Clopidogrel Plus Aspirin Cuts Vascular Events

BY DIANA MAHONEY

Adding clopidogrel to aspirin therapy significantly reduces the risk of stroke and other major vascular events in patients who have atrial fibrillation and are not candidates for anticoagulation therapy with a vitamin K antagonist, according to Dr. Stuart Connolly of the Population Health Research Institute in Hamilton, Ont.

The rate of major vascular events was 6.8% with clopidogrel and aspirin, vs. 7.6% with placebo and aspirin.

DR. CONNOLLY

The rate of major vascular events was 6.8% at a median 3.6 years of follow-up among 3,772 study participants randomized to receive 75 mg per day of the oral antiplatelet agent in addition to aspirin in the multicenter Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-A (ACTIVE-A). The rate of major vascular events was 7.6% among the 3,782 patients randomized to placebo and aspirin therapy.

The clopidogrel and aspirin regimen was associated "with an acceptable increase in risk of major hemorrhage," Dr. Connolly reported in a press conference at the annual meeting of the American College of Cardiology.

The rate of major hemorrhage, defined as requiring a transfusion of at least two units of blood, increased from 1.3% in the placebo and aspirin group to 2.0% in the clopidogrel and aspirin group. However, this risk is less than the risk of major hemorrhage that has been reported with warfarin therapy, he said.

Additionally, there was a nonsignificant trend toward an increased risk in fatal strokes from 0.2% per year to 0.3% per year with clopidogrel plus aspirin therapy.

To weigh the benefits and risks of adding clopidogrel to aspirin therapy in this population, consider 1,000 patients treated for 3 years, Dr. Connolly said. Adding clopidogrel would prevent 28 strokes, 17 of which would be disabling or fatal, and would avert six myocardial infarctions, three of which would be fatal, at a cost of 20 major bleeds.

Dr. Connolly emphasized that oral anticoagulation therapy with vitamin K antagonists such as warfarin is still the most effective way to reduce major vascular events in high-risk patients with atrial fibrillation. However, "40%-50% of the patients who are at high risk for stroke because of atrial fibrillation don't receive anticoagulation therapy because they've been judged to be unsuitable for this treatment. For these patients there is a major unmet medical need, which has now been addressed by the results of the ACTIVE-A trial."

Dr. Connolly and his colleagues in the ACTIVE-A investigation enrolled 7,554 patients who had atrial fibrillation and at least one risk factor for stroke between June 2003 and May 2006. Study participants were deemed either to be unsuitable for warfarin therapy because of bleeding risk or did not want to begin warfarin therapy. The mean patient age was 71 years.

The primary study outcome was any major vascular event, including stroke, non-CNS systemic embolism, myocardial infarction, or vascular death. The secondary outcomes included the occurrence of any of the primary outcomes, as well as major hemorrhage and total mortality, Dr. Connolly explained.

The primary composite outcome was reduced by 11% in the clopidogrel group relative to aspirin only, "a highly statistically significant result," Dr. Connolly noted. "What is of particular importance, however, is that this effect was driven almost entirely by a substantial reduction in strokes of all severities." Strokes were reduced from 3.3% per year to 2.4% per year (N. Eng. J. Med. 2009 March 31 [doi: 10.1056/NEJMoa09013101]).

There was a trend of fewer myocardial infarctions, 0.9% per year in the aspirin only group and 0.7% per year in the clopidogrel plus aspirin group, which did not achieve statistical significance, Dr. Connolly said. However the number of heart attacks in the study was relatively small (90 in the clopidogrel group, 115 in the aspirin plus placebo group), reducing the study's power to detect a significant difference. In studies of several other types of patients, clopidogrel has been shown to reduce heart attacks.

Most of the strokes that occurred in this study were either disabling or severe, "and clopidogrel reduces strokes that were both not so severe and the more severe disabling strokes to an almost equal extent," Dr. Connolly noted.

Dr. Connolly reported receiving consulting fees, lecture fees, and grant support from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim, and grant support from Portola Pharmaceuticals. ■

Increased Stroke Risk Seen in Women With Early Menopause

BY ROBERT FINN

SAN DIEGO — Women who reach menopause before the age of 42 years are twice as likely to suffer a stroke in later life as are women who reach menopause after age 42, according to a new analysis of data from the Framingham Heart Study presented at the International Stroke Conference.

