



**EDUCATIONAL OBJECTIVE:** Readers will consider dabigatran's indications, advantages, and disadvantages

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# Dabigatran: Will it change clinical practice?

## ■ ABSTRACT

Dabigatran (Pradaxa) is a new oral anticoagulant approved in the United States for the primary prevention of stroke and systemic embolization in patients with nonvalvular atrial fibrillation. It offers clinicians an alternative to warfarin (Coumadin), and it has received considerable interest because of its convenience of use, clinical efficacy, and safety profile. However, it is more expensive, and this may limit its widespread use.

## ■ KEY POINTS

Dabigatran is a potent, reversible, direct thrombin inhibitor. Available only in oral form, it has a rapid onset of action, a predictable anticoagulant response, and few major interactions.

Dabigatran does not require dose adjustments (except for renal insufficiency) or monitoring of its effect during treatment.

In trials in patients with nonvalvular atrial fibrillation, two different doses of dabigatran were compared with warfarin. Less bleeding occurred with the lower dose than with warfarin, while the higher dose was more effective than warfarin in preventing stroke and systemic embolization.

The American College of Cardiology, the American Heart Association, and the Heart Rhythm Society have given dabigatran a class I B recommendation for secondary stroke prevention in patients with nonvalvular atrial fibrillation.

**D**ABIGATRAN ETEXILATE (Pradaxa) is a new oral anticoagulant that has distinct advantages over warfarin (Coumadin) in terms of its ease of administration, efficacy, and safety.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY trial),<sup>1</sup> in patients with nonvalvular atrial fibrillation, dabigatran 110 mg twice a day was found to be as good as warfarin in preventing systemic embolization and stroke (the primary outcome of the study), and at 150 mg twice a day it was superior.<sup>1</sup> It has also shown efficacy in treating acute deep vein thrombosis and pulmonary embolism and in preventing these complications in orthopedic surgical patients.<sup>2-4</sup>

Dabigatran has been approved in 75 countries. It carries the trade name Pradaxa in Europe and the United States and Pradax in Canada. In October 2010, the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee endorsed two twice-daily doses (75 mg and 150 mg) of dabigatran for the prevention of systemic embolization and stroke in patients with nonvalvular atrial fibrillation.

However, dabigatran is relatively expensive, and its current high cost might be a barrier to its wider use.

## ■ MANY PATIENTS NEED ANTICOAGULATION

Anticoagulation plays a vital role in the primary and secondary prevention of stroke in patients with atrial fibrillation and of pulmonary embolism in patients with venous thromboembolism. It is also used during cardiothoracic and vascular surgery, endovascular procedures, and dialysis and in patients with mechanical heart valves and hypercoagulable conditions.

**TABLE 1**

**Anticoagulants currently available or in development in the United States**

<b>Parenteral agents</b>	<b>Oral agents</b>
Heparin	Vitamin K antagonists Warfarin (Coumadin, Jantoven)
Low-molecular-weight heparins Enoxaparin (Lovenox) Dalteparin (Fragmin) Tinzaparin (Innohep)	Direct thrombin inhibitor Dabigatran (Pradaxa)
Factor Xa inhibitor Fondaparinux (Arixtra)	Factor Xa inhibitors Rivaroxaban (Xarelto) Apixaban (Eliquis) (not yet approved in the United States)
Direct thrombin inhibitors Argatroban (Argatroban) Bivalirudin (Angiomax) Lepirudin (Refludan) Desirudin (Iprivask)	

**More than 10% of people older than 80 years have atrial fibrillation**

Atrial fibrillation affects 3.03 million people in the United States (2005 figures), and this number is predicted to be as high as 7.56 million by 2050.<sup>5</sup> More than 10% of people over the age of 80 years have it, and the lifetime risk of developing it is approximately 25%.<sup>6,7</sup> Its most serious complication is ischemic stroke (the risk of which increases with age) and systemic embolization.<sup>5,8</sup>

Until the recent introduction of dabigatran, the only oral anticoagulant available in the United States for treating patients with atrial fibrillation was warfarin. Although warfarin has a number of disadvantages (see below), it is actually very effective for preventing ischemic stroke, reducing the incidence by as much as 65%.<sup>9,10</sup>

Venous thromboembolism is the third most common cardiovascular disorder after myocardial infarction and stroke.<sup>11</sup> Although its exact incidence is unknown, nearly 1 million cases of it (incident or recurrent, fatal and nonfatal events) occur in the United States each year.<sup>12</sup> Many patients with venous thromboembolism need oral anticoagulation long-term, and currently warfarin remains the only option for them as well.

