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ONLINE EXCLUSIVE

An anticoagulation option for nonvalvular atrial fibrillation

Patients with a risk of stroke—particularly those taking warfarin with poorly controlled INR—may be candidates for dabigatran.

Mazen H. Shaheen, MD; Pranab Das, MD; Santhosh K.G. Koshy, MD; Sunil K. Jha, MD; Rajesh Kabra, MD
Division of Cardiology, Department of Internal Medicine, University of Tennessee Health Sciences Center, Memphis

rkabra@uthsc.edu

Dr. Das reports that he is on the speakers' bureau of AstraZeneca. Dr. Kabra reports that he serves on the speakers' bureau of Boehringer Ingelheim. Drs. Shaheen, Koshy, and Jha reported no potential conflict of interest relevant to this article.

PRACTICE RECOMMENDATIONS

› *Consider dabigatran as an alternative to warfarin for patients with nonvalvular paroxysmal or permanent atrial fibrillation and risk factors for stroke.* (A)

› *Avoid using dabigatran with patients who have a creatinine clearance <15 mL/min, a prosthetic heart valve, or hemodynamically significant valve disease.* (C)

› *Withhold dabigatran for at least 24 hours before planned surgery, or for a longer time if there is renal insufficiency or the procedure is high risk.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

There are an estimated 2.3 million cases of atrial fibrillation (AF) in the United States, and that number may increase to 5.6 million by the year 2050.[1] The stasis of blood during AF, in addition to proinflammatory factors, predisposes patients to clot formation in the left atrium, especially in the left atrial appendage. In 5% of AF patients each year, such a thrombus dislodges and causes a stroke, a rate 2 to 7 times higher than that of people without AF.[1-3] Patients with paroxysmal or permanent AF have similar risks of stroke.[4]

Stratifying stroke risk aids in treatment decisions. Multiple criteria have been devised to identify AF patients at a higher risk of stroke. The $CHADS_2$ risk index, used extensively in clinical settings, stratifies risk according to a cumulative score based on a patient's risk factors (**TABLE 1**).[5] A joint 2006 guideline released by the American College of Cardiology, American Heart Association, and European Society of Cardiology,[1] and a separate 2008 guideline by the American College of Chest Physicians[6] recommend that patients with a $CHADS_2$ score of ≥2 be treated with a vitamin K antagonist such as warfarin, while patients with a score of 1 may be treated with either antiplatelet or anticoagulant therapy.

The evidence behind the guidelines. These guidelines are based on a number of randomized clinical trials that demonstrated the superiority of dose-adjusted warfarin in preventing stroke compared with placebo: Stroke Prevention in Atrial Fibrillation (SPAF), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Copenhagen Atrial Fibrillation Aspirin Anticoagulation (AFASAK), Canadian Atrial Fibrillation Anticoagulation (CAFA), Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF), and European Atrial Fibrillation Trial (EAFT).[7-12]

Further support for anticoagulant therapy. In a meta-analysis conducted after release of the guidelines, dose-adjusted warfarin was associated with a 62% risk reduction

TABLE 1

$CHADS_2$ score for stratifying risk of stroke in a patient with nonvalvular atrial fibrillation[5]

Risk factor	Score
CHF (reduced EF%)	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/TIA	2
TOTAL	
$CHADS_2$ score	Treatment considerations[1,19,20]
0	Withhold treatment, or give aspirin
1	Give an antiplatelet or anticoagulant
≥2	Give an oral anticoagulant such as warfarin, dabigatran, or rivaroxaban

$CHADS_2$, acronym comprising initial letters of risk factors listed; CHF, congestive heart failure; EF, ejection fraction; TIA, transient ischemic attack.

