Dabigatran Outperforms Warfarin in AF Patients

BY MITCHEL L. ZOLER

BARCELONA — If a drug that clearly outperforms its control in a trial hits a home run, then the new oral anticoagulant dabigatran hit a grand slam against its comparator warfarin in a study that tested prevention of strokes and systemic embolism in patients with atrial fibrillation, according to several listeners.

The 18,000-patient Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) study compared the safety and efficacy of two different dosages of the direct thrombin inhibitor dabigatran against warfarin in atrial fibrillation (AF) patients who also had at least one additional risk factor for stroke, including prior stroke, low left ventricular ejection fraction, or age 75 or older. Patients randomized to receive 110 mg

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of dabigatran twice daily showed significantly noninferior efficacy, compared with a centrally administered warfarin program, plus significantly better safety, including fewer major hemorrhages during a median 2-year follow-up, Dr. Stuart J. Connolly said at the annual congress of the European Society of Cardiology.

Patients randomized to the 150-mg twice daily dabigatran regimen had a significant 34% relative reduction in the rate of strokes and systemic embolism with a safety profile that was as good as warfarin's with a similar major hemorrhage rate. Both dosages of the new drug also significantly dropped the rate of intracranial hemorrhage by relative rates of more than two-thirds.

Concurrent with the meeting report, the results appeared online (N. Engl. J. Med. 2009;361:10.1056/NEJMoa0905561). The study was funded by Boehringer Ingelheim Pharmaceuticals, the company developing dabigatran.

These findings coupled with two other important advantages dabigatran holds over warfarin—treatment with fixed dosages, and no need to monitor coagulation status by international normalized ratios (INRs)—led several experts to voice nearly unanimous enthusiasm for a new era of dabigatran anticoagulation for AF and the long-sought ouster of warfarin.

Leading the praise was Dr. John Camm, professor of cardiac and vascular sciences at St. George's, University of London, who was the invited discussant. "Dabigatran seems to be not merely superior treatment, but we must also regard this drug as a stimulus to a paradigm change in antithrombotic treatment of atrial fibrillation."

"Dabigatran is likely to be expensive, but we clearly must afford it," he added. "Perhaps reduced strokes and reduced monitoring will help make the drug affordable," said Dr. Camm, who has been a speaker for and adviser to Boehringer Ingelheim and other drug companies.

Other strongly positive reactions expressed at the meeting included:

"This is an absolute revolution in how we'll anticoagulate patients. For atrial fibrillation, this is a huge advance," said Dr. Christopher P. Cannon, a cardiologist at Brigham and Women's Hospital, Boston. He had no disclosures for Boehringer Ingelheim but does have relationships with several other drug companies.

"It's a real winner. Both physicians and patients will pick this up very rapidly," said Dr. Lars Wallentin, a professor of medicine at Uppsala (Sweden) University Hospital and a co-investigator in the study. Dr. Wallentin disclosed receiving consulting and lecture fees and grant support from Boehringer Ingelheim and several other drug companies.

"This is the first time we've seen an agent at least as effective as warfarin and, depending on the dose, even better at preventing stroke in atrial fibrillation. That's a real breakthrough," said Dr. Elliott M. Antman, director of the cardiac unit at Brigham and Women's Hospital in Boston. Dr. Antman disclosed no rela-

tionship with Boehringer Ingelheim, but has relationships with several other drug companies, including a company developing a rival direct thrombin inhibitor.

Understandably, the biggest praise came from Dr. Connolly himself: "This is a huge blockbuster breakthrough," he said in an interview. "We got the easy-to-use part, and no toxicity other than dyspepsia, and on top of that it's safer, a truly remarkable result. There is little doubt that dabigatran will largely be the anticoagulant of choice in the future. It's incredible that this agent is more effective than warfarin without causing more bleeding," said Dr. Connolly, professor of medicine and director of cardiology at McMaster University in Hamilton, Ont.

"I have no doubt this drug will get approved" by the Food and Drug Administration, despite data from just one study, but it is a study with 18,113 patients, including more than 12,000 patients randomized to receive dabigatran. Dr. Connolly guessed the FDA would finish its review next year. Dr. Connolly disclosed he has been a consultant to, a lecturer for, and a grant recipient from Boehringer Ingelheim.

A few notes of caution were voiced. Strictly speaking, the results only apply to patients like those enrolled in the study: Patients with AF plus at least one other risk factor, not all AF patients, said Dr. Clyde W. Yancy, medical director of the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas. Dr. Yancy had no disclosures. He also had other concerns: The results showed an inexplicable signal of an increased risk for myocardial infarction among patients on dabigatran, and the new drug's likely high cost. But the increased cost for dabigatran over warfarin is balanced by savings from eliminating monitoring of coagulation status.

The only notable adverse effect was an increase in dyspepsia and gastrointestinal bleeding, affecting nearly 12% of patients, an effect explained by a formulation that pairs dabigatran with tartaric acid to make the drug orally bioavailable. Patients with pre-existing dyspepsia need treatment with a proton pump inhibitor or other gastrointestinal agent to get their symptoms resolved before starting dabigatran, Dr. Connolly said. "We'll learn to manage the GI upset," he said.

This adverse effect "doesn't sound like a major concern," said Dr. Antman. ■