Warfarin Decreases Stroke in Elderly AF Patients

Results showed a 50% reduction in the primary end point of death or major disabling stroke.

BY BETSY BATES
Los Angeles Bureau

VANCOUVER, B.C. — Thromboprophylaxis using warfarin produced a "huge, highly significant, 50% reduction" in death and major disability from stroke in elderly patients with a history of atrial fibrillation, roundly outperforming aspirin prophylaxis in a randomized trial, Dr. Richard Hobbs reported at the annual meeting of the North American Primary Care Research Group.

Feared bleeding complications were no higher than with aspirin therapy in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, conducted in 262 general practices in England and Wales.

"We think warfarin should be routinely prescribed to any patient presenting with atrial fibrillation, regardless of age," declared Dr. Hobbs, lead investigator for the trial and professor and head of primary care and general practice at the University of Birmingham (England) School of Medicine.

The prevalence of atrial fibrillation increases with age, and 50% of all cases are in patients older than 75 years. It raises the risk of stroke fivefold and accounts for a third of all strokes in the elderly, explained Dr. Hobbs during an oral paper presentation at the meeting.

However, existing trial data supporting warfarin as a prophylaxis focused heavily on younger patients with atrial fibrillation who are believed to have a very different risk-benefit profile than patients older than 75. Indeed, among the few elderly patients enrolled in large-scale trials, the risk of bleeding events was high enough that the number needed to treat (46) was close to the number needed to harm (55).

"As a consequence of that, many physicians around the world were in equipoise about whether you should treat patients over 75 with warfarin or give them aspirin. Hence, this trial," Dr. Hobbs said.

The BAFTA trial identified more than 58,000 adults over the age of 75 who had been diagnosed with atrial fibrillation or screened for the condition based on an irregular pulse. Of a total of 973 men and women, 488 were randomized to receive warfarin, and 485 were assigned to receive aspirin. They were followed for a mean of 2.7 years.

The trial differed from original large-scale warfarin/aspirin studies in several ways. Patients, obviously, were much older (mean age 81, compared with about 60). Reflecting their advanced age, they were also less healthy, with many comorbidities and a relatively high mean $CHADS_2$ score (28% with a score from 3-6 on the stroke risk scale for AF patients of 0-6 points), which reflected an elevated baseline risk of stroke.

Few exclusions prohibited entry into the study "because we wanted it to be relevant to most providers' practices," he said.

Patients were not enrolled if they had active peptic ulcer disease, a history of rheumatic heart disease or intracranial hemorrhage, or a major nontraumatic hemorrhage in the past 5 years.

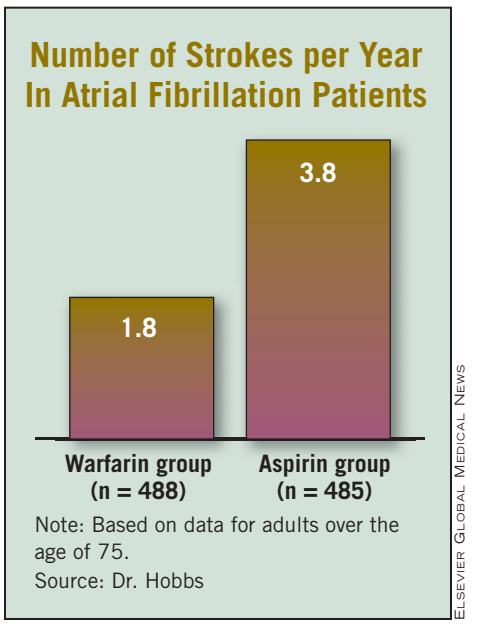
The primary outcome was specified as a fatal or disabling stroke, the latter defined as a stroke resulting in persistent symptoms after 48 hours, intracranial hemorrhage, or significant arterial embolism. Secondary outcomes included major extracranial hemorrhages or major nonstroke vascular events.

Aspirin was given at a dosage of 75 mg/day, and warfarin was prescribed at a target international normalized ratio (INR) of 2.5 within a range of 2-3. Dosages of both drugs were lower than those used in major trials and commonly prescribed by U.S. physicians, Dr. Hobbs said.

The results were clear, he said. "We showed a huge, highly significant, 50% reduction in the primary end point, in terms of death or major disabling stroke," he said.

The patient group receiving warfarin had 1.8 strokes per year, compared with 3.8 per year in the group receiving aspirin. One fatal or disabling stroke per year was prevented for every 50 patients receiving warfarin. "A very important question is, was that at the expense of bleeding?" he asked.

The answer was no, with every major bleeding variable equal between the two groups. A multivariate analysis showed that the results persisted when investigators controlled for age, gender, previous warfarin use, enrollment type (screening or previous atrial fibrillation diagnosis), $CHADS_2$ score, and comorbidities.



