

# Foot, Ankle Pain Leading Causes of OA Visits

BY SARA FREEMAN

**BIRMINGHAM, ENGLAND** — Foot and ankle pain affects more women than men after age 45 years, when osteoarthritis often manifests.

A systematic review of available literature from eight studies from around the world estimated that foot and ankle pain occurs in 15%-30% in women and 10%-20% of men.

It is not clear what proportion of people who have pain have OA, said Martin J. Thomas, a research physiotherapist at the Arthritis Research UK National Primary Care Centre of Keele (England) University.

Mr. Thomas, who reported the findings at the annual meeting of the British Society of Rheumatology, said that he aimed to establish the baseline prevalence of ankle pain in order to have a point of com-

parison for future work on the prevalence of symptomatic foot and ankle OA.

"Foot pain and foot problems are very common in primary care," said Dr. Edward Roddy, a consultant rheumatologist at the Haywood Hospital in Stoke-on-Trent, England, and part of the research team at Keele University. Compared with other regional pain sites, such as the knee and hand, the foot has been studied less and "is just generally

less well understood," he observed.

The researchers therefore plan to undertake a longitudinal study to better characterize the epidemiology of foot and ankle OA in primary care and determine the likely causes of foot pain. Already, the team has discovered that foot pain is the most common reason for older adults to consult a general physician.

Dr. Roddy and associates looked at the reasons for musculoskeletal foot consultations in a primary care cohort of people older than 50 years. They identified 5,706 people who were taking part in the North Staffordshire Osteoarthritis Project (NorStOP), a 3-year, population-based cohort study in which participants from three local general practices had first completed a general health survey. Patients who reported experiencing any pain in the hands, hips, knees, or feet in the previous 12 months then completed a more specific survey about their regional pain, and their permission was sought for researchers to assess their medical records and to recontact them. The team looked at only those patients who reported foot pain or foot problems in the preceding 12 months. After the exclusion of patients who had not consulted in the 18 months before being surveyed, there were 4,402 (71%) people who consented to allowing their medical records to be reviewed.

Linking the NorStOP data to an electronic consultations database revealed that 350 of 3,858 (9%) people in the general population cohort studied actually consulted for foot pain or problems after completing the regional pain survey, whereas 3,508 (91%) who had completed the survey did not subsequently consult.

Looking at the reasons why 9% of people consulted while the remainder who had completed the survey and reported foot pain or problems did not, the researchers found that experiencing foot pain was the most common reason for presenting to a primary care doctor for a musculoskeletal problem (odds ratio, 2.04). Frequent consultations for other health problems was another significant predictor of consulting for foot pain or problems (OR, 1.65), as was the belief that treatments were effective in controlling disease (OR, 1.54).

"We've only looked at musculoskeletal consultations, so we may have underestimated consultations," said Dr. Roddy. However, he conceded that the definition of foot pain was very broad.

Dr. Roddy said that the next challenge was to try to work out what exactly is causing the foot pain and whether this resulted from OA, another musculoskeletal condition, or perhaps another reason entirely. The Keele researchers will be performing a study asking people who consult their primary care practitioner to not only complete a questionnaire about their foot problems, but also attend the hospital for clinical examination. ■

**Bystolic** 

(nebivolol) tablets  
2.5 mg, 5 mg, 10 mg and 20 mg

**Rx Only**

**Brief Summary:** For complete details please see full Prescribing Information for BYSTOLIC.

#### INDICATIONS AND USAGE

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

#### CONTRAINDICATIONS

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

#### WARNINGS

##### Abrupt Cessation of Therapy

Patients with coronary artery disease 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 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. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, patients should be carefully observed and advised to minimize physical activity. BYSTOLIC should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that BYSTOLIC be promptly reinstated, at least temporarily.

##### Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in the setting of congestive heart failure, and β-blockade may result in further depression of myocardial contractility and precipitate more severe failure. In patients who have compensated congestive heart failure, BYSTOLIC should be administered cautiously. If heart failure worsens, discontinuation of BYSTOLIC should be considered.

##### 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

If BYSTOLIC is to be continued perioperatively, patients should be closely monitored under 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. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.

##### 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. Caution should be exercised in these patients.

##### 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, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

#### PRECAUTIONS

##### Use with CYP2D6 Inhibitors

Nebivolol exposure increases with inhibition of CYP2D6 (see **Drug Interactions**). The dose of BYSTOLIC may need to be reduced.

##### Impaired Renal Function

BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

##### Impaired Hepatic Function

BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population (see **CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION**).

##### 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 challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

In patients with known or suspected pheochromocytoma, an α-blocker should be initiated prior to the use of any β-blocker.

##### Information for Patients

Patients should be advised to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, the patient should take the next scheduled dose only (without doubling it). Patients should not interrupt or discontinue BYSTOLIC without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nebivolol should be used with caution in these patients.

#### Drug Interactions

BYSTOLIC should be used with care when 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, are used concurrently. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

BYSTOLIC should not be combined with other β-blockers. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, BYSTOLIC should be discontinued for several days before the gradual tapering of clonidine.

**CYP2D6 Inhibitors:** Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of festicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m<sup>2</sup> basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no significant effect on ACTH-stimulated mean serum cortisol AUC<sub>0-120 min</sub>, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four-week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, *in vitro* mouse lymphoma TK<sup>+</sup>, *in vitro* human peripheral lymphocyte chromosome aberration, *in vivo* Drosophila melanogaster sex-linked recessive lethal, and *in vivo* mouse bone marrow micronucleus tests).

#### Pregnancy: Teratogenic Effects. Pregnancy 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. BYSTOLIC should be used 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.

#### 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.

#### 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 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**).

#### ADVERSE REACTIONS

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. In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse events was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

#### Adverse Reactions in Controlled Trials

**Table 1** lists treatment-emergent signs and symptoms 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 Events with an Incidence (over 6 weeks) ≥1% in BYSTOLIC-Treated Patients and at a Higher Frequency than Placebo-Treated Patients**

	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1
Bradycardia	0	0	0	1
Dyspnea	0	0	1	1
Rash	0	0	1	1
Peripheral edema	0	1	1	1

#### Other Adverse Events Observed During Worldwide Clinical Trials

Listed below are other reported adverse events with an incidence of at least 1% in the more than 5300 patients treated with BYSTOLIC in controlled or open-label trials, whether or not attributed to treatment, except for those already appearing in **Table 1**, terms too general to be informative, minor symptoms, or events unlikely to be attributable to drug because they are common in the population. These adverse events 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 and hyperuricemia

**Nervous System Disorders:** paraesthesia

#### Laboratory

In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

#### Events Identified from Spontaneous Reports of BYSTOLIC Received Worldwide

The following adverse events have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse events have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Events common in the population have generally been omitted. Because these events 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/claudecaudation, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

#### 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 events reported with BYSTOLIC overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events 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.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β-blockers, the following general measures should be considered 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):** Patients should be carefully monitored and treated with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

**Congestive Heart Failure:** Initiate therapy with digitalis glycoside and diuretics. In certain cases, consideration should be given to the use of inotropic and vasodilating agents.

**Bronchospasm:** Administer bronchodilator therapy such as a short-acting inhaled β<sub>2</sub>-agonist and/or aminophylline.

**Hypoglycemia:** Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12-19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

Call the National Poison Control Center (800-222-1222) for the most current information on β-blocker overdose treatment.

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Rev. 08/08

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