**NEEDED: A BETTER ANTICOAGULANT**

Warfarin has been the most commonly prescribed oral anticoagulant in the United States

for more than 60 years. As of 2004, more than 30 million outpatient prescriptions for it were filled annually in this country alone.<sup>13</sup> However, warfarin has several important limitations.

Warfarin has a narrow therapeutic index. Patients taking it require monitoring of their international normalized ratio (INR) and frequent dose adjustments, and this is time-consuming and inconvenient. The target INR for patients with venous thromboembolism and atrial fibrillation is 2.0 to 3.0, whereas patients with a mechanical heart valve need a higher INR (2.5 to 3.5). If the INR is below these ranges, warfarin is less effective, with a risk of new thrombosis. On the other hand, if the INR is too high, there is a risk of bleeding.<sup>14</sup> In fact, the most important side effect of warfarin is the risk of major and minor bleeding.<sup>13</sup> However, even in well-designed clinical trials in which patients are closely managed, only 55% to 60% of patients regularly achieve their therapeutic target INR.<sup>1,2,14,15</sup>

Warfarin also interacts with many drugs and with some foods. Compliance is difficult. It has a slow onset of action. Genetic variations require dose adjustments. When switching from a parenteral anticoagulant, overlapping is required. Skin necrosis is a possible side effect. And warfarin is teratogenic.

Despite these limitations, the American College of Chest Physicians endorses warfarin to prevent or treat venous thromboembolism, and to prevent stroke in patients with atrial fibrillation.<sup>16</sup>

Recently, a number of new oral and parenteral anticoagulants have been developed (TABLE 1) with the aim of overcoming some of the drawbacks of warfarin and the other currently available agents, and to improve the prevention and treatment of thromboembolic disorders.

**DABIGATRAN, A THROMBIN INHIBITOR**

Dabigatran, developed by Boehringer Ingelheim, is a potent, competitive, and reversible inhibitor of both free and clot-bound thrombin, inhibiting both thrombin activity and generation (TABLE 2).<sup>17,18</sup>

A prodrug, dabigatran is rapidly absorbed and converted to its active form. Its plasma concentration reaches a peak 1.5 to 3 hours after an oral dose, and it has an elimination

half-life of 12 to 14 hours. About 80% of its excretion is by the kidneys and the remaining 20% is through bile.

Dabigatran is not metabolized by cytochrome P450 isoenzymes, and therefore it has few major interactions with other drugs. An exception is rifampin, a P-glycoprotein inducer that blocks dabigatran's absorption in the gut, so this combination should be avoided. Another is quinidine, a strong P-glycoprotein inhibitor that is contraindicated for use with dabigatran. Also, amiodarone (Cordarone), another P-glycoprotein inhibitor, increases blood levels of dabigatran, and therefore a lower dose of dabigatran is recommended if these drugs are given together.<sup>18-20</sup>

### ■ DOES DABIGATRAN NEED MONITORING? CAN IT EVEN BE MONITORED?

Dabigatran has a predictable pharmacodynamic effect, and current data indicate it does not need regular monitoring.<sup>18-20</sup> However, one may need to be able to measure the drug's activity in certain situations, such as suspected overdose, bleeding, need for emergency surgery, impaired renal function, pregnancy, and obesity, and in children.<sup>20</sup>

Dabigatran has little effect on the prothrombin time or the INR, even at therapeutic concentrations.<sup>19</sup> Further, its effect on the activated partial thromboplastin time (aPTT) is neither linear nor dose-dependent, and the aPTT reaches a plateau and becomes less sensitive at very high concentrations. Therefore, the aPTT does not appear to be an appropriate test to monitor dabigatran's therapeutic anticoagulant effect, although it does provide a qualitative indication of anticoagulant activity.<sup>18,19</sup>