Regardless of the setting of anticoagulation management with warfarin, the INR was in the therapeutic range only 64% of the time.

for stroke vs placebo, and a 39% risk reduction vs antiplatelet agents.[13] For high-risk patients in the SPAF III trial, dose-adjusted warfarin led to a 76% risk reduction of stroke and systemic embolism compared with combination therapy of aspirin and low-intensity fixed-dose warfarin.[14] The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial was stopped prematurely when it demonstrated that, in patients with AF who have one or more risk factors for stroke, warfarin was superior to the combination of aspirin and clopidogrel in preventing a combined end point of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death; secondary outcomes of stroke were also more favorable with warfarin.[15] The results of all 3 studies were noted during a follow-up of 1 to 2 years. In clinical practice, patients must continue antithrombotic agents for a much longer period.

Disadvantages of long-term warfarin use. The main drawback of warfarin therapy is the need for frequent laboratory monitoring. It also interacts unfavorably with other drugs and with certain foods. These factors often lead to patient discontinuation of therapy or to inadequate anticoagulation even when patients are compliant.[16] A meta-analysis of 67 clinical studies showed that, regardless of the setting of anticoagulation management with warfarin, the international normalization ratio (INR) was in the therapeutic range only 64% of the time.[17] These issues with warfarin have increased interest in developing novel oral anticoagulants that have better drug profiles. An oral direct thrombin inhibitor, ximelagatran, was shown to be as effective as warfarin in the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) V trial,[18] but it was associated with hepatotoxicity and did not receive US Food and Drug Administration (FDA) approval.

However, another thrombin inhibitor, dabigatran, was approved by the FDA for anticoagulation in nonvalvular AF, and has been incorporated into the ACCF/AHA/HRS guidelines as a therapeutic option.[19] Since this article was submitted for publication, rivaroxaban, an oral factor Xa inhibitor, was approved by the FDA for anticoagulation in AF, based on results of the study Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF).[20]

Dabigatran as an option for nonvalvular AF

Dabigatran's approval was based on the clinical outcomes of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.[21] This multicenter randomized noninferiority trial compared warfarin with 2 doses of dabigatran (110 and 150 mg twice daily) in patients who had AF and a risk of stroke. A total of 18,113 patients with AF, a mean age of 71 years, and a mean $CHADS_2$ score of 2.1 were randomly assigned in a blinded fashion to receive one of the

dabigatran doses or, in nonblinded fashion, warfarin. The primary outcome was stroke or systemic embolism. The primary safety outcome was major bleeding defined as a reduction in the hemoglobin level of at least 20 g/L, a need for transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. The mean follow-up period was 2 years.

The study showed that 110 mg dabigatran twice daily was statistically not inferior to warfarin in preventing stroke and systemic embolism (1.53% vs 1.69% per year; *P*<.001). In addition, this dose was associated with statistically lower rates of major bleeding (2.71% vs 3.36% per year; *P*=.003). However, dabigatran 150 mg twice daily was statistically superior to warfarin in reducing the risk of stroke and systemic embolism by 34% per year (1.11% vs 1.69%; *P*<.001) with rates of major bleeding similar to warfarin (3.11% vs 3.36% per year; *P*=.31). The beneficial effect of dabigatran was also seen in patients with higher $CHADS_2$ scores of 3 to 6, who comprised one-third of the study population and were at higher risk of stroke. Interestingly, both doses of dabigatran were associated with lower rates of intracranial hemorrhage than was warfarin. The 110-mg dose of dabigatran, however, was not approved by the FDA.

A higher incidence of myocardial infarction (MI) occurred in the dabigatran group compared with warfarin, but it was not statistically significant.[21,22] A recent meta-analysis of 7 randomized controlled trials, including RE-LY, found that dabigatran was significantly associated with a higher incidence of MI or acute coronary syndrome compared with heterogeneous control groups receiving placebo, warfarin, or enoxaparin (1.19% vs 0.79%, odds ratio, 1.33; *P*=.03).[23]

The exact reason for the difference is unknown. It may be due to a chance effect, given that the absolute number of events was small. Or warfarin may exert a protective effect against MI, as was seen in the WARIS II study, wherein warfarin, given alone or in combination with aspirin, was superior to aspirin in reducing the risk of reinfarction.[24] However, a true adverse effect of dabigatran cannot be ruled out. If it proves to be the case, 2 more cases of MI can be expected to occur in 1000 patients treated with dabigatran, compared with warfarin, at 1 year.

