Congenital Heart Surgery Better in Ped Hospitals

VITALS

Major Finding: Adolescents undergoing surgery for congenital heart disease have a mortality rate of 0.15% when the procedure is done in a children's hospital, compared with 0.7% when the surgery is done in an adult hospital, and 2.1% when the surgery is done in an adult hospital with a children's unit.

Data Source: A national sample representing 22 million hospital discharges of patients aged 20 years and below during 2000, 2003, and 2006.

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BY ROBERT FINN

FROM THE ANNUAL MEETING OF THE WESTERN THORACIC SURGICAL ASSOCIATION.

OJAI, CALIF. — Congenital heart surgery, once confined to infants and very young children, is increasingly being performed on older children and adults, the result of more effective medical and surgical treatments. A new study of a nationally representative database of pediatric hospital admissions has now shown that older children have a significantly lower mortality rate when their surgery is performed at a children's hospital instead of an adult hospital.

In 2006, for example, the mortality rate from congenital heart surgery for children and adolescents aged 14-20 years was 0.15% when the surgery was performed in a children's hospital. This is significantly lower than the mortality rate of 0.7% when the surgery was performed in an adult hospital or 2.1% when the surgery was performed in an adult hospital with a children's unit, Dr. Jeffrey S. Heinle reported at the annual meeting of the Western Thoracic Surgical Association.

"The vast majority of adolescent patients continue to be cared for in adult hospitals without a congenital unit," said Dr. Heinle of the Baylor College of Medicine, Houston. "If you do a large volume of congenital cases, your outcomes in adult patients are better. … Even lesions we would consider simple, such as a ventricular septal defect in an adult, are better cared for with better outcomes by congenital heart surgeons rather than adult surgeons."

The investigators used data from the Healthcare Cost and Utilization Project Kids' Inpatient Database, which provides nationally representative estimates of pediatric hospital discharges. Data for the 3 years studied—2000, 2003, and 2006—represent 22 million discharges, of which about 190,000 (0.8%) were for congenital heart surgery.

The number of congenital heart surgeries increased from about 57,000 in 2000 to about 70,000 in 2006. During that time the median age of children receiving congenital heart surgery rose significantly, from 6 years in 2000 to 8 years in 2003 and to 9 years in 2006.

The proportion of infant surgeries remained at about 33% during all 3 years studied. The proportion of surgeries in children aged 1-13 years decreased significantly from 29% to 23%. And the proportion of surgeries in adolescents aged 14-20 years increased significantly from 38% to 44%.

The in-hospital mortality rate declined significantly in infants, from 8.5% to 7.1%; and in adolescents, from 1.7% to 1.1%. Mortality remained between 1.5% and 1.7% for children aged 1-13 years.

The mean length of hospital stay rose significantly, from 13.7 days in 2000 to 16.3 days in 2006. This increase was driven largely by the increase in infants' average length of stay, from 29 to 38 days.

Infants and children 1-13 years of age were much more likely to be treated in a children's hospital or an adult hospital with a children's unit than in an adult hospital without a children's unit. On the other hand, about 75% of adolescents were treated in an adult hospital without a children's unit.

It wasn't only adolescents who had lower mortality when treated in a children's hospital. Infants too had significantly lower mortality: 6.1%, compared with 7.4% in adult hospitals and 7.7% in adult hospitals with a children's unit. ■

BYSTOLIC® (nebivolol) tablets **Rx Only**
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2007

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. **Thyrotoxicosis -** 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. HYPERTENSION: 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) ≥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/claudication, 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 overdosage 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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