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# Time to try this warfarin alternative?

## Dabigatran appears to be as effective as warfarin in preventing stroke and thromboembolism in patients with atrial fibrillation—and is easier to use.

**PRACTICE CHANGER**

Consider dabigatran, an oral anticoagulant that does not require monitoring, for the prevention of stroke and thromboembolism in patients with atrial fibrillation.[1]

**STRENGTH OF RECOMMENDATION**

**B:** Based on a single well-done randomized controlled trial (RCT).

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-1151.

**ILLUSTRATIVE CASE**

A 75-year-old man with persistent atrial fibrillation and diabetes comes to your office for a check of his international normalized ratio (INR). It has been hard to keep his INR within the normal range of 2 to 3 in recent months, and today is no different: The patient's INR is 1.7, although he insists he has been compliant with his warfarin regimen and has had no change in diet or other medications. What other anticoagulation options can you offer him?

Patients with atrial fibrillation have a 3% to 8% annual risk of stroke.[2] Both adjusted-dose warfarin and antiplatelet agents such as aspirin have been shown to be effective at reducing this risk, although warfarin is significantly more effective.[3]

Those who have atrial fibrillation and a previous history of thromboembolism or rheumatic mitral stenosis or more than one moderate risk factor (age ≥75 years, hypertension, heart failure, impaired left ventricular systolic function, or diabetes) have the highest stroke risk. The American College of Cardiology/American Heart Association Task Force/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for the management of atrial fibrillation recommend chronic anticoagulation with an oral vitamin K antagonist, such as warfarin, for these high-risk patients.[4]

### Warfarin therapy is challenging

We have all experienced the frustrations of maintaining our patients on warfarin at a therapeutic INR; the average patient is within this range only about 67% of the time, although this varies dramatically from patient to patient.[5] Many of our patients have experienced the inconvenience and cost of repeated monitoring, as well as the morbidity associated with both major and minor bleeding related to warfarin use. And there are many potential interactions between warfarin and foods or other drugs.

### Is the new oral anticoagulant a better bet?

There are anticoagulants that do not require monitoring (eg, enoxaparin), but few patients are willing to undergo daily subcutaneous injections, and the cost is often prohibitive. Now there is another alternative.

Dabigatran (Pradaxa), an oral direct thrombin inhibitor, was approved by the US Food and Drug Administration in October 2010 for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[6] Dabigatran is administered

twice daily in a fixed dose. Because it has a relatively short half-life (12-17 hours), it does not require INR monitoring. Dabigatran has no known interactions with foods and minimal interactions with other medications. Its value as a warfarin alternative for patients with atrial fibrillation was addressed in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study detailed below.

## STUDY SUMMARY

### At higher dose, dabigatran prevents more strokes than warfarin

RE-LY included 18,113 patients from 951 facilities in 44 countries. To be eligible for the study, patients had to have atrial fibrillation documented on an electrocardiogram and at least one additional risk factor for stroke.

Participants were randomized into one of 3 groups: dabigatran 110 mg twice daily, dabigatran 150 mg twice daily (both administered in a blinded fashion), or warfarin (administered in an unblinded fashion and dosed to maintain an INR between 2 and 3). Baseline characteristics, such as age, sex, and $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, prior stroke) score, were similar across all 3 groups. The median duration of follow-up was 2 years, and complete follow-up occurred in 99.9% of participants.

The primary outcome of the study was stroke or systemic embolism. The primary safety outcome was major hemorrhage, defined as a reduction in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area/organ. Other outcomes were death, myocardial infarction (MI), pulmonary embolism, transient ischemic attack, and hospitalization.

For the primary outcome of prevention of stroke or systemic embolism, the 150-mg dose of dabigatran was superior to warfarin (1.11% vs 1.69% per year, relative risk [RR], 0.66; 95% confidence interval [CI], 0.53-0.82; *P*<.001 for superiority). The major bleeding rates were similar for dabigatran 150 mg and warfarin, although major gastrointestinal bleeding rates were significantly higher with this dose of dabigatran compared with warfarin (**TABLE**). Minor bleeding was more common in the warfarin group (16.37% vs 14.84%; RR, 0.91; 95% CI, 0.85-0.97; *P*=.005).