In addition, there was a statistically significant higher incidence of major gastrointestinal hemorrhage with dabigatran 150 mg twice daily compared with warfarin. Most of these bleeding events occurred in the lower gastrointestinal tract. Here, too, the exact reason for the difference is unknown.

How dabigatran prevents thrombus formation

Dabigatran directly and competitively inhibits both free and fibrin-bound thrombin, thereby preventing thrombin-mediated effects on the coagulation cascade, including cleavage of fibrinogen to fibrin, activation of factors V, VIII, XI, and XII, and thrombin-induced platelet aggregation.[25-28]

The drug's pharmacokinetic profile. Dabigatran is given as a prodrug, dabigatran etexilate. Serum esterase converts it to its active form. Peak concentration is reached within 2 to 3 hours of oral dosing, and its half-life is 12 to 17 hours. It is taken twice daily, mornings and evenings. The drug is excreted unchanged, primarily by the kidneys (~80%); the remainder is metabolized by the liver. Therefore, dabigatran is contraindicated in patients with severe renal dysfunction (creatinine clearance <15 mL/min). Compared with warfarin, dabigatran has a more predictable anticoagulant function, no need for laboratory monitoring, and less interaction with other drugs and foods (**TABLE 2**).[29-32] No data are available regarding heterogenous genetic response to dabigatran.

Cost-effectiveness of dabigatran

The prescription cost of dabigatran is a lot higher than warfarin, although a recent study demonstrated its cost-effectiveness through a reduction in the need for laboratory monitoring and decreased complications due to over- and under-anticoagulation.[33]

Factors that come into play

Dabigatran is an alternative to warfarin for long-term anticoagulation in patients with nonvalvular AF who are at a higher risk of stroke with a $CHADS_2$ score of ≥1 or systemic thromboembolism.[18] While the main benefits of dabi-

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TABLE 2

How warfarin and dabigatran compare pharmacologically[29-32]

Attribute	Warfarin	Dabigatran
Administration	Oral	Oral
Mechanism of action	Inhibition of vitamin-K-dependent coagulation factors (II, VII, IX, X, and protein C and S)	Inhibition of thrombin
Oral bioavailability	100%	6.5%
Half-life	20-60 hours	12-17 hours
Metabolism	Hepatic	Renal (80%)
Time to onset	24-72 hours	1-2 hours
Protein binding	99%	35%
Antagonist	Vitamin K	None
Laboratory monitoring	Required	None required
Dose adjustment	Required for each individual	Reduction only for creatinine clearance of 15-30 mL/min
Interaction with diet	Interacts with foods rich in vitamin K (eg, cabbage, spinach)	No interaction with foods rich in vitamin K
Interaction with drugs	Interacts with amiodarone, antifungals, antibiotics, and alcohol, which may require dose adjustments of either warfarin or the concomitant agent	Dose adjustment of dabigatran may be required with ketoconazole and dronedarone

The choice of anticoagulant depends on a patient's preference and ability to comply with a twice-daily dosing regimen, availability of INR monitoring, and cost of treatment.

gatran are a quick onset of action, no need for laboratory monitoring, rare interactions with drugs and food, and a decrease in intracranial bleeding compared with warfarin, it did cause more gastrointestinal adverse effects, including bleeding, than warfarin in the RE-LY trial.