The study involved prospectively collected data from 1,430 women who were followed for an average of 22 years, said Lynda Lisabeth, Ph.D., of the University of Michigan, Ann Arbor. All participants were stroke-free at 60 years of age, experienced natural menopause, and had never taken estrogen before menopause. The use of self-reported data on the age of menopause was a limitation of the study, Dr. Lisabeth acknowledged.

In all, the women suffered 234 ischemic strokes at an average age of 80 years. The unadjusted rate of strokes was 23% among women who reached menopause before the age of 42 years, 16% among women who reached menopause between the ages of 42 and 54 years, and 11% among women who reached menopause at age 55 years or older.

After adjusting for age, systolic blood pressure, atrial fibrillation, diabetes, current smoking, cardiovascular disease, and estrogen use after menopause, the investigators determined that the age of menopause was an independent predictor of ischemic stroke.

Compared with women who reached menopause before age 42 years, those who reached menopause between ages 42 and 54 years were half as likely to experience a stroke, and those who reached menopause at age 55 or older were 69% less likely to have a stroke. In other words, women who reached menopause before age 42 years were 2.03-fold more likely to have a stroke. This difference was statistically significant.

The study showed that 4%-5% of strokes in women can be attributed to menopause before age 42, Dr. Lisabeth said.

About 1%-2% of women reach menopause at or before age 40 years. It is referred to as "premature ovarian failure" and its etiology remains unknown, but investigators are certain that it is different from natural menopause. About 3%-10% of women experience "early" menopause, defined as natural menopause before age 45 years.

Several possible mechanisms could account for the increased rate of stroke, Dr. Lisabeth said. Estrogen may play a role, since estrogen deficiency is thought to promote cardiovascular disease through functional or structural changes in arteries. Androgens and sex hormone–binding globulin also are risk factors for cardiovascular disease.

Additional studies with measures of endogenous hormones would be needed to unravel the relationship between the hormonal changes of menopause and ischemic stroke, she said.

The study was supported by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke. Dr. Lisabeth said that she had no conflicts of interest. ■

Dronedarone for Atrial Fib Impresses in Meta-Analysis

BY BRUCE JANCIN

ORLANDO — The novel multichannel-blocking antiarrhythmic agent dronedarone cut the risk of cardiovascular hospitalization or all-cause mortality by 24% in a meta-analysis of five placebo-controlled, randomized trials involving 6,157 patients with atrial fibrillation or atrial flutter.

Although this decrease in the combined end point was driven mainly by fewer cardiovascular hospitalizations, patients on dronedarone (Multaq) also experienced highly significant 29% and 51% reductions in cardiovascular death and sudden death, respectively, Dr. Stefan H. Hohnloser reported at the annual meeting of the American College of Cardiology.

Patients assigned to dronedarone took 400 mg twice daily for a collective 3,684 patient-years.

Dronedarone exhibited a favorable safety profile, most importantly with regard to its reassuringly low proarrhythmia potential. Only one case of torsade de pointes occurred in a dronedarone-treated patient, who had multiple torsade risk factors.

Cardiovascular hospitalization or death from any cause occurred in 25.9% of the dronedarone group compared with 34.3% of those on placebo. This is the only antiarrhythmic agent ever shown to reduce morbidity and mortality in patients with atrial fibrillation or flutter, said Dr. Hohnloser, professor of medicine at J.W. Goethe University, Frankfurt, Germany.

The most common side effects in dronedarone-treated patients were diarrhea or nausea/vomiting, which occurred in 15% of these patients, compared with 9% on placebo. Among those on the antiarrhythmic agent, 10% developed a rash, as did 7% of those on placebo. A rise in serum creatinine level occurred in 4% of those on the drug and 1.1% on of those placebo.

Prior analyses have established that dronedarone is effective both in controlling ventricular rate and in maintaining normal sinus rhythm.

The new meta-analysis incorporated the DAFNE, ADONIS, ATHENA, ERATO, and EURIDIS trials. The meta-analysis is timely, as a Food and Drug Administration advisory panel voted 10-3 in March to recommend marketing approval for dronedarone, a Sanofi-Aventis drug.

Dr. Hohnloser disclosed serving as a paid consultant to Sanofi-Aventis, Cardiome, ARYx Therapeutics, and Bristol-Myers Squibb. ■