HeartLines

TRENDS IN HEART AND VASCULAR DISEASE

A publication from Cardiovascular Consultants of South Florida | www.heartpartners.com | Volume 1 • Issue 1



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Etiology, Diagnosis, and Treatment

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HeartLines:
TRENDS IN HEART AND VASCULAR DISEASE

Volume 1 · Issue 1

Contents

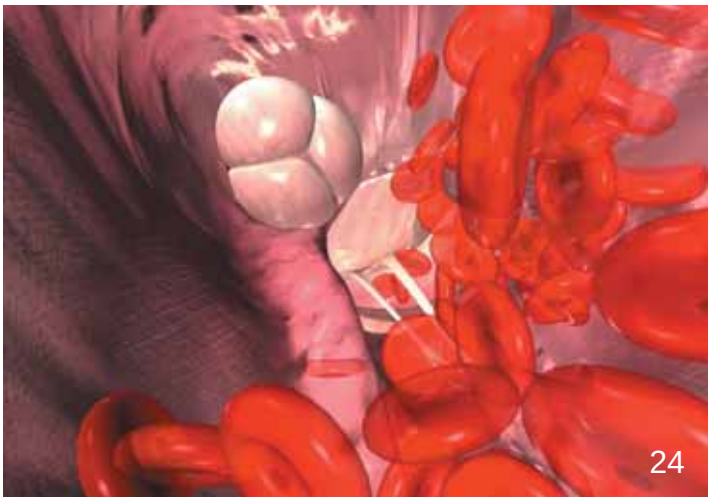
features

Evaluating Syncope
Etiology, Diagnosis, and Treatment 10

Proper Application of Pacer Technology
Exploring New Paradigms in Cardiac Pacing 14

New Treatment Options for Venous Disease
Evaluating Varicose Veins and Venous Insufficiency 22





departments

DIAGNOSTICS AND TREATMENT

Going Beyond the Heart
Stent and Angioplasty Procedures Provide Global Vascular Benefits 7

Advancing Treatments
The Changing Paradigm in Coronary Artery Disease 8

HEALTH CARE PRINCIPLES

Getting to the Heart of Things
Cardiology Center Focuses on All Aspects of Cardiovascular Care 13

Know the Law
Examining Critical Regulations Governing Medical Practices 19

REPORTS

Heart Failure Guidelines
Update Offers Effective Treatments 24

The Future of Medical Care
Electronic Medical Records Benefit Both Patient and Physician 26

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Welcome



It gives us great pleasure to welcome you to the inaugural issue of *HeartLines: Trends in Heart and Vascular Disease*. Since our group formed 10 years ago, our name has remained South Broward Cardiology Consultants, and we have continued to provide premier cardiovascular medical services to Broward County. In reality, however, we have a following all over South Florida, where we have taken the lead in vascular disease interventions. To reflect this expansion, we are changing our name to Cardiovascular Consultants of South Florida (CCSF).

With 16 full-time physicians, including noninvasive and invasive cardiologists, electrophysiologists, and vascular medicine specialists, we are one of the largest cardiovascular groups in Florida. Many of our physicians have practiced here for years. In fact, our invasive cardiologists have performed more than 25,000 procedures at Memorial Regional Cardiac Catheterization Laboratory since it opened under our direction more than a decade ago.

Because it makes sense to consider the heart and blood vessels as one system, our center recently incorporated a vascular program that emphasizes the nonsurgical treatment of peripheral vascular disease. Our registered vascular technicians use the newest in vascular diagnostic equipment, providing diagnostic testing for carotid, abdominal, and extremity disorders.

Our recent additions to the group include Raul Mitrani, MD, cardiac electrophysiologist, former associate professor at University of Miami School of Medicine, and Director of the Arrhythmia and Syncope Center at Jackson Memorial Hospital. Also joining us is Juan Pastor-Cervantes, MD, cardiac and vascular interventionalist, who completed a post-fellowship in peripheral vascular interventions at the renowned Cardiovascular Institute of the South. He joined us last year after spending a year on the University of Miami School of Medicine faculty. Dr. Pastor-Cervantes was also recently named National Spokesperson for Cordis's Healthy from the Heart program. Susan B. Fox, DO, vascular medicine specialist, was fellowship trained at The Cleveland Clinic and is board certified in vascular medicine. She joined our group this year, along with John Cogan, MD, who is board certified in cardiac electrophysiology.

