Reducing Stroke Rates in Patients With Atrial Fibrillation
How Low Can We Go?

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Strokes related to atrial fibrillation tend to be large, life-threatening, and disabling. Multiple factors have synergistically led, over the past 20 years, to an impressive reduction in atrial fibrillation–related stroke rates. Comparisons of these rates between studies are estimates because definitions of stroke and primary end points among trials differ. However, patients assigned to placebo or usual therapy from clinical trials conducted in the late 1980s and early 1990s found approximate rates for patients with the equivalent of a CHADS2 score (an acronym for congestive heart failure, hypertension, age ≥75, diabetes mellitus, and prior stroke or transient ischemic attack) of 2 of 6% to 8%.1,2 A CHADS2 score of 2 is the approximate stroke risk of patients entered in current trials, including A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Attrial Flutter (ATHENA).3 Anticoagulation with vitamin K antagonists has been the major contributor to the declining event rates; compared with placebo, vitamin K antagonists have reduced rates from 67% to 86% in completed trials, which translates into stroke rates of ≈1.4%/y.4,5 Novel anticoagulants designed to overcome the limitations of warfarin have been evaluated recently and have attained rates comparable to or slightly lower than coumadin, but at the price of either an increased incidence in major bleeding6 or liver toxicity.7,8 In a recent trial of elderly subjects with atrial fibrillation, warfarin was superior to aspirin,9 and in patients at intermediate to high risk for stroke, warfarin was superior to the combination of aspirin and clopidogrel with similar bleed rates.10 Thus, for time being, warfarin remains the only effective orally administered anticoagulant available.

Article see p 1174

Many patients with atrial fibrillation have comorbidities associated with an increased stroke risk found in patients both with and without atrial fibrillation. These are hypertension, hypercholesterolemia, diabetes mellitus, and systolic heart failure. Although statins are indicated in patients with hypercholesterolemia, hypercholesterolemia is not as clearly associated with stroke as it is with myocardial infarction.11 However, stroke reduction with statins is consistent. The reduction in stroke rates in patients treated with statins was identified in a subgroup analysis from the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial12 and was independent of the lipid-modifying effect. The reduction in stroke rate, the primary end point, was definitively shown in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.13 Better control of blood pressure has also contributed by reducing both ischemic strokes and intracerebral bleeds.14–16 In patients with heart failure in sinus rhythm, stroke rates were lower in warfarin-assigned patients than in those receiving aspirin (0.6% versus 2.3%; P = 0.016) and clopidogrel (0.6% versus 2.3%; P = 0.016), but at a risk of increased intracerebral bleeding in warfarin-assigned patients versus those taking clopidogrel (P = 0.063).17

In patients with atrial fibrillation, the driver to maintain sinus rhythm is the reduction of symptoms and improvement of quality of life.18 None of the studies thus far that have tested the strategies of rate control and anticoagulation against rhythm control have influenced stroke rates. Antiarrhythmic agents, although effective for maintenance of sinus rhythm, have always been associated with limiting side effects.19 ATHENA, however, has convincingly demonstrated that cardiovascular outcomes in patients with AF randomized to dronedarone, a complex multichannel blocking agent, reduced hospitalizations and deaths.3 A posthoc analysis published by the ATHENA investigators in this issue of Circulation raises, for the first time, the important concept that a predominantly antiarrhythmic agent may reduce strokes in patients with atrial fibrillation, some of whom were also protected by concomitant anticoagulants or antiplatelet agent, to stroke rates of 1.2%/y compared with 1.8%/y in the placebo group.20 The authors were careful to report the limitations of their study. The strokes were not adjudicated; the analysis was posthoc; and there was no clear demonstration of mechanism. The presumed, but unproven, mechanism was a reduction in atrial fibrillation burden, an interesting new and evolving marker of stroke risk in patients with atrial fibrillation.21 It is also possible that the antihypertensive effect of dronedarone may play a role in stroke reduction, but in ATHENA, the difference in blood pressure was relatively small. Dronedarone also appears to be anti-ischemic with respect to coronary events and may have pleiotropic mechanisms, yet to be identified, similar to the neuroprotective effect of statins.22 The electropharmacological profile of dronedarone is similar to that of amiodarone but with modifications to eliminate the adverse effects on the thyroid. Inhibition of slow L-type calcium currents, sodium currents, and potassium currents (Ica, If, IKach, and Ik1) by dronedarone has been demonstrated in isolated cardiomyocytes.23 It is not known whether dronedarone has antithrombotic properties. Thus, this

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.109.893438
report, although highly suggestive of a “stroke prevention” role of dronedarone, does not provide definitive proof. The report on stroke reduction attributable to dronedarone is particularly timely because, very important stroke prevention trials in patients with atrial fibrillation involving novel anticoagulants are being completed and reported. These trials are designed to demonstrate noninferiority to the comparator warfarin at an international normalized ratio of 2 to 3. It is entirely possible that the use of a drug such as dronedarone in concert with a predictable anticoagulant such as dabigatran, might reduce stroke rates to levels that are beyond reach currently. ATHENA will become a classic. With the advent of newer anticoagulants and antiarrhythmics such as dronedarone, the tantalizing question is whether stroke rates in atrial fibrillation will get so low that they equal the risk of stroke in patients without atrial fibrillation.

### Note Added In Proof

The RE-LY trial was recently published.24 Dabigatran etexilate in two doses, 150 mg and 110 mg BID, was compared to warfarin at an INR of 2.0–3.0. The stroke rates were 1.11, 1.53 and 1.69 %/year respectively. For the 150 mg BID dose which included 6076 patients followed for a median of 2 years, the event rate was very low, testing the highly speculative goal of the editorial. Remarkably, this was achieved without an increase in major bleeding in comparison to warfarin.

### Disclosures

Dr Ezekowitz has received grant support from Boehringer Ingelheim, ARYx Therapeutics, and PORTOLA and has served as a consultant for Boehringer Ingelheim, ARYx Therapeutics, Sanofi, Bristol Myers, PORTOLA, AstraZeneca, Daichi Sanko, and Medtronic. The other authors report no conflicts.

### References

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Circulation. 2009;120:1169-1170; originally published online September 14, 2009; doi: 10.1161/CIRCULATIONAHA.109.893438
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/13/1169

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