The thrombin time is a very sensitive method for determining if dabigatran is present, but the test lacks standardization; the ecarin clotting time provides better evidence of the dose but is not readily available at most institutions.<sup>18,19,21</sup>

### ■ EVALUATED IN CLINICAL TRIALS

Dabigatran has been evaluated in a number of trials for its ability to prevent ischemic stroke and systemic embolization in patients with

TABLE 2

### Dabigatran at a glance

**Brand names:** Pradaxa in the United States and in Europe, Pradax in Canada

**Type:** Prodrug

**Mechanism:** Direct reversible thrombin inhibitor

**United States indication:** Primary prevention of stroke and systemic embolization in nonvalvular atrial fibrillation

**Contraindications:** Active bleeding, hypersensitivity to dabigatran and in patients with a creatinine clearance less than 15 mL/min or on hemodialysis; dabigatran is not recommended for patients with moderate to severe hepatic impairment, Child-Pugh class B or C (defined as liver disease having ascites, encephalopathy, an elevated international normalized ratio, low albumin, or elevated bilirubin)

**Side effects:** Gastrointestinal intolerance and dyspepsia

**Recommended dose and route:** 150 mg taken orally twice daily, with or without food; a dose of 75 mg twice daily has been approved for patients with a creatinine clearance of 15 to 30 mL/min

**Storage:** Dabigatran must be dispensed and stored in the original bottle to prevent loss of potency

**Cost:** Approximately US \$6.75 to \$8.00 per day

atrial fibrillation and to prevent and treat venous thromboembolism in surgical orthopedic patients, and in patients with acute coronary syndrome (TABLE 3).<sup>1-4,22-25</sup>

### ■ DABIGATRAN IS EXPENSIVE BUT MAY BE COST-EFFECTIVE

The estimated price of dabigatran 150 mg twice a day in the United States is about \$6.75 to \$8.00 per day.<sup>26,27</sup>

Warfarin, in contrast, costs as little as \$50 per year.<sup>28</sup> However, this low price does not include the cost of monitoring the INR (office visits and laboratory testing), and these combined expenses are much higher than the price of the warfarin itself.<sup>29</sup> In addition, warfarin requires time-consuming management when bridging to a parenteral anticoagulant (for reversal of its anticoagulant action) before routine health maintenance procedures such as dental work and colonoscopy and interventional procedures and surgery. Any bleeding complication will also add to its cost and will be associated with a decrease in the

**Even in clinical trials, only 55%–60% of patients achieve their target INR on warfarin (Coumadin)**

**TABLE 3**

**Clinical trials of dabigatran**

TRIAL	NO. OF PATIENTS	TYPE OF PATIENTS	DABIGATRAN DOSE	COMPARISON DRUG	EFFICACY FOR PREVENTING VTE OR STROKE	BLEEDING
BISTRO II <sup>22</sup>	1,973	Total knee or hip replacement	50, 150, or 225 mg twice daily or 300 mg once a day	Enoxaparin 40 mg/day	VTE was significantly lower in patients receiving 150 mg twice daily	Less bleeding at the lower dose, increased bleeding at the higher dose
RE-NOVATE <sup>23</sup>	3,494	Total hip replacement	150 or 220 mg/day	Enoxaparin 40 mg/day	Not inferior to enoxaparin	Similar rates
RE-MOBILIZE <sup>3</sup>	2,615	Total knee replacement	220 or 150 mg/day	Enoxaparin 30 mg every 12 hours	Less effective than enoxaparin	Similar rates
RE-MODEL <sup>24</sup>	2,076	Total knee replacement	220 or 150 mg/day	Enoxaparin 40 mg/day the evening before surgery	Not inferior to enoxaparin	Similar rates
PETRO <sup>25</sup>	502	Atrial fibrillation with one risk factor	50, 150, or 300 mg twice a day with or without aspirin	Warfarin	Less efficacious at 50 mg dose for stroke	More bleeding with 300 mg and aspirin combined
RE-LY <sup>1</sup>	18,113	Atrial fibrillation with one risk factor	110 or 150 mg twice daily	Warfarin	110 mg dose with similar rates and 150 mg, lower rates of stroke	Less bleeding at 110 mg and similar with 150 mg
RE-COVER <sup>2</sup>	2,564	Acute VTE	150 mg twice daily	Warfarin	Similar	Similar
Meta-analysis <sup>4</sup> of RE-MODEL, <sup>24</sup> RE-NOVATE, <sup>23</sup> RE-MOBILIZE <sup>3</sup>	8,185	Total knee or hip replacement	220 mg once daily	Enoxaparin (see above)	Not inferior to enoxaparin	Similar rates
RE-DEEM Phase II	1,861	Acute coronary syndromes	50, 75, 110, or 150 mg twice daily	Placebo	Not available	Not available

