote is available to reverse the anticoagulant effects of dabigatran.17,19 The management of bleeding complications in patients receiving dabigatran etexilate should be individualized according to the location and severity of the hemorrhage (Figure 2).34 First, dabigatran etexilate should be discontinued. Discontinuation of the drug may suffice in patients with normal renal function who have mild bleeding. Second, the source of bleeding should be investigated, if possible, mechanically compressed, and, if necessary, controlled surgically. Third, an adequate diuresis must be maintained because dabigatran predominantly undergoes renal excretion. Fourth, transfusion of blood products (packed red cells or fresh-frozen plasma) may be required, depending on associated anemia or coagulopathy. Fresh-frozen plasma does not reverse the anticoagulant effect of dabigatran. If the above measures fail to control bleeding, the use of hemodialysis or administration of nonspecific prohemostatic agents may be considered.

Dabigatran is dialyzable because of its relatively low (~35%) plasma protein binding.34,37 In cases of severe bleeding or overdose (see below), when rapid reversal of the anticoagulant effects of dabigatran is required, hemodialysis could be effective in accelerating plasma clearance of dabigatran, especially in patients with renal impairment. The supporting data come from an open-label study in which a single 50-mg dose of dabigatran etexilate was administered to 6 patients with end-stage renal failure on maintenance hemo-
Recombinant activated factor VII (rFVIIa; NovoSeven, NovoNordisk, Bagsvaerd, Denmark) is an approved potent procoagulant and general hemostatic agent that can initiate hemostasis at sites of bleeding by directly activating thrombin on the surface of platelets in the absence of tissue factor. Healthy volunteer and ex vivo data suggest that rFVIIa antagonizes the anticoagulant effect of a variety of anticoagulants. In a rat tail model of template bleeding, addition of rFVIIa (0.1 or 0.5 mg/kg) significantly reduced bleeding time and prolongation of aPTT associated with high-dose dabigatran in a dose-dependent manner. rFVIIa at 0.5 mg/kg reduced bleeding time from 11.6-fold (ratio to control) to 1.1-fold and aPTT prolongation by dabigatran from 8.3-fold to 3.8-fold. However, the clinical utility of rFVIIa in patients taking dabigatran who are actively bleeding has not been established.

Prothrombin complex concentrates (PCCs) comprise activated PCCs (APCC) and nonactivated PCCs. Nonactivated PCCs are “4-factor concentrates” containing adequate amounts of vitamin K–dependent factors II, VII, IX, and X (eg, Beriplex, Octaplex, and ProplexT) or “3-factor concentrates” containing significantly lower amounts of factor VII (less than one third of factor IX) (eg, Prothrombinex-HT, Profilnine, and Bebulin). Activated PCCs such as Factor Eight Inhibitor Bypassing Activity, Vapor Heated (Feiba VH; Baxter, Vienna, Austria) contain vitamin K–dependent coagulation factors II, IX, and X and protein C, mainly in nonactivated forms, and factor VII, mainly in the activated form. In a rat tail model of template bleeding, addition of APCC (Feiba VH) at a dose of 50 or 100 U/kg significantly reduced prolongation of bleeding time effects associated with high-dose dabigatran. Activated PCCs at 100 U/kg reduced bleeding time prolongation by dabigatran from 11.6-fold (ratio to control) to 1.4-fold. The aPTT was not shortened in the presence of APCC. However, APCC preparations have also been reported to have thrombogenic potential, so the potential benefits need to be evaluated in the context of the potential risks. Findings similar to those reported with Feiba VH have been shown with nonactivated PCC BeriplexP/N (CSL Behring, Marburg, Germany); in a renal injury bleeding model in rabbits, bleeding with high-dose dabigatran was reduced after administration of Beriplex (data on file), although no effects on anticoagulation parameters of aPTT or TT were seen. Further in vitro studies using human plasma show complete reversal of the dabigatran-inhibited endogenous thrombin potential with APCC (Feiba VH) but not with rFVIIa (NovoSeven). Thus, the predictive value of ex vivo monitoring of neutralization of dabigatran anticoagulant activity for reversing bleeding is not yet well understood.

Other prohemostatic agents that might be considered if bleeding cannot be controlled include desmopressin, aprotinin, tranexamic acid, and aminocaproic acid. However, there is no evidence that any of these agents will reverse the anticoagulant effect of dabigatran.

**Patients With an Overdose of Dabigatran**

Dabigatran etexilate is a lipophilic molecule (log \( P = 3.8 \)) that has been shown in vitro to be successfully adsorbed by classic activated charcoal therapy. Although this has not been tested in vivo or in patients, it seems reasonable to administer charcoal within 1 to 2 hours of overdose before dabigatran etexilate is absorbed from the gastrointestinal tract. It is possible that dabigatran could be removed from plasma via hemoperfusion or a charcoal filter, but this has not been evaluated in humans.