Members of our staff have worked as chiefs of cardiology and medicine. At this time, Howard Berlin, President of CCSF, serves on the Institutional Review Board for Memorial Regional Hospital. Dr. Mitrani is Director of Electrophysiology for the Memorial Healthcare System. Jose Guzman, MD, is Chief of Medicine at Memorial Miramar, and Michael Braun, MD, sits on the Medical Executive Committee at Aventura Hospital.

In the past, our group distributed a *Heartlines* newsletter to all our patients with a focus on varying topics in cardiovascular disease. Last year's newsletter is available for viewing and download at www.heartpartners.com. This year, we decided to start a magazine for physicians in our area, highlighting important topics we hope you will find informative. We welcome your comments and questions. Feel free to e-mail *HeartLines* Editor Dr. Raul Mitrani with feedback at rmitrani@ccsfemail.com.

We thank the organizations that have partnered with us to make this publication possible. Each one is actively involved on some level with our group and was chosen to join us on this project.

Enjoy!



Judah Friedman, MEd, MBA, Chief Executive Officer

HeartLines:
TRENDS IN HEART AND VASCULAR DISEASE

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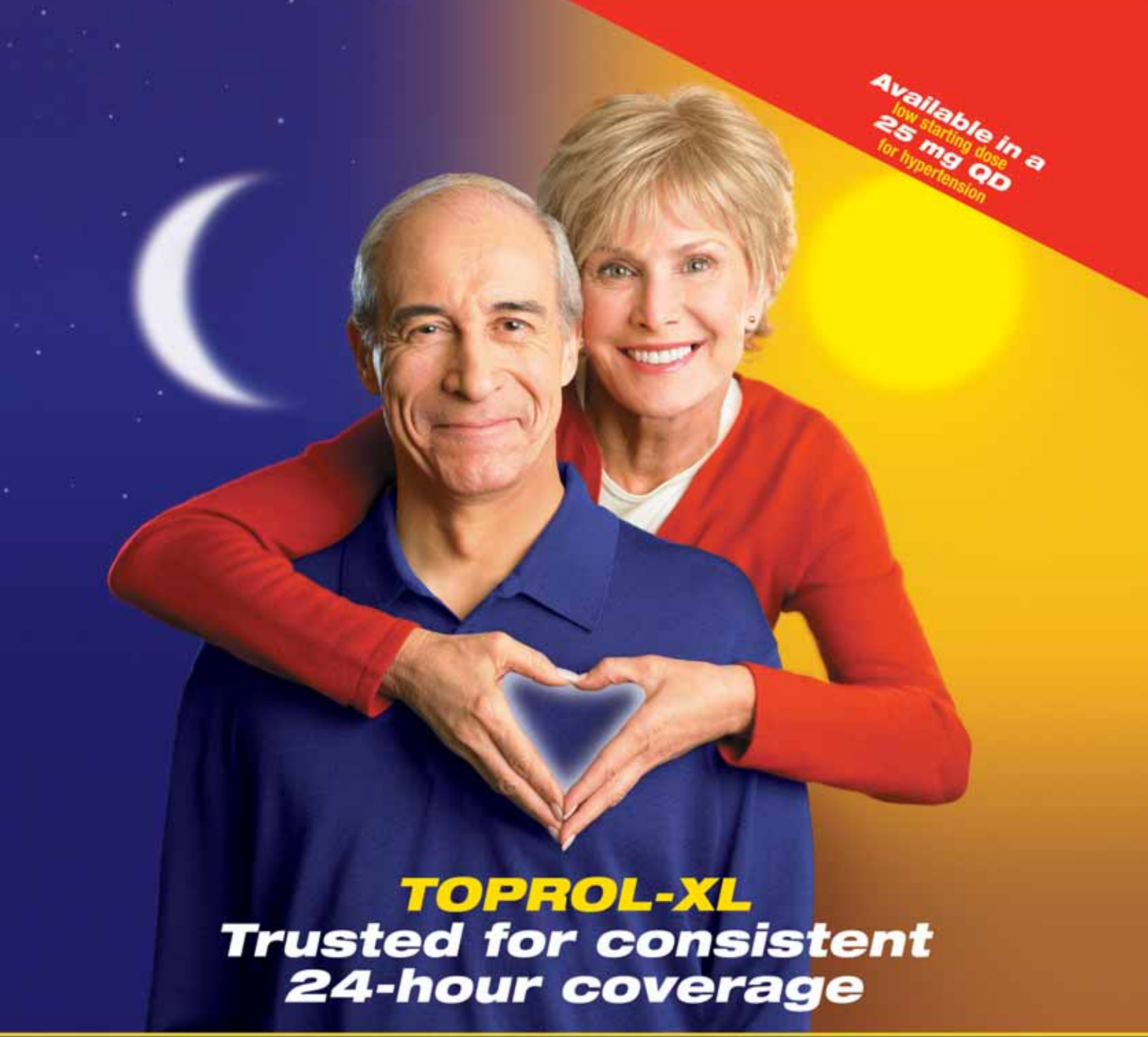
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HeartLines is an educational magazine published by Cardiovascular Consultants of South Florida to introduce our staff and facilities as well as communicate educational news and trends involving cardiovascular diseases and treatments as well as other articles of interest. The biannual publication is aimed at physicians throughout South Florida, as well as employer groups and other influential members of our community.