patient’s perceived health and quality of life, but this is true for both drugs.<sup>30</sup>

In today’s health care environment, controlling costs is a universal priority, but it may be unfair to compare the cost of dabigatran with that of warfarin alone. The expense and morbidity associated with stroke and intracranial bleeding are high, and if patients on dabigatran have fewer strokes (as seen in the RE-LY trial with dabigatran 150 mg twice a day) and no added expense of monitoring, then dabigatran may be cost-effective.

Freeman et al<sup>31</sup> analyzed the cost-effectiveness of dabigatran, using an estimated cost of \$13.70 per day and data from the RE-LY trial. They concluded that dabigatran may be a cost-effective alternative to warfarin in preventing ischemic stroke in patients considered at higher risk for ischemic stroke or intracranial hemorrhage, ie, those with a CHADS<sub>2</sub> score of 1 or higher or equivalent. (The CHADS<sub>2</sub> score is calculated as 1 point each for congestive heart failure, hypertension, age 75 or older, and diabetes mellitus; 2 points for prior

stroke or transient ischemic attack.)

As more new-generation oral anticoagulants become available (see below), the price of dabigatran will undoubtedly decrease. Until then, warfarin will remain a cost-effective and cost-saving drug that cannot yet be considered obsolete.

### ■ WHO SHOULD RECEIVE DABIGATRAN?

The ideal patient for dabigatran treatment is not yet defined. The decision to convert a patient's treatment from warfarin to dabigatran will likely depend on several factors, including the patient's response to warfarin and the physician's comfort with this new drug.

Many patients do extremely well with warfarin, requiring infrequent monitoring to maintain a therapeutic INR and having no bleeding complications. For them, it would be more practical to continue warfarin. Another reason for staying with warfarin would be if twice-a-day dosing would pose a problem.

Dabigatran would be a reasonable choice for a patient whose INR is erratic, who requires more frequent monitoring, for whom cost is not an issue, and for whom there is concern about dietary or drug interactions.

Another consideration is whether the patient has access to a health care facility for warfarin monitoring: this is difficult for those who cannot drive, who depend on others for transportation, and who live in rural areas.

Additionally, dabigatran may be a cost-effective alternative to warfarin for a patient with a high CHADS<sub>2</sub> score who is considered at a higher risk for stroke.<sup>31</sup>

In all cases, the option should be considered only after an open discussion with the patient about the risks and benefits of this new drug.

### ■ WHO SHOULD NOT RECEIVE IT?

Dabigatran is a twice-daily drug with a short half-life. No patient with a history of poor compliance will be a good candidate for dabigatran. Since there are no practical laboratory tests for monitoring compliance, one will have to reinforce at every visit the importance of taking this medication according to instructions.

TABLE 4

## Advantages and disadvantages of dabigatran

### Advantages

- Oral administration
- Predictable pharmacokinetics
- Rapid onset of action (0.5–2 hours)
- Does not require overlapping with a parenteral anticoagulant
- Efficacious and safe
- No monitoring required
- Does not cause heparin-induced thrombocytopenia
- Does not cause warfarin-induced skin necrosis

### Disadvantages

- Gastrointestinal intolerance (dyspepsia); taking with food may help with this side effect.
- Contraindicated in patients with creatinine clearance  $\leq$  15 mL/min or on dialysis; a dose reduction is recommended for patients with creatinine clearance 15 to 30 mL/min
- Use in pregnancy and the pediatric population is not known
- Drug interactions with rifampin and quinidine; dose adjustment is advised with amiodarone
- Twice-a-day dosing; therefore, compliance may be a concern
- No antidote and no evidence-based management plans for bleeding complications
- Cost

Patients with underlying kidney disease will need close monitoring of their creatinine clearance, with dose adjustment if renal function deteriorates.