**Long-Term Hepatic Safety**

No liver toxicity or significant excess elevation in liver enzymes has been recorded to date during extensive liver function monitoring in \( \approx 40,000 \) patients enrolled in clinical trials of dabigatran. A possible reason why the direct thrombin inhibitor ximelagatran may be hepatotoxic is that the oxidoreductases that cleave the hydroxyl-amidine group of the prodrug and convert it to melagatran, the active drug, are present mostly in the liver, which results in short-lived but measurable plasma concentrations of ximelagatran (\( \approx 0.3-\))
μmol/L peaks). One study has demonstrated that ximelagatran in concentrations of 10 μmol/L increases membrane fluidity by changing membrane lipid composition in human hepatocytes in vitro, whereas melagatran does not. In contrast, esterases that convert dabigatran etexilate to its active form are located throughout the body, including plasma and the liver. Consequently, dabigatran etexilate is almost immediately converted to the active dabigatran, so levels of the prodrug in the plasma are only just above levels of detection, even at peak, and are not detectable after 2 hours.

### Potential Advantages of Dabigatran

The potential advantages and disadvantages of dabigatran compared with warfarin and other vitamin K antagonists are shown in Tables 4 and 5.

### Prevention of VTE

#### Evidence

After the phase II Boehringer Ingelheim Study in Thrombosis (BISTRO) trials showed that dabigatran etexilate was effective for the prevention of VTE, 2 doses of dabigatran etexilate were evaluated in phase III trials for venous thromboprophylaxis after hip or knee arthroplasty: 150 or 220 mg once daily started postoperatively with a half-dose of 75 or 110 mg on the day of surgery (Table 6).

The Dabigatran Etexilate 150 mg or 220 mg Once Daily Versus Enoxaparin 40 mg Once Daily for Prevention of Thrombosis After Knee Surgery (RE-MODEL) trial and the Dabigatran Etexilate Compared With Enoxaparin in Prevention of VTE Following Total Hip Arthroplasty (RE-NOVATE I and II) trials compared dabigatran etexilate with enoxaparin given at the European approved dose of 40 mg once daily, starting the evening before surgery. The Dabigatran Etexilate Versus Enoxaparin in Prevention of VTE Post Total Knee Replacement (RE-MOBILIZE) trial compared dabigatran with enoxaparin given at the North American approved dose of 30 mg twice daily, starting 12 to 24 hours after surgery (Table 6).

#### Table 4. Advantages of Dabigatran Compared With Warfarin and Other Oral Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>No need for bridging</td>
</tr>
<tr>
<td>Predictable anticoagulant effect</td>
<td>No need for routine coagulation monitoring</td>
</tr>
<tr>
<td>Specific coagulation enzyme</td>
<td>Low risk of off-target adverse effects</td>
</tr>
<tr>
<td>Target</td>
<td></td>
</tr>
<tr>
<td>Low potential for food interactions</td>
<td>No dietary precautions</td>
</tr>
<tr>
<td>Low potential for drug interactions</td>
<td>Few drug restrictions</td>
</tr>
</tbody>
</table>

#### Table 5. Disadvantages of Dabigatran Compared With Warfarin and Other Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiarity</td>
<td>Extensive</td>
<td>Minimal</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Well established (INR)</td>
<td>Uncertain (TT, ECT, aPTT)</td>
</tr>
<tr>
<td>Clearance</td>
<td>Nonrenal</td>
<td>Renal 80%</td>
</tr>
<tr>
<td>Reversal</td>
<td>Vitamin K, FFP, PCC</td>
<td>Nil</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; TT, thrombin time; ECT, ecarin clotting time; aPTT, activated partial thromboplastin time; FFP, fresh-frozen plasma; and PCC, prothrombin complex concentrate.