TOPROL-XL is indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

Initiate with 25 to 100 mg once daily. Increase at weekly or longer intervals to optimize clinical response. Dosages above 400 mg per day have not been studied.

TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place).

Patients taking TOPROL-XL should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain ß-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. The dosage should be reduced gradually over a 1- to 2-week period, and the patient should be carefully monitored.

Please see brief summary of full Prescribing Information, including boxed WARNING regarding abrupt cessation of therapy on adjacent page.

ONCE-A-DAY

TOPROL-XL®

(metoprolol succinate) extended-release tablets 25 mg 50 mg 100 mg 200 mg

www.toprol-xl.com

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BRIEF SUMMARY: For full Prescribing Information, see package insert.

INDICATIONS AND USAGE Hypertension: TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. **Angina Pectoris:** TOPROL-XL is indicated in the long-term treatment of angina pectoris. **Heart Failure:** TOPROL-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, TOPROL-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

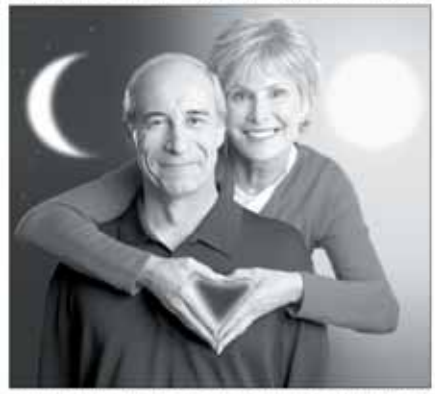
CONTRAINDICATIONS TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS) and in patients who are hypersensitive to any component of this product.

WARNINGS

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TOPROL-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$-selectivity, however, TOPROL-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of TOPROL-XL should be used (see DOSAGE AND ADMINISTRATION). ***Major Surgery:*** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. TOPROL-XL, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers. ***Diabetes and Hypoglycemia:*** TOPROL-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. ***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm. ***Peripheral Vascular Disease:*** Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals. ***Calcium Channel Blockers:*** Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

PRECAUTIONS General: TOPROL-XL should be used with caution in patients with impaired hepatic function. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. Worsening cardiac failure may occur during up-titration of TOPROL-XL. If such symptoms occur, diuretics should be increased and the dose of TOPROL-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of TOPROL-XL. **Information for Patients:** Patients should be advised to take TOPROL-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue TOPROL-XL without consulting the physician. Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with TOPROL-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking TOPROL-XL. Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath. **Laboratory Tests:** Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase. **Drug Interactions:** Catecholamine-depleting drugs (eg, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. **Pregnancy Category C:** Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when TOPROL-XL is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Clinical studies of TOPROL-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients. Of the 1,990 patients with heart failure randomized to TOPROL-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Risk of Anaphylactic Reactions:** While taking beta-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 reaction.

ADVERSE REACTIONS Hypertension and Angina: Most adverse effects have been mild and transient. The following adverse reactions have been reported for immediate release metoprolol tartrate. *Central Nervous System:* Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported. *Cardiovascular:* Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS). *Respiratory:* Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS). *Gastrointestinal:* Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients. *Hypersensitive Reactions:* Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported. *Miscellaneous:* Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol. **Potential Adverse Reactions:** In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to TOPROL-XL. *Central Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Cardiovascular:* Intensification of AV block (see CONTRAINDICATIONS). *Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Hypersensitive Reactions:* Fever combined with aching and sore throat, laryngospasm, and respiratory distress. **Heart Failure:** In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse events vs. 12.2% of placebo patients. The table below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Events Occurring in the MERIT-HF Study at an Incidence ≥1% in the TOPROL-XL Group and Greater Than Placebo by More Than 0.5%

