

Vascular Surgeon Pans Data Behind Carotid Stent Approval

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NEW YORK — The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy trial was flawed from its inception and should have been stopped because of its multiple shortcomings, according to Dr. Anthony J. Comerota.

Instead, the Food and Drug Administration used data from the SAPHIRE trial in its decision to approve carotid stents in high-risk patients, and the results of the study were published in the *New England Journal of Medicine* (2004; 351:1493-501), “arguably the most influential medical journal in the world,” said Dr. Comerota, who served on the FDA panel that reviewed the data.

SAPHIRE was based on an improperly designed and executed feasibility study, which was undertaken to determine if carotid angioplasty and stenting (CAS) could be performed with less than two times the 6.7% stroke and death rate of carotid endarterectomy found in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), Dr. Comerota argued.

However, only truly high-risk patients with symptomatic atherosclerosis were enrolled in NASCET, whereas the majority of patients in the SAPHIRE feasibility study were asymptomatic, Dr. Comerota said at the Veith symposium on vascular medicine sponsored by the Cleveland Clinic. Fewer than 20% of CAS patients had more than 80% stenosis, 72% were asymptomatic, and 26% had recurrent stenosis. “These are low-risk patients,” said Dr. Comerota, director of the Jobst Vascular Center, Toledo (Ohio) Hospital.

Furthermore, SAPHIRE was designed as a randomized trial, yet a majority of patients were not randomized, but instead were entered into registries, and enrollment was terminated after only 334 of the target 2,900 had entered the study. “Termination was due to poor enrollment because of ‘competing registries’—yet it was the sponsoring company’s own registry that led to termination,” Dr. Comerota said.

Another flaw in the study design was the inclusion of troponin-based MI as part of the primary end point, which also included stroke and death. The reason for this inclusion, according to the authors, was that patients with non-Q-wave MI have a 27-fold increased risk of an MI in the next 6 months. This was not borne out in the investigators’ report of long-term outcomes, when there was no signal of an increased rate of MI, Dr. Comerota said.

“Furthermore, the statistical analysis was not done according to protocol, but rather was a unique triangular analysis I have not seen before or since SAPHIRE,” he added.

The FDA panel that reviewed the data for approval of the device included six

cardiologists, two interventional radiologists, two vascular surgeons, and one neurologist. “There was no statistician on the panel, and the vote to recommend was 6-5. You can draw your own conclusions,” said Dr. Comerota.

SAPHIRE was supported by Cordis Corp., the manufacturer of the stent used in the study. ■



Some consider carotid stenting to be the ideal solution (right) to stenosis (left) in high-risk patients, but the patients in the SAPHIRE registry were not high risk, said Dr. Anthony J. Comerota. Fewer than 20% of CAS patients had more than 80% stenosis.

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IMPORTANT CORRECTION OF DRUG INFORMATION ABOUT BYSTOLIC® (NEBIVOLOL) TABLETS

An advertisement in professional journal publications for Bystolic® (nebivolol) tablets for the treatment of hypertension was the subject of a Warning Letter issued by the U.S. Food and Drug Administration (FDA) in August 2008.

Forest would like to take this opportunity to clarify the content of this advertisement.

Indications and Usage

Bystolic is indicated for the treatment of hypertension. Bystolic may be used alone or in combination with other antihypertensive agents.

Unsubstantiated Superiority and Mechanism of Action Claims

The FDA objected to claims that Bystolic was a novel and next generation beta blocker with a unique mechanism of action including cardioselective beta blockade and vasodilation. The FDA stated that these claims were misleading because they suggested that Bystolic is different from and superior to other β -adrenergic receptor blocking agents in the treatment of hypertension, when these implications have not been demonstrated by substantial evidence or substantial clinical experience. In extensive metabolizers (most of the population) and at doses ≤ 10 mg, Bystolic is preferentially β_1 selective. The FDA also stated that the presentation of the mechanism of action implied that it had been established, when the package insert states that the mechanism of action of the antihypertensive response of Bystolic has not been definitively established.

Omission and Minimization of Risk Information

The FDA stated that the advertisement did not disclose the following important safety information, which is contained in Bystolic’s full Prescribing Information:

Warning: In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered.

Precautions: CYP2D6 Inhibitors: Use caution when Bystolic is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc).

Drug interactions: Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When Bystolic is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for d-nebivolol.

The FDA objected to the claim, “Favorable tolerability profile with a low incidence of beta blocker-related side effects.” The FDA determined that this claim implied that the tolerability profile of Bystolic is better than the tolerability profile of other β -adrenergic receptor blocking agents, when this has not been demonstrated by substantial evidence or substantial clinical experience. The FDA also objected to the claim, “Favorable tolerability profile,” stating that it minimized the risks associated with Bystolic.

Unsubstantiated Efficacy Claims

The FDA objected to the claim, “Efficacy demonstrated across a broad range of patients.” The FDA stated that the cited claim implied that efficacy was demonstrated within each subgroup (obese, poor metabolizers, and diabetic) presented in conjunction with this claim, when this has not been supported by substantial evidence or substantial clinical experience. None of the efficacy trials for Bystolic were specifically designed to evaluate effectiveness in patients who were obese, poor metabolizers, or diabetic. The FDA is not aware of any studies with Bystolic demonstrating efficacy in the above referenced subgroups. Effectiveness was established in black hypertensive patients and was similar in subgroups analyzed by age and sex.

Important Safety Information

Patients being treated with Bystolic should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported following the abrupt cessation of therapy with beta blockers. When discontinuation is planned, the dosage should be reduced gradually over a 1- to 2-week period and the patient carefully monitored.

Bystolic is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh $>B$), and in patients who are hypersensitive to any component of this product.

Bystolic should be used with caution in patients with peripheral vascular disease, thyrotoxicosis, in patients treated concomitantly with beta blockers and calcium channel blockers of the verapamil and diltiazem type (ECG and blood pressure should be monitored), severe renal impairment, and any degree of hepatic impairment or in patients undergoing major surgery. In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered. Caution should also be used in diabetic patients as beta blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

When Bystolic is administered with CYP2D6 inhibitors such as fluoxetine, significant increases in d-nebivolol may be observed (ie, an 8-fold increase in AUC).

In general, patients with bronchospastic disease should not receive beta blockers.

Bystolic should not be combined with other beta blockers.

The most common adverse events with Bystolic versus placebo (approximately $\geq 1\%$ and greater than placebo) were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema.

Please see the accompanying brief summary of Prescribing Information for full risk information.



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