#### Approval Status

Dabigatran etexilate is licensed in >75 countries worldwide for the prevention of VTE after elective hip or knee arthro-
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>No.</th>
<th>Intervention</th>
<th>Duration of Treatment</th>
<th>Primary Outcome, % or %/y (n/N)</th>
<th>Rate Ratio (95% CI)</th>
<th>Absolute Risk Difference (95% CI), %</th>
<th>Major Bleed, % or %/y (n/N)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevention of VTE</strong></td>
<td></td>
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</tr>
<tr>
<td>RE-MODEL41</td>
<td>TKA</td>
<td>2101</td>
<td>Enoxaparin SC 40 mg OD</td>
<td>6–10 d</td>
<td>37.7% (193/512)</td>
<td>1.3% (9/694)</td>
<td>1.3 (7.3–4.6)</td>
<td>1.5% (10/679)</td>
<td>1.14 (0.46–2.78)</td>
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<tr>
<td></td>
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<td>Dabigatran 220 mg OD</td>
<td></td>
<td>36.4% (183/503)</td>
<td>0.97 (0.82–1.13)</td>
<td>−1.3 (−7.3–4.6)</td>
<td>1.3% (9/703)</td>
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<td>Dabigatran 150 mg OD</td>
<td></td>
<td>40.5% (213/526)</td>
<td>2.6 (−3.1–8.7)</td>
<td>1.3% (9/703)</td>
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<tr>
<td>RE-NOVATE42</td>
<td>THA</td>
<td>3494</td>
<td>Enoxaparin SC 40 mg OD</td>
<td>28–35 d</td>
<td>6.7% (60/897)</td>
<td>1.6% (18/1154)</td>
<td>0.7 (2.9–1.6)</td>
<td>2.0% (23/1146)</td>
<td>1.29 (0.70–2.37)</td>
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<td></td>
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<td>Dabigatran 220 mg OD</td>
<td></td>
<td>6.0% (53/880)</td>
<td>0.90 (0.63–1.29)</td>
<td>−0.7 (−2.9–1.6)</td>
<td>2.0% (23/1146)</td>
<td>1.29 (0.70–2.37)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Dabigatran 150 mg OD</td>
<td></td>
<td>8.6% (75/874)</td>
<td>1.9 (−0.6–4.4)</td>
<td>1.3% (15/1163)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-MOBILIZE43</td>
<td>TKA</td>
<td>2615</td>
<td>Enoxaparin SC 30 mg BID</td>
<td>12–15 d</td>
<td>25.3% (163/643)</td>
<td>1.4% (12/868)</td>
<td>1.1 (3.8 to 1.6)</td>
<td>1.4% (14/1010)</td>
<td>1.54 (0.67–3.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 220 mg OD</td>
<td></td>
<td>31.1% (188/604)</td>
<td>1.23 (1.03–1.47)</td>
<td>5.8 (0.8–10.8)</td>
<td>0.6% (5/857)</td>
<td>0.42 (0.15–1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 150 mg OD</td>
<td></td>
<td>33.7% (219/649)</td>
<td>8.4 (3.4–13.3)</td>
<td>0.6% (5/871)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE II44</td>
<td>THA</td>
<td>2055</td>
<td>Enoxaparin SC 40 mg OD</td>
<td>28–35 d</td>
<td>8.8% (69/785)</td>
<td>0.9% (9/1003)</td>
<td>1.4% (14/1010)</td>
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<tr>
<td></td>
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<td></td>
<td>Dabigatran 220 mg OD</td>
<td></td>
<td>7.7% (61/792)</td>
<td>0.88 (0.63–1.22)</td>
<td>−1.1 (−3.8 to 1.6)</td>
<td>1.4% (14/1010)</td>
<td>1.54 (0.67–3.55)</td>
</tr>
<tr>
<td><strong>Treatment of VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>RE-COVER45</td>
<td>Acute VTE</td>
<td>2564</td>
<td>Warfarin (INR 2.0 to 3.0)</td>
<td>6 mo</td>
<td>2.1% (27/1265)</td>
<td>1.9% (24/1265)</td>
<td>1.10* (0.65–1.84)</td>
<td>0.4 (−0.8–1.5)</td>
<td>1.6% (20/1274)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 150 mg BID</td>
<td></td>
<td>2.4% (30/1274)</td>
<td>1.10* (0.65–1.84)</td>
<td>0.4 (−0.8–1.5)</td>
<td>1.6% (20/1274)</td>
<td>0.82* (0.45–1.48)</td>
</tr>
<tr>
<td><strong>Prevention of stroke and systemic embolism in AF</strong></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY48,49</td>
<td>AF</td>
<td>18 113</td>
<td>Warfarin (INR 2.0 to 3.0)</td>
<td>2.0 y (median)</td>
<td>1.71%/y (202/6022)</td>
<td>3.57%/y (421/6022)</td>
<td>1.11%/y (134/6076)</td>
<td>0.65 (0.52–0.81)</td>
<td>3.32%/y (399/6076)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 150 mg BID</td>
<td></td>
<td>1.11%/y (134/6076)</td>
<td>0.65 (0.52–0.81)</td>
<td>3.32%/y (399/6076)</td>
<td>0.93 (0.81–1.07)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dabigatran 110 mg BID</td>
<td></td>
<td>1.54%/y (183/6015)</td>
<td>0.90 (0.74–1.10)</td>
<td>2.87%/y (342/6015)</td>
<td>0.80 (0.70–0.93)</td>
<td></td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; BID, twice daily; VTE, venous thromboembolism; TKA, total knee arthroplasty; THA, total hip arthroplasty; INR, international normalized ratio; AF, atrial fibrillation; RE-MODEL, Dabigatran Etexilate 150 mg or 220 mg Once Daily Versus Enoxaparin 40 mg Once Daily for Prevention of Thrombosis After Knee Surgery; RE-NOVATE, Dabigatran Etexilate Compared With Enoxaparin in Prevention of VTE Following Total Hip Arthroplasty; RE-MOBILIZE, Dabigatran Etexilate Versus Enoxaparin in Prevention of VTE Post Total Knee Replacement; RE-COVER, Dabigatran Etexilate Versus Warfarin in the Treatment of Acute Venous Thromboembolism; and RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy.

