Dabigatran Effective, Safer Than Warfarin

VITALS

Major Finding: The relative risk reduction of intracranial bleeds ranged from 60% to 70% for each of the three CHADS2 risk levels at both dabigatran dosages in patients with atrial fibrillation.

Data Source: The RE-LY trial, with 18,113 patients with atrial fibrillation, randomized to either of two dosages of dabigatran or to warfarin and treated and followed for a median of 2 years.

Disclosures: The RE-LY trial was sponsored by Boehringer Ingelheim. Dr. Oldgren has received financial support from Boehringer Ingelheim and Astra Zeneca. Dr. Kowey has received fees and honoraria from Boehringer Ingelheim and other pharmaceutical companies. He is part owner of Cardionet.

BY MITCHEL L. ZOLER

FROM THE THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

ATLANTA — Treatment with the investigational direct thrombin inhibitor dabigatran proved safe and effective across the entire spectrum of risk in patients with atrial fibrillation in a secondary analysis of data from the drug's pivotal trial with more than 18,000 patients.

Finding that the lower dose of dabigatran tested cut the stroke and systemic embolization rate as well as warfarin while leading to significantly fewer major bleeds than warfarin in low-risk atrial fibrillation patients potentially opens the door to offering low-risk patients a better anticoagulant option than aspirin, Dr. Jonas Oldgren said.

"Today, low-risk patients are treated with no anticoagulant or only with aspirin, which is clearly less effective. …We don't treat them with warfarin because of the bleeding risk, but dabigatran is a much safer drug," said Dr. Oldgren, head of the coronary care unit at Uppsala (Sweden) University, and a coinvestigator in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial.

But extrapolating from the safety results of RE-LY, which compared dabigatran against warfarin, to the safety and efficacy of dabigatran compared with aspirin in atrial fibrillation patients leaps beyond the current data, commented Dr. Peter R. Kowey, chief of cardiovascular disease at Main Line Health in Wynnewood, Pa.

The RE-LY data "show that [dabigatran] is safer than warfarin, not that it's safer than aspirin in these [low-risk] patients. …You haven't proven that dabigatran is better than aspirin," said Dr. Kowey, who is also a professor of medicine and clinical pharmacology at Thomas Jefferson University in Philadelphia, and did not participate in the RE-LY trial.

The primary RE-LY results, published last September, showed that a 110-mg b.i.d. oral dosage of dabigatran had noninferior efficacy relative to warfarin while causing fewer major bleeds, and that a 150 mg b.i.d. oral dosage of dabigatran was superior to warfarin's efficacy while causing a similar rate of major bleeds (N. Engl. J. Med. 2009;361:1139-51). Dabigatran also has the advantage of administration at a fixed dosage with no need for regular monitoring or dosage changes.

The new analysis assessed the performance of the three treatments tested in three patient subgroups divided on the basis of their CHADS2 scores. CHADS2 scoring is commonly used to quantify the risk from stroke, systemic embolism, or bleeding that patients with atrial fibrillation face based on their comorbidities. The scoring system assigns one point for congestive heart failure (C), hypertension (H), age of 75 or older (A), and diabetes (D) and assigns two points for patients with a history of stroke (S2) or a transient ischemic attack. Thus, a patient's CHADS2 score can range from 0 to 6. Current guidelines from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology call for routine treatment with an oral anticoagulant, such as warfarin, in patients with a CHADS2 score of 2 or higher. In lower-risk atrial fibrillation patients, with a score of 0 or 1, aspirin is the usual anticoagulant.

Most of the RE-LY patients had CHADS2 scores of 1, 2, or 3. For the analysis, Dr. Oldgren divided the patients into three roughly equal-sized groups by their scores: 5,775 with a score of 0 or 1; 6,455 patients with a score of 2; and 5,882 patients with a score of 3-6.

The results (see box) showed several notable findings: For the primary efficacy end point of preventing stroke and systemic embolism, the higher dabigatran dosage surpassed warfarin in all three CHADS2 subgroups, while the lower dabigatran dosage showed noninferiority across all three risk subgroups. For the primary safety end point of major bleeds, the lower dabigatran dosage performed better than warfarin in all three risk subgroups, while the higher dabigatran dosage showed noninferiority. And in the outcome of net clinical benefit—a combined efficacy and safety end point that included stroke, systemic embolism, MI, pulmonary embolism, all deaths, and major bleeds—the higher dabigatran dosage proved significantly superior to warfarin at both the low- and moderate-risk levels and was noninferior in the highest-risk patients, while the lower dabigatran dosage showed noninferiority in all three risk levels.