Additionally, one should use caution when prescribing dabigatran to obese patients, pregnant women, or children until more is known about its use in these populations.

### ■ ADVANTAGES AND DISADVANTAGES OF DABIGATRAN

In addition to its pharmacologic advantages, dabigatran demonstrated two other major advantages over warfarin in the RE-LY trial in patients with atrial fibrillation (TABLE 4). First,

the rate of intracranial bleeding, a major devastating complication of warfarin, was 60% lower with dabigatran 150 mg twice a day than with warfarin—and lower still with dabigatran 110 mg twice a day.<sup>1</sup> Second, the rate of stroke or systemic embolism was 34% lower in the group that got dabigatran 150 mg twice a day than in the group that got warfarin.

A reason may be that patients with atrial fibrillation and poor INR control have higher rates of death, stroke, myocardial infarction, and major bleeding.<sup>14</sup> In most clinical trials, only 55% to 60% of patients achieve a therapeutic INR on warfarin, leaving them at risk of thrombosis or, conversely, bleeding.<sup>1,2,15,32</sup> Dabigatran has predictable pharmacokinetics, and its twice-daily dosing allows for less variability in its anticoagulant effect, making it more consistently therapeutic with less potential for bleeding or thrombosis.<sup>1</sup>

The Canadian Cardiovascular Society included dabigatran in its 2010 guidelines on atrial fibrillation, recommending it or warfarin.<sup>33</sup> The American College of Cardiology, the American Heart Association, and the Heart Rhythm Society now give dabigatran a class I B recommendation (benefit greater than risk, but limited populations studied) in secondary stroke prevention.<sup>34</sup>

On the other hand, major concerns are the lack of an antidote for dabigatran and a lack of experience in treating bleeding complications. Since dabigatran is not monitored, physicians may be uncertain if we are overdosing or undertreating. As we gain experience, we will learn how to treat bleeding complications. Until then, it will be important to anticipate this problem and to develop an algorithm based on the best available evidence in managing this complication.

Although the overall rates of bleeding in the RE-LY trial were lower with dabigatran than with warfarin, there were more gastrointestinal bleeding events with the 150-mg dose of dabigatran, which was not readily explained.

Further, the rate of dyspepsia was almost twice as high with dabigatran than with warfarin, regardless of the dose of dabigatran. There were also more dropouts in the 2nd year of follow-up in the dabigatran groups, with gastrointestinal intolerance being one of the major reasons. Therefore, dyspepsia may cause

intolerance and noncompliance.<sup>1</sup>

Dabigatran must be taken twice a day and has a relatively short half-life. For a noncompliant patient, missing one or two doses will cause a reversal of its anticoagulation effect, leaving the patient susceptible to thrombosis. In comparison, warfarin has a longer half-life and is taken once a day, so missing a dose is less likely to result in a similar reversal of its anticoagulant effect.

## ■ SPECIAL CONDITIONS

### Switching from other anticoagulants to dabigatran

When making the transition from a subcutaneously administered anticoagulant, ie, a low-molecular-weight heparin or the anti-Xa inhibitor fondaparinux (Arixtra), dabigatran should be started 0 to 2 hours before the next subcutaneous dose of the parenteral anticoagulant was to be given.<sup>21,35</sup>

When switching from unfractionated heparin given by continuous intravenous infusion, the first dose of dabigatran should be given at the time the infusion is stopped.

When switching from warfarin, dabigatran should be started once the patient's INR is less than 2.0.