	TOPROL-XL N=1990 % of patients	Placebo N=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Other adverse events with an incidence of > 1% on TOPROL-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue. **Post-Marketing Experience:** The following adverse reactions have been reported with TOPROL-XL in worldwide post-marketing use, regardless of causality: *Cardiovascular:* 2nd and 3rd degree heart block; *Gastrointestinal:* hepatitis, vomiting; *Hematologic:* thrombocytopenia; *Musculoskeletal:* arthralgia; *Nervous System/Psychiatric:* anxiety/nervousness, hallucinations, paresthesia; *Reproductive, male:* impotence; *Skin:* increased sweating, photosensitivity, urticaria; *Special Sense Organs:* taste disturbances.

OVERDOSAGE Acute Toxicity: There have been a few reports of overdosage with TOPROL-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since TOPROL-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to TOPROL-XL. **Signs and Symptoms:** Overdosage of TOPROL-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis. **Treatment:** In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed: ***Elimination of the Drug:*** Gastric lavage should be performed. ***Bradycardia:*** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. ***Hypotension:*** A vasopressor should be administered, eg, levarterenol or dopamine. ***Bronchospasm:*** A $beta_2$-stimulating agent and/or a theophylline derivative should be administered. ***Cardiac Failure:*** A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

DOSAGE AND ADMINISTRATION TOPROL-XL is an extended release tablet intended for once daily administration. For treatment of hypertension and angina, when switching from immediate release metoprolol to TOPROL-XL, the same total daily dose of TOPROL-XL should be used. Dosages of TOPROL-XL should be individualized and titration may be needed in some patients. TOPROL-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed. **Hypertension:** The usual initial dosage is 25 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied. **Angina Pectoris:** The dosage of TOPROL-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1–2 weeks (see WARNINGS). **Heart Failure:** Dosage must be individualized and closely monitored during up-titration. Prior to initiation of TOPROL-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of TOPROL-XL is 25 mg once daily for two weeks in patients with NYHA class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of TOPROL-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. The dose of TOPROL-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce TOPROL-XL. If heart failure patients experience symptomatic bradycardia, the dose of TOPROL-XL should be reduced.

HOW SUPPLIED Tablets containing metoprolol succinate equivalent to the indicated weight of metoprolol tartrate, USP, are white, biconvex, film-coated, and scored.

Tablet	Shape	Engraving	Bottle of 100 NDC 0186-	Unit Dose Packages of 100 NDC 0186-
25 mg*	Oval	A | I	1088-05	1088-39
50 mg	Round	A mq	1090-05	1090-39
100 mg	Round	A mq	1092-05	1092-39
200 mg	Oval	A my	1094-05	N/A

*The 25-mg tablet is scored on both sides.

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.)

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Made in Sweden

Rev. 02/05

AstraZeneca



BY JUAN A. PASTOR-CERVANTES, MD

Going Beyond the Heart

Stent and Angioplasty Procedures Provide Global Vascular Benefits

Over the last 50 years, technological advances in treating cardiovascular diseases have allowed patients to live longer and better lives. In the mid-1960s, for example, researchers developed a revolutionary concept — the coronary bypass — for patients with severe coronary disease. The advent of this technique marked a huge step forward in caring for these individuals. In the mid-1970s, another landmark breakthrough happened: the balloon angioplasty procedure.

Today, after years of hard work and dedication developing new techniques, physicians use minimally invasive cardiovascular interventions to treat most patients, shifting away from the old standard of performing surgery to correct coronary or peripheral artery blockages. Now more than one million coronary angioplasties are performed annually in the United States, compared to 300,000 surgeries, to improve blood flow to the heart muscle.

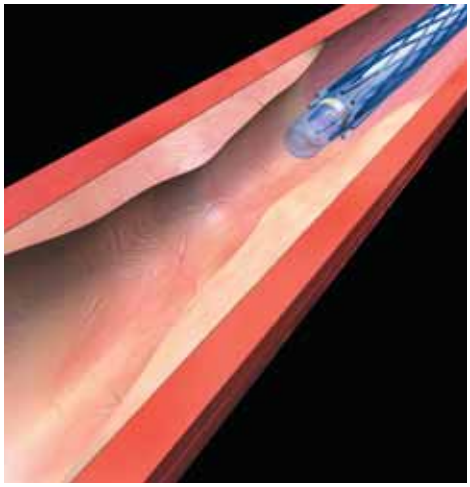
Coronary Stent Advances

Over the last 15 years, physicians have used coronary stents to improve outcomes for coronary angioplasties. But more importantly, over the last two years, we have begun implanting medicated stents, better known as drug-eluting stents. This advance has improved results so less than one in 10 patients returns for further treatments in the area of the stent implant.