*Hazard ratio.
The approved dosage for most patients is a fixed oral dose of 220 mg once daily administered as a single capsule of 110 mg (half-dose) between 1 and 4 hours after surgery and then continuing with 2 capsules (220 mg) once daily thereafter for a total of 10 days in patients undergoing total knee replacement and 28 to 35 days in those undergoing total hip replacement. A lower dose of 150 mg administered as a single capsule of 75 mg (half-dose) between 1 and 4 hours after surgery and then continuing with 2 capsules (150 mg) once daily thereafter is approved for patients 75 years of age (at higher risk of bleeding) and those with moderate renal impairment (creatinine clearance, 30 to 50 mL/min) or concurrently taking moderate p-glycoprotein inhibitors such as amiodarone or verapamil. Dabigatran etexilate is contraindicated in patients undergoing major orthopedic surgery who have a creatinine clearance <30 mL/min.

### Table 7. Information for Patients

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Enoxaparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar</td>
<td>Similar</td>
<td>Different</td>
</tr>
<tr>
<td>Low potential for interaction with diet and other medications</td>
<td>High potential for interaction with diet and other medications</td>
<td>Low potential for interaction with diet and other medications</td>
</tr>
<tr>
<td>May interact with some commonly used drugs, including the heart medications amiodarone and verapamil and antifungals such as ketoconazole</td>
<td>May interact with some commonly used drugs, including the heart medications amiodarone and verapamil and antifungals such as ketoconazole</td>
<td>May interact with some commonly used drugs, including the heart medications amiodarone and verapamil and antifungals such as ketoconazole</td>
</tr>
<tr>
<td>Currently marketed under the name Pradax or Pradaxa</td>
<td>Currently marketed under the name Prexphi or Prephina</td>
<td>Currently marketed under the name Novax or Novas</td>
</tr>
</tbody>
</table>
Optimal Dosing for AF

The Dabigatran With or Without Concomitant Aspirin Compared With Warfarin Alone in Patients With Nonvalvular Atrial Fibrillation (PETRO) trial was a randomized, controlled phase II trial designed to identify a safe dose of dabigatran etexilate in 502 patients with chronic AF as determined by the occurrence of bleeding and clinical events. Secondary objectives included identification of anticoagulant activity through aPTT and D-dimer generation.

Dabigatran etexilate monotherapy, in doses of 50, 150, and 300 mg twice daily, was compared with dabigatran etexilate (in doses of 50, 150 and 300 mg twice daily) plus aspirin 81 or 325 mg once daily and with warfarin monotherapy (dosed to reach a target INR of 2 to 3) in a 3 × 3 factorial design. The choice of aspirin dose was at the discretion of the investigator. The primary outcome was the frequency of major and/or clinically relevant bleeding events.

Major hemorrhages occurred only in patients assigned dabigatran etexilate 300 mg BID plus aspirin (4 of 64 patients) and were significantly more common than among patients assigned dabigatran etexilate 300 mg BID monotherapy (0 of 105; P<0.02). Consequently, aspirin was discontinued in the former group, and those patients were merged with the 300 mg BID monotherapy group. Total bleeding events were more frequent in the 300 mg BID (39 of 169, 23%) and 150 mg BID (30 of 169, 18%) dabigatran groups compared with the 50 mg BID groups (7 of 107, 7%; P=0.0002 and P=0.01, respectively). Thromboembolic events were limited to the 50 mg BID dabigatran dose groups (2 of 107, 2%).

Among the secondary outcomes, trough aPTT values were 1.2, 1.5, and 1.8 times the baseline level for the 50, 150, and 300 mg BID dabigatran groups, respectively. Trough aPTTs demonstrated low variability, with coefficients of variation of 13% to 21%, suggesting that routine coagulation monitoring is not necessary. The mean trough D-dimer measurements were suppressed for the 2 highest doses of dabigatran and warfarin (INR, 2 to 3).

Serious liver toxicity was not seen. Aminotransferase levels >3 times the upper limit of normal were observed in 0.9% of the dabigatran etexilate recipients and in none of the warfarin recipients.

Evidence From Phase III Trials

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial was a phase III, multicenter, prospective, open-label, randomized trial with blinded evaluation of all outcomes that aimed to determine whether at least 1 dose of dabigatran etexilate would be noninferior to warfarin in patients with AF.

A total of 18 113 patients with nonvalvular AF and at least 1 additional risk factor for stroke were enrolled from 951 centers in 44 countries and randomly assigned to receive, in a blinded fashion, fixed doses of dabigatran (110 or 150 mg twice daily) or, in an unblinded fashion, adjusted-dose warfarin (INR, 2 to 3). Half were naive to previous oral anticoagulation (ie, anticoagulation starters). Among patients assigned warfarin, the mean time in the therapeutic range, excluding the first week of therapy, averaged 64.4% (67% for patients with warfarin experience, 61% for warfarin naive), indicating a quality of warfarin management similar to that achieved in contemporary trials. After a median of 2 years of follow-up, 21% of participants had discontinued dabigatran etexilate compared with 17% who had discontinued warfarin. Only 20 patients (0.1%) were lost to follow-up.

