Warfarin Best for Stroke Prevention, Trial Shows

The medicine was superior only in patients in whom anticoagulation intensity was optimally maintained.

BY BRUCE JANCIN
Denver Bureau

DALLAS — Oral anticoagulation with warfarin proved superior to clopidogrel plus aspirin for prevention of stroke and other vascular events in patients with atrial fibrillation in the massive Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events, Dr. Stuart J. Connolly said at the annual scientific sessions of the American Heart Association.

Warfarin remains the most effective available therapy for this purpose, and the standard of care, despite its well-documented shortcomings.

But ACTIVE-W contained a large caveat: Warfarin's superiority was restricted to patients in whom anticoagulation intensity was optimally maintained. Patients on warfarin whose International Normalized Ratio (INR) values fell outside the therapeutic range more than 35% of the time did no better than those on clopidogrel plus aspirin in terms of vascular event rates, and they actually did worse from the standpoint of major bleeding, added Dr. Connolly, professor of medicine and director of the division of cardiology at McMaster University, Hamilton, Ont.

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ACTIVE-W involved 6,706 patients with atrial fibrillation (AF) and an average of two additional stroke risk factors. The patients were treated at 522 centers in 31 countries. Overall, 77% were on warfarin at entry. Participants were randomized to warfarin or to 75 mg/day of clopidogrel plus 75-100 mg/day of aspirin.

The hypothesis was that dual antiplatelet therapy would provide an easy-to-use alternative with efficacy similar to that of warfarin. The rationale for this belief lay in the well-established efficacy of clopidogrel plus aspirin in patients with MI or acute coronary syndromes as well as in percutaneous interventions—all situations in which arterial clot figures prominently.

But ACTIVE-W was halted a quarter of the way through when investigators determined that the rate of the primary combined end point—stroke, non-CNS systemic embolism, MI, and/or vascular death—was 5.64%/year with clopidogrel plus aspirin, a 47% relative increase over the 3.93%/year rate with warfarin.

The investigators had anticipated major bleeding would be significantly less with clopidogrel plus aspirin. Not so. The rate was 2.2%/year, compared with 2.4%/year with warfarin.

Control of anticoagulation intensity was excellent, with nearly two-thirds of patients on warfarin having INRs consistently within the therapeutic range of 2-3. They proved 80% less likely to experience a primary end point than those assigned to clopidogrel plus aspirin. In contrast, patients whose INR values were outside the target range more than 35% of the time had a primary event rate similar to and a major hemorrhage rate higher than that in the antiplatelet therapy group.

Discussant Dr. Jonathan Halperin called the study "convincing" and observed that "for those seeking treatment easier to manage than chronic anticoagulation, the ACTIVE-W results may seem like another in a series of disappointments."

But the study also provides important insights into principles of antithrombotic therapy. For example, a secondary analysis showed that warfarin-naive enrollees randomized to the drug had a much greater risk of adverse outcomes and stood to gain more from alternative therapy than did patients who entered the trial already on warfarin, said Dr. Halperin, professor of medicine at Mount Sinai School of Medicine, New York.

ACTIVE-W also underscored a key point: "Patients don't get the benefit of warfarin just from taking the tablet. Its effectiveness depends on how well it's managed," he said. "Maintaining anticoagulant intensity within a relatively narrow therapeutic range is no easy feat, especially since the typical elderly patient with AF is taking nearly a dozen prescribed drugs."

Help for physicians and patients frustrated with warfarin may be on the way. Many novel antithrombotic agents will enter phase II or phase III trials for AF in 2006, including the oral direct thrombin inhibitor dabigatran, the indirect thrombin inhibitor odiparcil, and idraparinux, a once-weekly injectable selective factor Xa inhibitor.

The two sister studies to ACTIVE-W remain ongoing and should provide answers to key clinical questions. The 7,500-patient ACTIVE-A trial will show whether clopidogrel plus aspirin is superior to aspirin alone in AF patients unable or unwilling to take warfarin. Aspirin has been shown to reduce stroke risk by about 20%, compared with placebo in high-risk patients, while warfarin reduces the risk by more than 60%.

The ACTIVE-I trial is a 3-year, 9,000-patient study randomizing patients to irbesartan or placebo. It tests the hypothesis that inhibition of the renin-angiotensin-aldosterone system will reduce stroke risk in patients with AF, Dr. Halperin noted.