Dabigitran was also associated with a higher incidence of MI in RE-LY and an increased risk of MI or acute coronary syndrome in the meta-analysis, but the absolute risk increase in both cases was very small.[21-23] Thus, for many patients, the choice of anticoagulant depends on individual preference and ability to comply with a twice-daily dosing regimen, availability of INR monitoring, and cost of treatment.[34]

Patients who should not receive dabigatran

Dabigatran is contraindicated for patients with a creatinine clearance <15 mL/min, a prosthetic valve, significant valve disease, a history of serious allergic reaction to the drug, or a high risk of bleeding (eg, from recurrent falls, bleeding peptic ulcer).[35]

Initiating dabigatran therapy

Start dabigatran at a dose of 150 mg twice daily if the creatinine clearance is >30 mL/min, or at 75 mg twice daily if creatinine clearance is 15 to 30 mL/min. In switching a patient from parenteral anticoagulation, you may start dabigatran ≤2 hours before the next scheduled dose of the parenteral agent (eg, low-molecular-weight heparin) or the termination of a continuously administered agent (eg, unfractionated heparin). For patients taking warfarin, withhold dabigatran until the INR is <2.[29]

Thrombin time is the most reliable measure of drug effect

Dabigatran has a variable and unpredictable effect on the INR, which should not be used to measure the drug's anticoagulation

TABLE 3

Recommendations for withholding dabigatran before elective surgery[29]

Renal function (creatinine clearance), mL/min	Estimated half-life (range), h	Discontinue dabigatran before surgery	
		High risk of bleeding*	Standard risk
>50-80	~15 (12-17)	2-3 days before	24 hours before (2 doses)
30-50	~18 (18-24)	4 days before	At least 2 days (48 hours) before
<30	~27 (>24)	>5 days before	2-5 days before

*Surgeries that confer a high risk of bleeding include, but are not limited to, cardiac surgery, neurosurgery, abdominal surgery, or procedures involving a major organ. Procedures involving spinal anesthesia or spinal tap may also be considered as having a high risk of bleeding.

effect. While therapeutic concentrations modestly elevate the INR, there have been some reports of significant INR elevation.[29] However, lab results with the ecarin clotting test (ECT) or thrombin time (TT) correlate well with dabigatran serum concentrations. ECT is primarily a research tool and not commonly available in hospitals; TT, however, is readily available. Activated partial thromboplastin time (aPTT), also commonly available, is prolonged in a nonlinear fashion with dabigatran use. None of these tests has been systematically studied and correlated with clinical outcomes of dabigatran use.[29]

Adverse effects to watch for

In the RE-LY study, dyspepsia was the most commonly reported adverse effect of dabigatran (11%).[21] As with warfarin, other adverse effects, such as dizziness, dyspnea, and fatigue, were reported for dabigatran. Unlike ximelgatran, there is no significant effect on liver enzymes. There is, however, a risk of major and minor bleeding complications.

Bleeding with dabigatran. In the event of a bleeding complication, discontinue dabigatran. There is no specific antidote for this drug; supportive therapy relies on surgical intervention and transfusion of fresh frozen plasma and packed cells. Maintaining adequate diuresis may enhance elimination of the drug. Given dabigatran's low protein-binding potential, dialysis may be considered; however, data supporting this treatment decision are limited.[29]

Patients taking dual antiplatelet agents are at a higher risk of bleeding if they also receive either dabigatran or warfarin, although it is not known if one anticoagulant confers a higher risk than the other. In such patients, carefully weigh the risk of bleeding against the benefits of stroke prevention.

Discontinue dabigatran before surgery

Withhold dabigatran from patients scheduled for elective surgery (**TABLE 3**).[29] For those with a high risk of bleeding, measure TT 6 to 12 hours before the procedure to ensure normalization of the value. An acceptable alternative measure, although less precise, is the aPTT. For emergency procedures, fresh frozen plasma may be used to acutely reverse the drug's effect. JFP

CORRESPONDENCE
Rajesh Kabra, MD, University of Tennessee Health Sciences Center, 1325 Eastmoreland Avenue, Suite 460, Memphis, TN 38104; rkabra@uthsc.edu

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