After database lock on August 15, 2009, and publication of the results on September 17, 2009, additional primary efficacy and safety outcome events were identified during routine clinical site closure visits. A revised analysis has been published, but the main results and interpretation of the study are unchanged.

Compared with warfarin, dabigatran etexilate 150 mg BID significantly reduced the rate of the primary outcome, stroke (including hemorrhagic stroke), or systemic embolism (warfarin, 1.71%/y; dabigatran 150 mg BID, 1.11%/y; RR, 0.65; 95% CI, 0.52 to 0.81; P<0.001 for superiority) and death resulting from cardiovascular causes (RR, 0.85; 95% CI, 0.72 to 0.99) despite a higher discontinuation rate for dabigatran.
Dabigatran 110 mg

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>0.90 (0.74-1.10)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.80 (0.70-0.93)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.31 (0.17-0.56)</td>
</tr>
<tr>
<td>Death</td>
<td>0.91 (0.80-1.03)</td>
</tr>
</tbody>
</table>

Dabigatran 150 mg

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>0.65 (0.52-0.81)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.93 (0.81-1.07)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.26 (0.14-0.49)</td>
</tr>
<tr>
<td>Death</td>
<td>0.88 (0.77-1.00)</td>
</tr>
</tbody>
</table>

Figure 5. Forest plot showing the results of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial for the primary outcome event of stroke or systemic embolism.\(^{48,49}\) The point estimate of each relative risk is indicated by a square; the 95% confidence interval (CI) of each relative risk by a horizontal line. Modified from Eriksson et al.\(^{13}\)

( Figures 5 and 6 and Table 6).\(^{48,49,54}\) No significant difference in the same outcomes was found between dabigatran etexilate 110 mg BID and warfarin (stroke or systemic embolism: warfarin, 1.71% per year; dabigatran 110 mg BID, 1.54% per year; RR, 0.90; 95% CI, 0.74 to 1.10; \(P<0.001\) for noninferiority, 0.30 for superiority; Table 6 and Figures 5 and 6).\(^{48,49}\)

Compared with warfarin, dabigatran etexilate 110 mg BID significantly reduced the rate of the primary safety outcome, major hemorrhage (warfarin, 3.57% per year; dabigatran 110 mg BID, 2.87% per year; RR, 0.80; 95% CI, 0.70 to 0.93; \(P=0.003\)). No significant difference in major hemorrhage was found between dabigatran etexilate 150 mg BID and warfarin (warfarin, 3.57% per year; dabigatran 150 mg BID, 3.32% per year; RR, 0.93; 95% CI, 0.81 to 1.07; \(P=0.31\) for superiority; Table 6).\(^{48,49}\)

Both doses of dabigatran etexilate were associated with fewer intracranial bleeds than warfarin (warfarin: 0.76% per year vs dabigatran 110 mg bid: 0.23% per year [RR: 0.30, 95% CI: 0.19 to 0.45], and dabigatran 150 mg bid: 0.32% per year [RR: 0.41, 95% CI: 0.28 to 0.60]).\(^{49}\) However, dabigatran etexilate 150 mg bid significantly increased gastrointestinal bleeding (1.56% per year) compared with warfarin (1.07% per year; RR: 1.48, 95% CI: 1.18 to 1.85) and dabigatran etexilate 110 mg bid (1.15% per year; RR: 1.36, 95% CI: 1.09 to 1.70).\(^{49}\) Co-administration of aspirin and dabigatran increased the risk of major bleeding compared with dabigatran alone (hazard ratio, 1.91; \(P<0.001\)) without any evidence of benefit in reducing stroke and other serious vascular events.\(^{48}\) However, aspirin use did not interact with treatment; ie, the increased bleeding risk with aspirin use was observed for all 3 treatment groups (both doses of dabigatran etexilate and warfarin), regardless of age or creatinine clearance.\(^{55}\) Similarly, renal impairment increased the risk of bleeding with dabigatran etexilate, but again there was no treatment interaction.\(^{55}\)

Rates of MI were higher with both doses of dabigatran etexilate compared with warfarin (warfarin, 0.64% per year [75 per 11 794 patient-years]; dabigatran 110 mg BID, 0.82% per year [98 per 11 899 patient-years] [RR, 1.29; 95% CI, 0.96 to 1.75]; dabigatran 150 mg BID, 0.81% per year [97 per 12 033 patient-years] [RR, 1.27; 95% CI, 0.94 to 1.71]).\(^{48,56}\) When both doses of dabigatran are considered together, the rate of MI was 0.81% per year (195 per 23 932 patient years) compared with warfarin (0.64% per year; RR, 1.29; 95% CI, 1.05 to 1.60, Mantel-Haenszel method, fixed-effects model). The reason for the higher rate of MI with dabigatran is unclear. Baseline subject characteristics and medication use were similar between treatment arms and do not explain the higher rate of MI with dabigatran.\(^{56}\) The imbalance in MIs was seen on drug and off drug.\(^{56}\) It is unclear whether the higher rate of MI with dabigatran represents the play of chance, an adverse effect of dabigatran, or beneficial effects of warfarin in preventing MI.\(^{56,57}\)

Dabigatran etexilate showed no evidence of hepatotoxicity. However, rates of dyspepsia (including abdominal pain) were elevated with dabigatran (11.8% with 110 mg BID, 11.3% with 150 mg BID) compared with warfarin (5.8%), presumably related to the tartaric acid content of the dabigatran.
etexilate capsule. Patients receiving the P-glycoprotein inhibitors amiodarone and verapamil had efficacy and safety outcomes similar to those not receiving these medications.

