

Bleeding Drops in Elective PCI With Bivalirudin

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WASHINGTON — The risk of adverse events such as major bleeding during elective coronary artery stenting is significantly lower when the procedure is performed with bivalirudin antithrombotic monotherapy than with other combinations based on unfractionated heparin, according to two Italian randomized trials.

The antithrombotic effects of bivalirudin have been shown to reduce bleeding rates after percutaneous coronary intervention (PCI), compared with unfractionated heparin (UFH) alone, but few data exist that compare bivalirudin monotherapy with UFH in combination with a glycoprotein (GP) IIb/IIIa inhibitor such as tirofiban (Aggrastat) or with the heparin-reversing drug protamine.

One of bivalirudin's advantages over UFH is its short, 25-minute half-life. Investigators in the ARNO (Antithrombotic Regimens and Outcome) trial tried to see if this advantage could be equalized by administering protamine immediately after PCI to reverse the effects of UFH.

The ARNO trial featured 850 patients who were randomized to bivalirudin (Angiomax) or UFH plus protamine. Patients in both arms had a mean age of about 69 years; 22% had diabetes.

Bivalirudin monotherapy was associated with significantly fewer in-hospital major bleeding events than was therapy with UFH and protamine (0.5% and 2.1%, respectively). At 1 month after the procedure, bivalirudin still was associated with significantly fewer major bleeding events (0.9% vs. 2.8%), Dr. David Antoniucci reported at *Transcatheter Cardiovascular Therapeutic 2008*.

The combined rate of MI, target vessel revascularization, and death at 1 month was significantly lower in bivalirudin-treated patients (2.8%) than in heparin-treated patients (6.4%), said Dr. Antoniucci of the cardiology division at Careggi Hospital, Florence, Italy.

The second trial presented was conducted to determine the safety of bivalirudin in diabetic patients undergoing PCI by Dr. Carlo Briguori and his coinvestigators in the interventional cardiology laboratory at Clinica Mediterranea, Naples, Italy. They randomized 335 diabetic patients with an average age of about 65 years to treatment with either bivalirudin alone or UFH plus tirofiban. Aspirin and clopidogrel (Plavix) were

given before the procedure to all patients in the trial, called NAPLES (Novel Approaches for Preventing or Limiting Event Study). The severity of bleeding risk was distributed similarly in both groups of diabetic patients.

Despite having diabetes, only 13% of the patients had multivessel disease. Only 11%-19% of the patients had unstable angina. None had acute coronary syndrome with elevated biomarkers.

Bivalirudin was associated with a significantly lower rate of adverse clinical events than was UFH plus tirofiban (12% vs. 21%, respectively). The difference was due primarily to a significantly higher rate of bleeding of 8% in the combination therapy patients, compared with the 2% rate in bivalirudin-treated patients.

In both ARNO and NAPLES, patients received aspirin and clopidogrel before undergoing PCI. Bivalirudin was ad-

ministered in a single 0.75-mg/kg IV bolus, followed by an infusion of 1.75 mg/kg per hour during PCI. Patients in the NAPLES trial received 70 U/kg UFH, followed by additional boluses if their activated clotting time was less than 250 seconds, whereas those in the ARNO trial initially received 100 U/kg UFH.

Both Dr. Antoniucci and Dr. Briguori reported having no financial conflicts of interest related to their studies. ■

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.



Forest Laboratories, Inc.

New Carotid Stent

The Food and Drug Administration has approved the Carotid Wallstent Monorail Endoprosthesis for treatment of patients with carotid artery disease who are at high risk of surgery. The stent's closed-cell design is engineered for optimal lesion coverage. It is the leading carotid artery stent in Europe and other international markets. For more information, contact Boston Scientific Corp. by visiting www.bostonscientific.com. ■