

BMD at Bisphosphonate's End Predicts Fractures

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FROM THE ANNUAL MEETING OF
THE AMERICAN SOCIETY FOR BONE
AND MINERAL RESEARCH

TORONTO – The stronger a patient's bones are when bisphosphonate treatment is stopped, the less likely the bones are to fracture later, based on an analysis of 437 patients.

In contrast, changes in bone mineral

density following the end of bisphosphonate therapy had no significant link with subsequent fracture risk, Dr. Douglas C. Bauer said at the meeting.

The finding calls into doubt the common practice of running annual dual-energy x-ray absorptiometry examinations on patients who have withdrawn from bisphosphonate treatment.

Routine BMD measurement "1-2 years after stopping prolonged alendronate

therapy may not be useful for predicting the patient's fracture risk," said Dr. Bauer, professor of medicine, epidemiology, and biostatistics at the University of California, San Francisco. BMD at the time of alendronate discontinuation "was highly predictive of who was going to fracture."

Patients who stopped alendronate therapy with a total hip BMD T score of -1.4 or greater had a 9% rate of clinical fracture during 5 years of follow-up. Patients

with a T score of -2.1 to -1.5 when they stopped bisphosphonate treatment had a 23% fracture rate during 5 years of follow-up, and those who stopped with a T score lower than -2.1 had a 33% fracture rate over the next 5 years. The between-group differences were statistically significant.

These data "are helpful as I try to decide which of my patients I should leave on a bisphosphonate," commented Dr. Elizabeth Shane, a professor of medicine at Columbia University in New York.

"Patients below -2.1 were at very high risk of fracture, but even those in the

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INDICATIONS AND USAGE: Hypertension - BYSTOLIC is indicated for the treatment of hypertension [see Clinical Studies (14.1)]. BYSTOLIC may be used alone or in combination with other antihypertensive agents [see Drug Interactions (7)].

CONTRAINDICATIONS: BYSTOLIC is contraindicated in the following conditions: Severe bradycardia; Heart block greater than first degree; Patients with cardiogenic shock; Decompensated cardiac failure; Sick sinus syndrome (unless a permanent pacemaker is in place); Patients with severe hepatic impairment (Child-Pugh >B); Patients who are hypersensitive to any component of this product.

WARNINGS AND PRECAUTIONS: Abrupt Cessation of Therapy - Do not abruptly discontinue BYSTOLIC therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β -blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β -blockers, when discontinuation of BYSTOLIC is planned, carefully observe and advise patients to minimize physical activity. Taper BYSTOLIC over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, restart BYSTOLIC promptly, at least temporarily. **Angina and Acute Myocardial Infarction** - BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI. **Bronchospastic Diseases** - In general, patients with bronchospastic diseases should not receive β -blockers. **Anesthesia and Major Surgery** - Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta-blockers should generally continue treatment throughout the perioperative period. If BYSTOLIC is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β -blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. The β -blocking effects of BYSTOLIC can be reversed by β -agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β -blockers. **Diabetes and Hypoglycemia** - β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities. **Thyrototoxicosis** - β -blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β -blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm. **Peripheral Vascular Disease** - β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. **Non-dihydropyridine Calcium Channel Blockers** - Because of significant negative inotropic and chronotropic effects in patients treated with β -blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents. **Use with CYP2D6 Inhibitors** - Nebivolol exposure increases with inhibition of CYP2D6 [see Drug Interactions (7)]. The dose of BYSTOLIC may need to be reduced. **Impaired Renal Function** - Renal clearance of nebivolol is decreased in patients with severe renal impairment. BYSTOLIC has not been studied in patients receiving dialysis [see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]. **Impaired Hepatic Function** - Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic impairment [see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]. **Risk of Anaphylactic Reactions** - While taking β -blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. **Pheochromocytoma** - In patients with known or suspected pheochromocytoma, initiate an α -blocker prior to the use of any β -blocker.

