

Aortic Stenosis Patients Fail to Get Valve Replaced

BY MITCHEL L. ZOLER

ATLANTA — Many patients with severe aortic stenosis and clear indications for aortic-valve replacement fail to get surgery, according to findings in two independent reports at the annual meeting of the American College of Cardiology.

Physicians “need to tell patients they have symptomatic aortic stenosis, and without surgery their risk is very high,”

said Dr. Ramdas G. Pai, senior investigator on one of the studies and medical director of the Heart and Imaging Center at Loma Linda (Calif.) University.

“Symptoms are often wrongly ascribed to chronic obstructive pulmonary disease,” he noted. In addition, “a major barrier is that patients don’t want thoracotomy, and they fear physical and mental debilitation” from surgery. But “the risks from surgery are often overestimated.

Even in octogenarians and nonagenarians surgical mortality [for aortic valve replacement] is 1%,” Dr. Pai said.

The study from his center reviewed 187 consecutive patients diagnosed with severe aortic stenosis based on an echocardiography examination during 2006-2008 that identified an aortic valve with a surface area less than 1.0 cm². Their average age was 74, 56% were men, and their average aortic valve area was 0.72 cm².

Exertional symptoms secondary to aortic stenosis occurred in 79% of the patients, including chest pain, dyspnea, or dizziness with syncope. Another 13 of the 187 patients lacked aortic stenosis symptoms but had a left ventricular ejection fraction of less than 50%, which meant that a total of 160 patients (86%) had a class 1 indication for aortic valve replacement based on existing guidelines of the American College of Cardiology and the American Heart Association, said Dr. Aman Dua, a physician at Loma Linda University who presented the report.

The physicians who managed the patients referred 128 (68%) for aortic valve-replacement surgery, and 95 of these patients actually underwent replacement surgery. Among the 92 patients who did not undergo valve replacement, 39 refused surgery, physicians decided that 23 had comorbidities that precluded surgery (advanced age, frailty, dementia, chronic kidney disease, or porcelain aorta), and in 22 patients the physicians judged the aortic stenosis not severe even though it met the severity criteria of the ACC/AHA guidelines. (Dr. Dua did not provide a reason for the remaining eight patients who did not have surgery.) The decision not to have

Bystolic
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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 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. 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.

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. 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 testicular 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/m² 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_{0-120 min}, 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⁺, *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) $\geq 1\%$ 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_2 -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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Doctors 'need to tell patients they have symptomatic aortic stenosis, and without surgery their risk is very high.'



DR. PAI

surgery originated with the patient in 42% of the 92 cases, with a cardiologist in 36%, and with a cardiac surgeon in 17%. (Dr. Duo did not report the source of the decision in the remaining 5%.)

The patients who did not undergo surgery were older, with an average age of 77 compared with an average age of 70 in those who underwent surgery; 40% were asymptomatic, compared with a 4% asymptomatic rate in the surgery patients; the patients who did not have valve replacement had larger aortic valves, with an average area of 0.77 cm² compared with an average 0.69 cm² in the surgery patients; and the patients who had no surgery had more comorbidities with an average Euroscore of 21% compared with 15% in the surgery patients. All of these between-group differences were statistically significant.

“Patient reluctance is the major factor leading to nonsurgical management,” Dr. Dua said. “The physician’s discussion with the patient may have a significant role in this process, he said.

The second report focused on 328 patients aged 75 or older with severe aortic stenosis (valve area less than 1.0 cm²) managed at Aurora Health Care hospitals in the Milwaukee area during 2006-2008. In this group, 56 (17%) underwent valve-replacement surgery and 272 (83%) did

Continued on following page

Mitral Repair Is Safer Option for Octogenarians

BY MITCHEL L. ZOLER

ATLANTA — Carefully selected octogenarians with mitral regurgitation generally had good outcomes following mitral valve repair in a series of 322 patients at two medical centers.