In addition, in what Dr. Oldgren called "astonishing results," both dabigatran dosages showed a statistically significant reduction in the rate of intracranial bleeds compared with warfarin in all three risk subgroups. The relative risk reduction ranged from 60%-70% for each of the three CHADS2 risk levels in both dabigatran dosage levels. This finding "is very important because this is the most feared complication of oral anticoagulant therapy," Dr. Oldgren said. ■

Annual Incidence Outcomes Across Atrial Fibrillation Risk Subgroups

Outcome	CHADS2 score	Incidence, % (dabigatran 110 mg b.i.d.)	Incidence, % (dabigatran 150 mg b.i.d.)	Incidence, % (warfarin)
Stroke or systemic embolism	0-1	1.06	0.65	1.05
	2	1.43	0.84*	1.38
	3-6	2.12	1.88*	2.68
Major bleeds	0-1	1.81*	1.98	2.70
	2	2.71	2.80	3.14
	3-6	3.82	4.84	4.28
Intracranial bleeds	0-1	0.20*	0.20*	0.51
	2	0.22*	0.24*	0.64
	3-6	0.26*	0.49*	1.07
Net clinical benefit	0-1	4.86	4.25*	5.32
	2	7.84	6.40*	7.66
	3-6	8.81	10.19	9.30

*Statistically significantly different from warfarin-treated patients
Note: Based on 18,113 patients with atrial fibrillation enrolled in the RE-LY trial.
Source: Dr. Oldgren

ELSEVIER GLOBAL MEDICAL NEWS

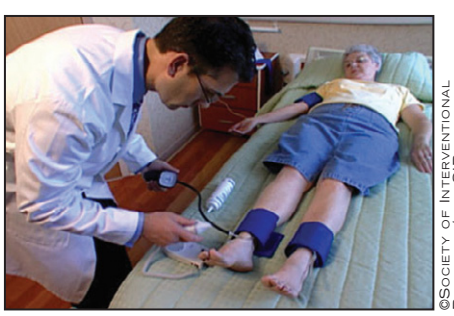
ABI May Predict Coronary Disease in Low-Risk Patients

BY KERRI WACHTER

FROM THE ANNUAL MEETING OF THE SOCIETY OF INTERVENTIONAL RADIOLOGY

TAMPA — More than 10% of patients with low to intermediate risk for coronary heart disease have an abnormal ankle brachial index, putting them at a higher risk for MI and coronary death than predicted by conventional measures.

In a study of 822 individuals screened for peripheral artery disease (PAD), 11% of those with a low-risk Framingham Risk Score (FRS) for coronary disease and 13% of those with an intermediate-risk score had an abnormal ankle brachial index (ABI).



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Ankle brachial index may help detect individuals at risk for coronary events.

Abnormal ABI has been associated with increased risk of coronary heart disease (CHD) events and mortality, even in individuals at low to intermediate CHD risk (JAMA 2008;300:197-208), but prevalence estimates of abnormal ABI among older screening populations with low-intermediate FRS have not been reported previously.

"The prevalence of abnormal ABI is high, even in those a without high Framingham Risk Score. … The use of abnormal ABI in screening has the potential to improve risk prediction," Dr. Raj Dhangana said.

The findings are good news, given that at least 60% of CHD events occur in individuals who were not known to be at high risk (BMJ 2003;327:1267). In fact, almost two-thirds of events occur in individuals who are at low or intermediate risk using the FRS (Am. Heart J. 2002;144:95-100).

The use of ABI for screening could help improve risk prediction for CHD, said Dr. Dhangana, a research fellow at Rhode Island Hospital, Providence.

The researchers analyzed data from the PEDAL Study (Population-Based Examinations to Determine Ankle-Brachial Index)—a multicenter, cross-sectional study conducted at 23 sites of the Legs for Life national free public PAD screening program in 2007-2009.

The FRS was calculated for each participant to determine 10-year risk of CHD. Based on their FRS, patients were stratified into three risk categories: low (less than 6%), intermediate (6%-19%), and high (at least 20%). An abnormal ABI was defined as less than 0.9 and/or greater than 1.4 in either leg.

A low FRS was observed in 256 individuals (31%), and 414 (50%) had an intermediate risk. ■

Disclosures: *Dr. Dhangana has no relevant financial conflicts.*