The ACTIVE clinical trials are sponsored by Sanofi-Aventis and Bristol-Myers Squibb. ■

Ablation Plus Amiodarone Prevents Recurrent Atrial Fib

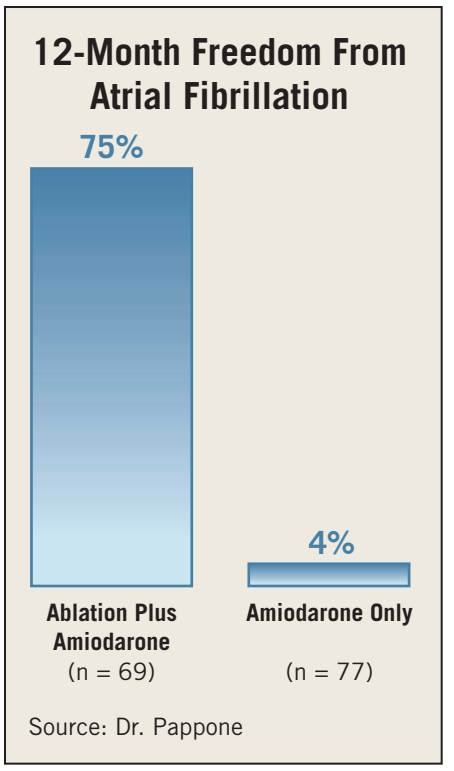
BOSTON — Catheter ablation plus amiodarone therapy was substantially better than amiodarone treatment alone for preventing recurrent atrial fibrillation during 1 year of follow-up in a randomized, controlled study with 146 patients.

"This is the first illustration in a randomized study that patients with chronic atrial fibrillation can be kept in sinus rhythm," Dr. Carlo Pappone said at an international symposium on atrial fibrillation sponsored by Massachusetts General Hospital.

The study enrolled patients with chronic atrial fibrillation for more than 6 months. Their average age was 56, and about 23% of patients had structural heart disease, most commonly nonischemic cardiomyopathy. Their average left ventricular ejection fraction was 55%, and the average duration of atrial fibrillation was more than 4 years. All patients had failed prior therapy with an average of two antiarrhythmic drugs.

A total of 69 patients were randomized to circumferential pulmonary vein ablation (PVA) using radiofrequency followed by daily treatment with amiodarone for 3 months, and 77 patients were randominzed to amiodarone only.

Patients were then followed in a blinded manner by daily, transtelephonic monitoring. During 1 year of follow-up, 75% of patients treated with PVA remained free of episodes of atrial fibrillation, compared with 4% of the control group, said Dr. Pappone, director of the division of arrhythmology at San Raffaele Hospital in Milan.



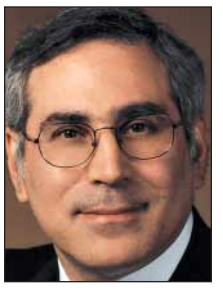
Dr. Pappone's group at San Raffaele used catheter ablation to treat more than 9,000 patients starting in the 1990s. The rate of major complications was 0.4%, with no deaths. But the outcomes varied from center to center, Dr. Pappone said at the conference, also sponsored by the Academy of Health Care Education.

—Mitchel L. Zoler

Ablation Called Sole Second-Line Treatment for Atrial Fibrillation

BOSTON — Catheter ablation for atrial fibrillation has been set as the sole second-line therapy for all patients in the treatment guidelines scheduled to be released later this year by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology.

By the new guidelines, patients have to fail only one drug before they become eligible for catheter ablation. This recommendation applies to all patients with atrial fibrillation, including those with concurrent heart failure, coronary artery disease, or hypertension, said Dr. Eric Prystowsky, a member of the guideline-writing committee, at an international symposium on atrial fibrillation sponsored by Massachusetts General Hospital.



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DR. PRYSTOWSKY

There isn't enough evidence of safety and efficacy in many laboratories to label ablation as first-line treatment, he added.

"The problem with ablation of atrial fibrillation is that it is so operator dependent," Dr. Prystowsky said. The best outcomes are in high-volume, highly experienced laboratories. Labs with less experience produce fewer cures and complication-free results, he said. The drugs set as potential first-line treatments in the guidelines are the standard agents, including sotalol, flecainide, and propafenone.

The guidelines will allow certain patients to skip a trial with an antiarrhythmic drug and proceed directly to ablation, including patients for whom the only possible drug treatment is amiodarone, patients who refuse to take an antiarrhythmic drug, and patients who cannot be treated with warfarin.

Ablation may also be a first option for patients treated in experienced laboratories that have a record of high success rates, said Dr. Prystowsky, director of the clinical electrophysiology laboratory at St. Vincent Hospital in Indianapolis.

—Mitchel L. Zoler