

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

A large trial suggests dabigatran's noninferiority to warfarin in preventing strokes, but many questions remain to be answered.

Antithrombotic therapy with the oral anticoagulant warfarin is a well-established, reasonably safe, effective way to significantly reduce risk for embolic stroke in patients with atrial fibrillation. However, the therapy increases the risk for major intracranial hemorrhage and internal hemorrhage. It is currently cumbersome, requiring frequent blood tests and dose adjustments. Even under the best conditions, patients with atrial fibrillation receiving warfarin are sometimes out of the therapeutic range (international normalized ratio [INR], 2–3).

The direct thrombin inhibitor dabigatran etexilate, currently available in Europe and Canada, is a potential alternative to warfarin. Researchers conducted this large, manufacturer-supported, randomized trial to test dabigatran for noninferiority to warfarin (target INR, 2–3) in 18,113 patients with atrial fibrillation. The primary outcome was stroke (defined as "the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified") or systemic embolism. The primary safety outcome was major bleeding, defined as a 20 g per liter or greater reduction in hemoglobin level, a 2-unit transfusion, or symptomatic bleeding in a vital organ or area. Median follow-up was 2 years.

Two doses of dabigatran (110 mg and 150 mg, twice daily) were tested and found to be noninferior to warfarin for the primary outcome; the 150-mg dose was slightly but significantly superior to warfarin (relative risk, 0.66). The rate of major bleeding with the 150-mg dose (3.11% per year) was not significantly different from that with warfarin (3.36% per year) and was somewhat higher than with the 110 mg dose (2.71% per year).

Comment: This was a well designed and executed study conducted by experts in the field. Nonetheless, the study raises two basic questions.

First, the precision of diagnosis of endpoints must be considered in a study with 18,113 participants from 951 centers in 44 countries. The primary endpoints of this trial included stroke (presumably ischemic), intracranial hemorrhage (including intracerebral hemorrhage, subdural hematoma, and subarachnoid hemorrhage), and uncertain type of stroke. Because we do not know many patients with clinically suspected stroke endpoints did *not* have a CT scan, the ischemic stroke subtypes and the actual number

and subtypes of hemorrhagic strokes cannot be determined precisely. Were there major hemorrhages, particularly intracerebral hemorrhages, that were not counted as such? The actual number of intracranial hemorrhages is therefore brought into question. The second question regards the long-term safety of dabigatran. Although the number of patient years studied is probably enough to answer basic questions, for assessing toxicity, the follow-up duration for each patient was short (≤ 2 years). Long-term follow-up is lacking. The ease of administering dabigatran has great appeal, but research is needed to determine the precise effect dabigatran has on thrombin generation and activity. Were some patients resistant to the thrombin-inhibition effect of dabigatran? Were they the ones more likely to have ischemic stroke? Were some patients overly sensitive to dabigatran, and were these the patients with intracranial hemorrhage? Two obvious areas of further study are as follows: First, the actual effect of warfarin on the level of thrombin circulating at a given time can be estimated (*Stroke* 1993; 24:1360 and *Neurology* 2004; 63:777). Is there a similar measurement for dabigatran (e.g., measurement of prothrombin time)? Second, the study results suggest a possible stroke protective benefit of 150 mg of dabigatran versus warfarin. Thus a smaller, more-precise safety/efficacy trial of dabigatran (150 mg) versus warfarin (INR 2–3) may be possible and could offer the opportunity to study the direct effects of both antithrombotic therapies as well as the longer-term toxicity of dabigatran (*Stroke* 1993; 24:1360 and *Neurology* 2004; 63:777). Most importantly, it would provide some confirmatory evidence of the beneficial effect of dabigatran noted in this trial.

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