ADVERSE REACTIONS: Clinical Studies Experience - BYSTOLIC has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. **HYPER-TENSION:** In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse reactions was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse reactions that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%). **Table 1** lists treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg, or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group. **Table 1.** Treatment-Emergent Adverse Reactions with an Incidence (over 6 weeks) $\geq 1\%$ in BYSTOLIC-Treated Patients and at a Higher Frequency than Placebo-Treated Patients are listed below in the following order: System Organ Class Preferred Term [Placebo (n = 205), Nebivolol 5 mg (n = 459), Nebivolol 10 mg (n = 461), Nebivolol 20-40 mg (n = 677)] **Cardiac Disorders:** Bradycardia (0, 0, 0, 1); **Gastrointestinal Disorders:** Diarrhea (2, 2, 2, 3); Nausea (0, 1, 3, 2); **General Disorders:** Fatigue (1, 2, 2, 5); Chest pain (0, 0, 1, 1); Peripheral edema (0, 1, 1, 1); **Nervous System Disorders:** Headache (6, 9, 6, 7); Dizziness (2, 2, 3, 4); **Psychiatric Disorders:** Insomnia (0, 1, 1, 1); **Respiratory Disorders:** Dyspnea (0, 0, 1, 1); **Skin and Subcutaneous Tissue Disorders:** Rash (0, 0, 1, 1). Listed below are other reported adverse reactions with an incidence of at least 1% in the more than 4300 patients treated with BYSTOLIC in controlled or open-label trials except for those already appearing in **Table 1**, terms too general to be informative, minor symptoms, or adverse reactions unlikely to be attributable to drug because they are common in the population. These adverse reactions were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies. **Body as a Whole:** asthenia. **Gastrointestinal System Disorders:** abdominal pain. **Metabolic and Nutritional Disorders:** hypercholesterolemia. **Nervous System Disorders:** paraesthesia. **Laboratory Abnormalities** - In controlled monotherapy trials of hypertensive patients, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count. **Postmarketing Experience** - The following adverse reactions have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere.

These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Adverse reactions common in the population have generally been omitted. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second- and third-degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudeication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

DRUG INTERACTIONS: CYP2D6 Inhibitors - Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) [see Clinical Pharmacology (12.5)]. **Hypotensive Agents** - Do not use BYSTOLIC with other β -blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β -blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, discontinue BYSTOLIC for several days before the gradual tapering of clonidine. **Digitalis Glycosides** - Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. **Calcium Channel Blockers** - BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects, Category C - Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance. In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD). **Labor and Delivery** - Nebivolol caused prolonged gestation and dystocia at doses ≥ 5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). No studies of nebivolol were conducted in pregnant women. Use BYSTOLIC during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** - Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk. Because of the potential for β -blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing. **Pediatric Use** - Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility [see Nonclinical Toxicology (13.1)]. **Geriatric Use** - Of the 2800 patients in the U.S.-sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients. **Heart Failure** - In a placebo-controlled trial of 2128 patients (1067 BYSTOLIC, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens consider discontinuation of BYSTOLIC.

OVERDOSAGE: In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdose are bradycardia and hypotension. Other important adverse reactions reported with BYSTOLIC overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β -blocker overdose include bronchospasm and heart block. The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhidrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure, and vomiting. The patient recovered. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β -blockers, consider the following general measures, including stopping BYSTOLIC, when clinically warranted: **Bradycardia:** Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary. **Hypotension:** Administer IV fluids and vasopressors. Intravenous glucagon may be useful. **Heart Block (second- or third-degree):** Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary. **Congestive Heart Failure:** Initiate therapy with digitalis glycosides and diuretics. In certain cases, consider the use of inotropic and vasodilating agents. **Bronchospasm:** Administer bronchodilator therapy such as a short-acting inhaled β_2 -agonist and/or aminophylline. **Hypoglycemia:** Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required. Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours. Call the National Poison Control Center (800-222-1222) for the most current information on β -blocker overdose treatment.

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Measurement of BMD '1-2 years after stopping prolonged alendronate therapy may not be useful.'

DR. BAUER

middle tertile, with less than -1.5, were at a risk almost as high." Dr. Bauer's study "provides me with some comfort [on whom] I can stop safely."

The investigators used data collected in the FLEX (Fracture Intervention Trial Long-Term Extension) study, which randomized 1,099 postmenopausal women who had completed 5 years of treatment with alendronate to either continue on alendronate for another 5 years or switch to placebo (JAMA 2006;296:2927-38). They focused on the 437 patients who switched to placebo, and assessed the BMD measures that were associated with fracture risk during follow-up.

Even among patients who had relatively substantial bone loss during 1 year of follow-up, the amount of lost BMD did not significantly correlate with their follow-up fracture rate. The researchers saw no significant link to fracture rate among the 21% of patients who lost at least 3% of their BMD during the first year of follow-up, or among the 8% of patients who lost at least 5% of their BMD during 1 year of follow-up.

When a patient starts bisphosphonate treatment, the BMD typically rises sharply for a couple of years, and then plateaus and remains stable, Dr. Bauer said. After patients stop bisphosphonate treatment, their BMD usually declines gradually. Prior analysis of the FLEX data showed that patients who failed to reach a BMD of at least -2.5 usually benefited with fewer fractures when they remained on bisphosphonate treatment. The new findings suggest that patients with T scores of less than -1.5 may also benefit from continued treatment. On the other hand, when patients reach an adequate BMD (greater than -1.5), "it's not unreasonable to talk with the patient about the potential risks and benefits of a drug holiday," Dr. Bauer said.

The FLEX study was funded by Merck, the company that markets alendronate (Fosamax). Dr. Bauer said that he has received research funding from Amgen, Merck, and Novartis. ■