The benefits of dabigatran 150 mg BID in reducing stroke, dabigatran 110 mg BID in reducing bleeding, and both doses in reducing intracranial bleeding compared with warfarin were consistent, regardless of the quality of INR control by the study centers among patients assigned warfarin (measured by the centers’ time in the therapeutic range as a proxy for INR control). However, for secondary outcomes such as all vascular events, nonhemorrhagic events, and mortality, the advantages of dabigatran in RE-LY were greater at sites with poor INR control than at those with good INR control, indicating that local standards of care affect the benefits of vitamin K anticoagulants. The finding of consistently lower rates of intracranial bleeding in both dabigatran groups compared with the warfarin group, regardless of the centers’ quality of INR control, suggests that warfarin may predispose to intracranial bleeding by mechanisms other than poor INR control.

A predefined analysis investigated the consistency of results in the subgroup of 3623 patients with prior stroke or transient ischemic attack. Stroke or systemic embolism occurred in 65 patients (2.78%/y) assigned warfarin, 55 patients (2.32%/y) assigned dabigatran 110 mg BID (RR, 0.84; 95% CI, 0.58 to 1.20), and 51 patients (2.07%/y) allocated dabigatran 150 mg BID (RR, 0.75; 95% CI, 0.52 to 1.08). After testing for interaction, the results indicate that the treatment effects of both doses of dabigatran in patients with prior stroke or transient ischemic attack are consistent with those for patients without prior stroke or transient ischemic attack.

The benefit of dabigatran etexilate over warfarin in patients with prior stroke or transient ischemic attack was driven by a reduction in hemorrhagic stroke: 18 patients (0.77%/y) on warfarin, 2 (0.08%/y) on dabigatran 110 mg BID (RR, 0.11; 95% CI, 0.03 to 0.47), and 5 (0.20%/y) on dabigatran 150 mg BID (RR, 0.27; 95% CI, 0.10 to 0.72). The rate of major bleeding was also significantly lower in patients assigned dabigatran 110 mg BID compared with warfarin (RR, 0.66; 95% CI, 0.48 to 0.90), including intracranial bleeding (RR, 0.20; 95% CI, 0.08 to 0.47). However, the rate of major bleeding among patients assigned dabigatran 150 mg BID was similar to that among patients assigned warfarin (RR, 1.01; 95% CI, 0.77 to 1.34).

An economic analysis of dabigatran compared with adjusted-dose warfarin for preventing ischemic stroke in patients ≥65 years of age with nonvalvular AF, based on data from the RE-LY trial and other published sources of anticoagulation, suggested that dabigatran is likely to be cost-effective compared with warfarin (incremental cost-effectiveness ratio less than US $50 000 per quality-adjusted life-year) if daily costs of dabigatran do not exceed US $9.36 for low-dose (110 mg BID) therapy and $13.70 for high-dose (150 mg BID) therapy.

There are no direct comparisons of dabigatran etexilate with placebo or antiplatelet therapy. However, a recent network meta-analysis of all randomized, controlled trials of antithrombotic treatments for stroke prevention in patients with AF estimated, from indirect comparisons of dabigatran etexilate with placebo and antiplatelets, that dabigatran etexilate 150 mg BID may reduce the risk of any stroke by 75% (RR, 0.25; 95% CI, 0.12 to 0.51) compared with placebo, by 63% (RR, 0.37; 95% CI, 0.20 to 0.69) compared with aspirin monotherapy, and by 61% (RR, 0.39; 95% CI, 0.21 to 0.72) compared with aspirin plus clopidogrel. This analysis also estimated that dabigatran etexilate 150 mg BID may not significantly increase the risk of extracranial hemorrhage compared with aspirin monotherapy (RR, 0.96; 95% CI, 0.39 to 2.37) or aspirin plus clopidogrel (RR, 0.99; 95% CI, 0.60 to 1.63), or increase the risk of intracranial hemorrhage compared with aspirin monotherapy (RR, 1.04; 95% CI, 0.28 to 3.90) or aspirin plus clopidogrel (RR, 1.00; 95% CI, 0.30 to 3.32).