### Switching from dabigatran to a parenteral anticoagulant

When switching from dabigatran back to a parenteral anticoagulant, allow 12 to 24 hours after the last dabigatran dose before starting the parenteral agent.<sup>21,35</sup>

### Elective surgery or invasive procedures

The manufacturer recommends stopping dabigatran 1 to 2 days before elective surgery for patients who have normal renal function and a low risk of bleeding, or 3 to 5 days before surgery for patients who have a creatinine clearance of 50 mL/min or less. Before major surgery or placement of a spinal or epidural catheter, the manufacturer recommends that dabigatran be held even longer.<sup>35</sup>

### If emergency surgery is needed

If emergency surgery is needed, the clinician must use his or her judgment as to the risks of bleeding vs those of postponing the surgery.<sup>21,35</sup>

**80% of dabigatran's excretion is via the kidneys; 20% is via the bile**

### Overdose or bleeding

No antidote for dabigatran is currently available. It has a short half-life (12–14 hours), and the treatment for overdose or bleeding is to discontinue it immediately, maintain adequate diuresis, and transfuse fresh-frozen plasma or red blood cells as indicated.

The role of activated charcoal given orally to reduce absorption is under evaluation, but the charcoal must be given within 1 to 2 hours after the overdose is taken.<sup>21</sup>

Dabigatran does not bind very much to plasma proteins and hence is dialyzable—an approach that may be necessary in cases of persistent or life-threatening bleeding.

Recombinant activated factor VII or prothrombin complex concentrates may be additional options in cases of severe bleeding.<sup>18,21</sup>

### TOPICS OF FUTURE RESEARCH

A limitation of the dabigatran trials was that they did not enroll patients who had renal or liver impairment, cancer, or other comorbidities; pregnant women; or children. Other topics of future research include its use in patients weighing less than 48 kg or more than 110 kg, its efficacy in patients with thrombophilia, in patients with mechanical heart valves, and in long-term follow-up and the use of thrombolytics in patients with acute stroke who are on dabigatran.

### WILL DABIGATRAN CHANGE CLINICAL PRACTICE?

Despite some of the challenges listed above, we believe that dabigatran is likely to change medical practice in patients requiring anticoagulation.

Dabigatran's biggest use will most likely be in patients with atrial fibrillation, mainly because this is the largest group of people receiving anticoagulation. In addition, the incidence of atrial fibrillation rises with age, the US population is living longer, and patients generally require life-long anticoagulation once this condition develops.

Dabigatran may be approved for additional indications in the near future. It has already shown efficacy in primary and secondary prevention of venous thromboembolism. Other

important areas to be studied include its use in patients with mechanical heart valves and thrombophilia.

Whether dabigatran will be a worthy substitute for the parenteral anticoagulants (heparin, low-molecular-weight heparins, or factor Xa inhibitors) is not yet known, but it will have an enormous impact on anticoagulation management if proved efficacious.

If dabigatran becomes a major substitute for warfarin, it will affect the anticoagulation clinics, with their well-trained staff, that are currently monitoring millions of patients in the United States. These clinics would no longer be needed, and laboratory and technical costs could be saved. A downside is that patients on dabigatran will not be as closely supervised and reminded to take their medication as patients on warfarin are now at these clinics. Instead, they will likely be supervised by their own physician (or assistants), who will need to become familiar with this anticoagulant. This may affect compliance with dabigatran.

### OTHER NEW ORAL ANTICOAGULANTS ARE ON THE WAY

Other oral anticoagulants, including rivaroxaban (Xarelto) and apixaban (Eliquis), have been under study and show promise in preventing both thrombotic stroke and venous thromboembolism. They will likely compete with dabigatran once they are approved.

Rivaroxaban, an oral direct factor Xa inhibitor, is being investigated for stroke prevention in patients with atrial fibrillation. It has also been shown to be not inferior to (and to be less expensive than) enoxaparin in treating and preventing venous thromboembolism in patients undergoing hip or knee arthroplasty.<sup>32,36,37</sup> Rivaroxaban has recently been approved by the FDA for this indication.

Apixaban, another direct factor Xa inhibitor, is also being studied for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. To date, there are no head-to-head trials comparing dabigatran with either of these new oral anticoagulants. ■

**Not needing anticoagulation clinics, patients on dabigatran will likely not be as closely supervised**

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