“Mitral valve surgery can be performed with good mid- and long-term outcomes in carefully selected octogenarian patients in whom mitral repair may confer a survival benefit over replacement,” Dr. David H. Adams said at the annual meeting of the American College of Cardiology.

In the series of consecutive octogenarian patients who underwent valve surgery

placement is favored in elderly patients “is not valid,” commented Dr. Steven F. Bolling, professor of surgery and director of the mitral valve clinic at the University of Michigan in Ann Arbor. He noted results he recently reported from an analysis of more than 28,000 U.S. patients who underwent mitral valve surgery during 2005-2007 and entered into the Society of Thoracic Surgeons database. That analysis showed that age was not an in-

dependent predictor for whether patients underwent valve repair or replacement.

In Dr. Adams’ analysis, significant predictors of valve replacement included active endocarditis, which boosted the replacement rate by more than 10-fold, and need for coronary artery bypass grafting in degenerative patients, which raised the rate of valve replacement by almost 4-fold. Independent predictors of mortality included emergency surgery, a left

ventricular ejection fraction of 30% or less, and renal failure. In octogenarian patients with a left ventricular ejection fraction greater than 30% who underwent valve repair that was not emergency surgery and did not also have coronary artery bypass the operative mortality rate was 4%, Dr. Adams said.

Dr. Adams has served as a consultant to and was an inventor for Edwards Lifesciences. Dr. Bolling had no disclosures. ■



Elective valve replacement linked with a 60% increased risk of death compared with valve repair.

DR. ADAMS

for mitral regurgitation during 1998-2008 at Mount Sinai and at the Heart Center of the University of Leipzig, Germany, 227 patients (70%) underwent valve repair and 95 (30%) had valve replacement. The operative mortality rates were 11% and 19%, respectively. In a multivariate analysis, elective valve replacement was linked with a 60% increased risk of death versus valve repair, a significant difference, said Dr. Adams, professor and chairman of cardiothoracic surgery at Mount Sinai Medical Center in New York.

The conventional wisdom that re-

Continued from previous page

not, even though 166 of those who did not get surgery had symptoms, reported Dr. M. Fuad Jan, of the Milwaukee Heart Institute at Aurora Sinai Medical Center.

The patients who did not undergo surgery had significantly more comorbidities, with an average Euroscore of 35%, compared with an average 15% score in the patients who had their valve replaced. The patients who did not receive valve replacement were also older, with an average age of 85, compared with an average age of 82 in those who had surgery. Advanced age constituted the sole reason for not performing surgery in 43% of the patients, age plus comorbidities explained 50% of the cases that did not have surgery, patient refusal occurred in 4% of the cases, and no reason was identified in the remaining 3%.

The analysis also documented the potential benefit from valve replacement surgery. During 2 years of follow-up, the survival rate in the 56 patients who underwent valve replacement was 88%, significantly better than the 50% survival rate in the 272 patients who did not undergo valve replacement, Dr. Jan said.

Dr. Dua and Dr. Jan said that they had no disclosures. ■

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*2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update).

INDICATIONS AND USAGE

Effient is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI

IMPORTANT SAFETY INFORMATION

WARNING: BLEEDING RISK

Effient® (prasugrel) can cause significant, sometimes fatal, bleeding. Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients ≥75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered. Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery. Additional risk factors for bleeding include: body weight <60 kg, propensity to bleed, concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs]). Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient. If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

- Effient is contraindicated in patients with active pathological bleeding, such as from a peptic ulcer or intracranial hemorrhage, or a history of transient ischemic attack (TIA) or stroke
- Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued. Effient should also be discontinued for active bleeding and elective surgery
- Premature discontinuation of Effient increases risk of stent thrombosis, MI, and death
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Please see Brief Summary of Prescribing Information on adjacent pages.

Reference: 1. Kushner FG, Hand M, Smith SC Jr, et al. *Circulation*. 2009;120:2271-2306.



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