Studies comparing the use of angioplasty and medicated coronary stents to coronary bypass surgery have found in favor of the coronary stent technique. Patients receiving the stents were much less likely to suffer debilitating or fatal heart attacks or strokes in the first year after their procedures. Also with the stents and angioplasty, only three patients in 100 returned in the first year for correction of a reblocked artery.

Stent and Angioplasty Success in Other Areas

Physicians have demonstrated similar success using angioplasty and stents to treat carotid arteries. Traditionally, carotid artery endarterectomy is the first choice to treat blockages in these vessels. Over the last few years, however, it was proven that carotid artery stenting with embolic protection devices (filters that trap clots during the stent implantation) is the best way to treat high-risk surgical patients. Soon we hope to show this approach is the best choice for all patients with carotid artery problems.



More than one million coronary angioplasties are performed annually in the United States, compared to 300,000 surgeries, to improve blood flow to the heart muscle.

Stents have allowed patients to avoid other high-risk surgeries, such as subclavian artery bypass, abdominal aortic aneurysm resection, renal artery bypass, and celiac trunk or mesenteric artery bypasses. These lower-risk procedures typically produce better results and require shorter hospital stays (usually less than 24 hours).

Intermittent claudication is another area where stents and angioplasties are being used more commonly. With this condition, patients have blockages of the arteries that provide blood to the legs. The incapacitating disease can gradually decrease blood flow to such a degree that the limb needs to be removed. Severely diminished circulation to the extremities is responsible for more than 150,000 amputations in our country every year. Sadly, fewer than 30% of these patients return to their normal functioning after the amputation. The use of stents and angioplasties, however, can help restore blood flow and reduce the incidence of amputation in many instances.

Moving Ahead

As a physician, I am a firm advocate of ensuring my patients clearly understand their conditions and the possible courses they may take. I am also a firm believer in making patients aware of all treatment options available to them, including the latest advances in medical techniques and technology. Physicians are continually working to develop devices, like the medicated stents, and procedures, like balloon angioplasties, that achieve better outcomes with less risk, less pain, and shorter recovery times for patients. The encouraging results for stents and angioplasties are just one example of how the search for the best treatment approach is moving forward every day. ■

Juan A. Pastor-Cervantes, MD, FACC, is a graduate of Universidad La Salla School of Medicine, Mexico City, Mexico. He completed an internship, a residency, and cardiology and interventional cardiology fellowships at the University of Miami's Jackson Memorial Hospital. Dr. Pastor-Cervantes has worked as an interventional cardiologist and a peripheral vascular interventionalist, as well as Assistant Professor of Medicine at the University of Miami School of Medicine.



BY FRANK J. PEARL, MD, FACC, FCCP, FACP

Advancing Treatments

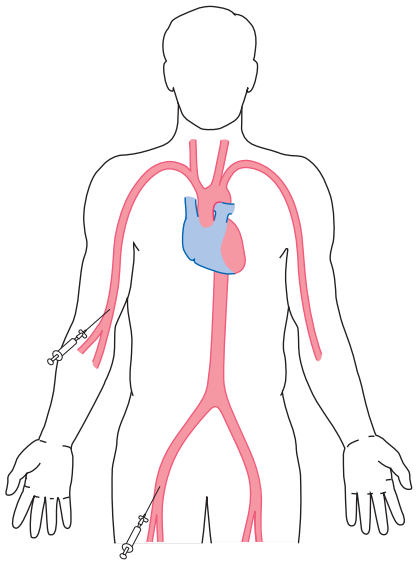
The Changing Paradigm in Coronary Artery Disease

There are many exciting new advances in the diagnosis and treatment of coronary artery disease (CAD), which is also known as atherosclerosis ("hardening") of the coronary arteries. These arteries supply blood back to the heart muscle. The past 25 years have seen major advances from the days of difficult diagnosis and very little treatment of this disease.