The 110-mg dose of dabigatran (which is not available in the United States) was neither inferior nor superior to warfarin for the prevention of stroke or systemic embolism. This dose of dabigatran had a lower risk of major bleeding compared with warfarin.

### Mortality rates are similar

Rates of death from any cause were similar among the 3 treatment groups. The rates of hemorrhagic stroke were lower in both dabigatran groups compared with the warfarin group, while rates of MI were lower in the warfarin group than in either of the dabigatran groups.

Dyspepsia was the only other adverse effect that was significantly more common among dabigatran users vs warfarin users. Rates of hepatotoxicity, which was a problem with earlier oral direct thrombin inhibitors, were similar for both drugs. Multiple subgroup analyses revealed no significant interaction between the treatment effect of dabigatran and variables such as sex, body mass index, creatinine clearance, $CHADS_2$ score, aspirin use, or previous long-term use of a vitamin K antagonist.

**On average, patients on warfarin are within a therapeutic range only 67% of the time.**

## WHAT'S NEW

### This easier-to-use oral anticoagulant is a viable option

Dabigatran gives physicians and patients with atrial fibrillation an option that is more convenient than warfarin for stroke prevention. Its 150-mg dose is more effective in preventing stroke compared with warfarin, and comparable in terms of bleeding risk.

## CAVEATS

### Unknown long-term effects, potential for bias

The median follow-up in the RE-LY study was 2 years. Longer-term efficacy and safety data may differ from the initial results.

The trial was funded by Boehringer Ingelheim, the manufacturer of dabigatran (Pradaxa). However, study coordination, data management, and analysis were performed independently by the Population Health Research Institute, McMaster University and Hamilton

**TABLE**

## Dabigatran vs warfarin: A look at the evidence[1]

| Event | Incidence (%/y) | | NNT/NNH with dabigatran instead of warfarin | Relative risk (95% CI) | *P* value |
|---|---|---|---|---|---|
| | Dabigatran (150 mg) | Warfarin | | | |
| Stroke or systemic embolism | 1.11 | 1.69 | NNT: 173 | 0.66 (0.53-0.82) | <.001*<br><.001 |
| Hemorrhagic stroke | 0.10 | 0.38 | NNT: 477 | 0.26 (0.14-0.49) | <.001 |
| MI | 0.74 | 0.53 | NNH: 477 | 1.38 (1.00-1.91) | .048 |
| Death from any cause | 3.64 | 4.13 | NS | 0.88 (0.77-1.00) | .051 |
| Major bleeding | 3.11 | 3.36 | NS | 0.93 (0.81-1.07) | .31 |
| Intracranial bleeding | 0.30 | 0.74 | NNT: 228 | 0.40 (0.27-0.60) | <.001 |
| GI bleeding | 1.51 | 1.02 | NNH: 205 | 1.50 (1.19-1.89) | <.001 |
| Life-threatening bleeding | 1.45 | 1.80 | NNT: 286 | 0.81 (0.66-0.99) | .04 |

CI, confidence interval; GI, gastrointestinal; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NS, no significant difference.
**P* value for noninferiority; all other *P* values are for superiority.

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Patients taking dabigatran received the medication in a blinded fashion, but the warfarin group could not be blinded because of the need for INR monitoring and dosage adjustments. To decrease potential bias, the outcome events were assessed by 2 independent investigators who were blinded to the treatment assignments.

### CHALLENGES TO IMPLEMENTATION

#### Cost of dabigatran may be a barrier

The wholesale price of dabigatran, as quoted by Boehringer Ingelheim, is $6.75 per day; the retail price for a 30-day supply is approximately $235, according to drugstore.com, Walgreens, and Walmart). In comparison, a one-month supply of warfarin is about $15. Out-of-pocket costs for many patients will likely be high until dabigatran is added to insurers' formularies. When costs for monitoring and hospitalizations or treatment for complications associated with warfarin are factored in, however, dabigatran is cost effective, a recent study indicates.[7] **JFP**

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