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 8%. 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/Atrial Flutter (ATHENA). 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. 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 bleeding or liver toxicity. In a recent trial of elderly subjects with atrial fibrillation, warfarin was superior to aspirin and clopidogrel (0.6% versus 2.3%; P = 0.016) and compared with placebo, 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. 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. 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 (I_{Kr}, I_{Ks}, I_{KAC}, and I_{Km}) by dronedarone has been demonstrated in isolated cardiomyocytes. It is not known whether dronedarone has antithrombotic properties. Thus, this
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 with 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

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References


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