**Approval**

On the basis of the results of RE-LY trial, which showed that dabigatran etexilate was noninferior to warfarin at a lower dosage and superior at a higher one for preventing thromboembolic stroke in paroxysmal or permanent AF, a Food and Drug Administration advisory panel unanimously recommended to its Cardiovascular and Renal Drugs Advisory Committee on September 20, 2010, that dabigatran etexilate be approved for the prevention of stroke in patients with AF. On October 20, 2010, the Food and Drug Administration approved dabigatran etexilate at the higher dose (150 mg BID) but did not approve the lower dose because of concerns that it did not offer efficacy advantages over warfarin. On the basis of pharmacokinetic modeling data, the Food and Drug Administration also approved a 75 mg BID dose of dabigatran etexilate for stroke prevention in AF patients with a creatinine clearance of 15 to 30 mL/min.

On October 27, 2010, Health Canada, the Canadian health authority, approved dabigatran etexilate for the prevention of stroke and systemic embolism in patients with AF in whom anticoagulation is appropriate. The 150 mg BID dose was recommended and the 110 mg BID dose was available specifically for elderly patients >80 years of age and for patients at high risk of bleeding.

The implication of this approval announcement for clinicians in North America is that most patients with AF at high risk of stroke will have a choice of 2 highly effective oral anticoagulant regimens. Many will prefer dabigatran because it is rapidly effective, does not interact with foods and most medications (which are particularly problematic for patients taking warfarin), does not require monitoring, and is associated with a lower risk of ischemic stroke and intracranial bleeding than warfarin. Even patients taking warfarin and achieving good INR control may prefer dabigatran, because the benefits of dabigatran 150 mg BID in reducing stroke and intracranial bleeding compared with warfarin appear consistent, regardless of the quality of INR control among patients assigned warfarin. Dabigatran at a dose of 75 mg BID may be used in patients with a creatinine clearance of 15 to 30 mL/min, but close monitoring is required because renal function may deteriorate with time, leading to increased plasma concentrations of dabigatran.
Switching from warfarin to dabigatran will require warfarin to be stopped and the INR to be monitored daily. When the INR falls below 2.0, usually 2 to 3 days later, dabigatran can be started.

Warfarin will remain the treatment of choice for patients with a creatinine clearance <15 mL/min, those who cannot afford dabigatran, and those in whom there are concerns about compliance with the twice-daily dose of dabigatran (eg, patients taking multiple medications and those who are poorly motivated, forgetful, or have difficultyaffording dabigatran) because the risks of ischemic stroke are likely to increase substantially with poor adherence to this short-acting drug. Warfarin will also probably remain the treatment of choice for patients in whom there are concerns about dyspepsia as an adverse effect, the possible need for rapid reversal of the anticoagulant effect, and the potentially greater risks of gastrointestinal hemorrhage and MI with dabigatran etexilate compared with warfarin. If MI is truly a drug-related adverse event, then treating 1000 subjects for 1 year may cause 2 excess MIs compared with treating with warfarin. This possible increased risk of MI with dabigatran is unlikely to outweigh the benefits of dabigatran in most patients, however. For patients with liver dysfunction, dabigatran may be preferred over warfarin because it was well tolerated by patients with mild to moderate hepatic impairment in 1 study, although both drugs are at least partly metabolized in the liver.

An attraction of dabigatran etexilate is that in situations where 2 effective doses are approved, customized dosing may be possible; ie, patients at higher risk of hemorrhage (and lower risk of stroke) may be prescribed the lower dose and those at higher risk of stroke (and lower risk of hemorrhage) may be prescribed the higher dose. However, the RE-LY trial did not specifically evaluate this strategy, so it is not an evidence-based strategy. Although a choice of doses offers clinicians and patients more flexibility, the lower dose could become a default for those clinicians who tend to be more concerned about safety than efficacy (in contrast to many patients who are more concerned about the risk of stroke) and thereby compromise efficacy.

Given the looming epidemic of fatal and disabling stroke caused by AF (as the population ages), the enormous cost of these strokes to the community, the suboptimal anticoagulation of a large proportion of the AF population, and the cost and inconvenience of INR monitoring among those prescribed warfarin, it is likely that the incremental cost-effectiveness of dabigatran compared with warfarin will be favorable, provided that the daily cost of high-dose dabigatran tablets is less than US $13.70.31,54,64

Acute Coronary Syndrome

Optimal Dosing
The phase II Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome (RE-DEEM) study (NCT00621855) randomized 1861 patients with acute coronary syndrome and at least 1 cardiovascular risk factor (which included prior MI in 29%, diabetes mellitus in 31%, and heart failure in 12%) to placebo or dabigatran at 1 of the 4 dosages (50 mg, 75 mg, 110 mg, and 150 mg) twice daily, starting within a few days (mean, 7.4 days) after acute ST-elevation MI or non–ST-elevation MI and continuing for 6 months. Patients were already taking aspirin and clopidogrel, and about half had undergone percutaneous coronary intervention at the time of randomization. The results were reported at the American Heart Association 2009 Scientific Sessions, but have not yet been published.50