A crucial element in the study was the low INR used to guide warfarin therapy, because bleeding risk rises sharply at an INR of 3.5 or higher, he added.

The absolute risk of a major adverse event was 1.9% for patients taking warfarin and 2% for those taking aspirin. Because there was no placebo group, it is unknown whether those events were related to the drugs or were reflective of the background event rate in that population, Dr. Hobbs said in an interview.

The BAFTA study was funded by the Medical Research Council. ■

Drug-Eluting Stents Cut Mortality and Revascularization Rates

BY MITCHEL L. ZOLER
Philadelphia Bureau

ORLANDO — The safety of drug-eluting coronary stents, compared with bare-metal stents, received a substantial boost in an analysis of data from more than 10,000 patients who received coronary stents in Massachusetts during 2003-2004.

Data collected by the Massachusetts Department of Public Health, which sponsored the study, on all patients who received a coronary stent in the state showed that use of drug-eluting stents (DES) was associated with a significantly lower risk of death or need for revascularization and a similar incidence of myocardial infarctions, compared with patients treated with bare-metal stents (BMS), Dr. Laura Mauri reported at the annual scientific sessions of the American Heart Association.

"The results are very reassuring" regarding the relative safety of DES, said Dr. Mauri, a cardiologist at Brigham and Women's Hospital, Boston. These are the first large-scale registry data that compare DES with BMS using only patients treated in the United States. And because the study used data collected from nearly 19,000 patients, Dr. Mauri and her associates were able to use an extensive propensity-score analysis that closely matched patients in the DES and BMS groups on 63 clinical and demographic variables.

The findings "are reassuring for patients who have or may get drug-eluting stents," Dr. Robert O. Bonow said in an interview.

"Data like these may lead to a resurgence in DES use," said Dr. Bonow, professor of cardiology and chief of cardiology at Northwestern University, Chicago. Use of coronary DES in the United States (and elsewhere) dropped substantially this year after several reports over the past 15 months that raised questions about their safety, compared with BMS.

The Massachusetts Department of Public Health requires reporting on all patients who receive coronary stents in the state. The new study used data collected by the department for more than 21,000 patients who received one or more coronary stents during April 1, 2003–Sept. 30, 2004. This period was selected for the analysis because DES first went on sale in the United States in April 2003, and because all patients in this group had at least 2 years of follow-up data.

The analysis included more than 11,000 patients who received exclusively DES, and more than 6,000 patients who received only BMS. The analysis excluded more than 1,000 patients who received both DES and BMS.

During the early portion of the study period, about 90% of patients received BMS and about 10% received DES. This ratio shifted over the next 18 months, so that by September 2004 the situation was reversed and about 90% of patients who got coronary stents received DES and about 10% got BMS. Throughout the entire period, about 65% of the patients got DES and about 35% received BMS.

This level of DES use was substantially higher than in other registry data that have been reported for coronary stents, in which DES were about 30%-40% of all stents used. This includes data from the Swedish national registry that were published early this year, in which about 30% of patients received DES. In the Massachusetts data, about 70% of the DES used were sirolimus-eluting stents (Cypher). The other 30% of the DES used were placitaxel-eluting stents (Taxus).

The high rate of BMS use early on and the high rate of DES use later were strengths of the new study. A broad population of patients received each stent type, which helped the investigators when they attempted to match very similar patients in the two groups, Dr. Mauri said.

Application of the propensity-score analysis, which matched patients from the two groups based on 63 variables, led to a final-analysis group of 5,441 patients treated with one or more DES and an equal number of patients who received one or more BMS.

The incidence of death during 2 years of follow-up was 9.4% in the DES group and 11.9% in the BMS group, a difference that was highly statistically significant. The total revascularization rate was 20.1% in the DES group and 23.9% in the BMS group, also a highly significant difference. Rates of nonfatal myocardial infarction were 10.8% in the DES patients and 11.8% in the BMS recipients, a difference that was not statistically significant.

The revascularization rate for the DES patients may seem unexpectedly high, but was probably caused by a very liberal approach in which any additional coronary stenting that patients received was counted. Many of the subsequent stenting procedures involved lesions that had not been treated initially, Dr. Mauri said.

The analysis has not yet specifically compared the rates of stent thrombosis in the DES and BMS groups. A major concern about DES safety has been that they might cause a higher incidence of stent thrombosis, compared with BMS. Clinically significant thrombotic events would manifest as death or myocardial infarction, she noted. During most of the study period, patients receiving DES were routinely treated with dual antiplatelet therapy—aspirin and clopidogrel—for 3-6 months. Today, the recommended length of dual therapy is 1 year.

Dr. Mauri has received honoraria from Abbott Vascular, Boston Scientific, Cordis, and Metronic Vascular. ■