The 6-month rates of the primary outcome, major or clinically relevant minor bleeding, were 2.4% among the 371 patients assigned placebo, 3.5% for those assigned 50 mg BID, 4.3% for those taking 75 mg BID, 7.9% for those taking 110 mg BID, and 7.8% of the 347 patients assigned 150 mg BID, indicating a significant dose-related rise in the risk of bleeding complications (P<0.001).50

The rates of major bleeding were lower and ranged from 0.5% among patients assigned the placebo to 2.0% among those assigned dabigatran 110 mg BID. The absolute increase in major bleeds of not >1.5% with dabigatran compared with placebo was considered low and acceptable by the investigators. Clinical event rates in the trial were also low, although the trial was not powered for clinical outcomes.50

It is uncertain whether a large phase III trial of dabigatran in acute coronary syndrome is being planned, and, if so, which dose will be evaluated and what the control group will be (ie, which antiplatelet regimen).

Unresolved Issues and Challenges

Thrombin plays an important role not only in coagulation but also in immune response, infection, angiogenesis, endothelial function, and tumor growth. The safety and efficacy of inhibiting the generation of thrombin with drugs such as dabigatran in the longer term (beyond 2 years [mean] of follow-up in RE-LY) are uncertain and being evaluated in an ongoing long-term follow-up study of RE-LY patients (Long Term Multi-Center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial [RELY-ABLE]; NCT00808067).65

Other unresolved issues include the potential safety and utility of the lower 110-mg dose in older patients with moderate renal impairment or patients with body weight <50 kg, the safety of combining dabigatran with antiplatelet drugs and p-glycoprotein–affecting drugs (prescribed to ~42% of hospitalized AF patients66), the ability to monitor the anticoagulant effect of dabigatran, and the ability to rapidly reverse the anticoagulant effect of dabigatran in the event of acute bleeding or urgent surgery.

A forthcoming challenge will be the accurate interpretation of indirect comparisons of the effects of dabigatran and the oral factor Xa inhibitors rivaroxaban, apixaban, and edoxaban when compared directly with conventional anticoagulation (heparins or warfarin) in large phase III trials involving patients at risk of VTE and patients with AF.67–72 Until more reliable direct comparisons of the new oral anticoagulants (ie, against each other) are available, the lessons learned about the potentially misleading conclusions derived from previous indirect comparisons of antithrombotic regimens will be salutary.73
**Conclusions**

Dabigatran etexilate is a prodrug of the active moiety dabigatran, an oral, reversible, direct thrombin inhibitor that inhibits both clot-bound and circulating thrombin. After oral administration, dabigatran has a fast onset of action, reaching peak plasma concentrations within 0.5 to 2 hours, thereby potentially negating the need for initial treatment with a rapidly acting injectable anticoagulant. The presence of dabigatran in the blood can be detected by a prolonged TT or aPTT, but the anticoagulation response is sufficiently predictable that routine coagulation monitoring is not required. Dabigatran has a low potential for food and drug interactions, a half-life of 12 to 14 hours in patients with normal renal function that permits once- or twice-daily administration, and a fast offset of action. About 80% of the drug is excreted unchanged by the kidneys.

Dabigatran etexilate has demonstrated noninferiority and safety similar to once-daily enoxaparin for the prevention of VTE in patients undergoing hip and knee arthroplasty. Given its efficacy, safety profile, and attractive pharmacological characteristics, it has been approved for this indication in >75 countries worldwide. Dabigatran has demonstrated noninferiority to and improved safety compared with warfarin for the treatment of VTE and noninferiority to warfarin at a lower dosage and superiority at a higher dose for preventing stroke and systemic embolism in patients with nonvalvular AF. Both doses of dabigatran have demonstrated improved safety compared with warfarin in AF. The Food and Drug Administration has recently approved dabigatran as a replacement for warfarin in patients with AF. The American College of Cardiology and American Heart Association have recently recommended that dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function). 74

The Hemocon test has been approved in Europe for the quantitative determination of dabigatran plasma levels. For patients taking dabigatran who bleed, there is no specific antidote. Discontinuation of the drug and supportive measures usually suffice because the anticoagulant effect of dabigatran is short-lived. In emergencies, dabigatran can be dialyzed; failing that, nonspecific hemostatic agents such as rFVIIa and prothrombin complex concentrates can be considered. In case of overdose, the efficacy of early administration of activated charcoal and charcoal filtration is undergoing clinical evaluation.

Outstanding issues relating to the use of dabigatran etexilate include the lack of a test of anticoagulant activity, lack of an antidote, limited evaluation in patients with severe renal impairment, interaction with other drugs that are substrates of the p-glycoprotein transporter, and unknown long-term safety. The long-term safety of dabigatran etexilate is being evaluated in ongoing studies. Additional trials are needed to establish the efficacy and safety of dabigatran etexilate for other antithrombotic indications such as acute coronary syndrome, acute transient ischemic attack and ischemic stroke, and mechanical heart valves.

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**Disclosures**

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**References**


**Key Words:** anticoagulants, atrial fibrillation, dabigatran etexilate, direct thrombin inhibitor, stroke
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