For instance, there is the recognition of much lower limits of "normal" blood pressure and serum cholesterol with information obtained from the Framingham Heart Study. The ongoing Framingham study follows numerous parameters such as blood pressure and cholesterol levels of the population of Framingham, Massachusetts, over several decades.

Defining Normal Pressure

Normal blood pressure is no longer considered a patient's age plus 100. Today, normal blood pressure is considered less than 120/80 (systolic/diastolic). In addition, it is now recognized that both the systolic and diastolic pressures are important. Prehypertension is now defined as a systolic pressure 120 to 139 or a diastolic pressure 80 to 89.



Cardiac catheterization, shown in this image with two typical entry points — popliteal and femoral, is no longer used just for diagnosis.

Total cholesterol was previously considered normal up to 300. It is now known that ideal total cholesterol is less than 200; and there are many important fractions of the total cholesterol that we need to evaluate, including high-density lipoprotein (HDL, the good cholesterol) and low-density lipoprotein (LDL, the bad cholesterol). High cholesterol is an important CAD risk factor. However, 80% of patients who develop CAD have the same cholesterol values as those who do not develop the disease.

Now physicians can look not only at total cholesterol, HDL, LDL, and triglycerides, but with information from the Berkeley HeartLab, we can also evaluate subfractions of HDL and LDL, Lp(a), and

In the Forefront of Advanced Techniques

Cholesterol Tests Lead to Better CAD Diagnosis

For decades, cholesterol has been a recognized major risk factor for coronary artery disease (CAD). Millions of Americans watch their diets, exercise, or take cholesterol-lowering medications to reduce the risk of life-threatening heart attacks. However, approximately half of the 1.5 million heart attacks occurring each year affect people with "normal" cholesterol tests.

Fortunately, new refined diagnostic tools are becoming available in South Florida that can provide a more accurate assessment of an individual's heart attack risk.

"The average cholesterol profile today doesn't adequately address risk issues," says Frank J. Pearl, MD, FACC, FCCP, FACP, a board-certified cardiologist with Cardiovascular Consultants of South Florida. "It takes more sophisticated laboratory testing and new diagnostic tools."

Dr. Pearl notes that hypertension (high blood pressure) and cholesterol are among the key risk factors for heart attacks, along with smoking and genetic factors. The big news is the release of new studies that foster advanced medical understanding of cholesterol's role.

The lowering of low-density lipoprotein (LDL) cholesterol with statins reduces cardiovascular events by 30% to 40%. What about the other 60% to 70%? One in three senior men and one in five postmenopausal women have LDL "Pattern B," with extra small particles of LDL in their blood, which increases the risk of heart disease by as much as 300% compared to patients with LDL "Pattern A," with larger particles. "Fortunately, treatment with niacin-based drugs and/or fibrates increases LDL size, reducing the risk, provided the pattern is identified in time," says Dr. Pearl. In addition, the importance of raising high-density lipoprotein (HDL) cholesterol and lowering triglycerides is receiving a great deal of attention. These goals are also achieved with the use of niacin and fibrates.

By finding atherosclerosis at an early (asymptomatic) stage, before the development of a positive stress test, angina, or a heart attack, proper treatment can be instituted that will stop progression, possibly achieve regression, and keep the patient asymptomatic and "healthy."

homocysteine, as well as a number of inflammatory markers.

Improved Testing Accuracy

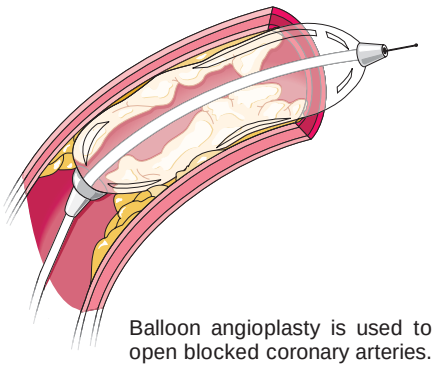
Testing for CAD has evolved from the master's two-step (walking up and down a two-step platform) to computerized treadmill exercise testing and sophisticated nuclear scanning of the heart's blood supply and function. Such testing allows for both improved sensitivity and specificity.

Unfortunately, a patient will not have a positive stress test until he or she has at least a 50% blockage in a coronary artery. Recently, electron beam computerized tomography (EBCT) arrived on the scene. This technology allows for visualization and quantification of coronary calcification. The greater the amount of calcification, the more coronary plaque present.

The presence of plaque does not necessarily equate to hemodynamically significant blockage, however. Once coronary calcification is determined as present, stress testing can determine its physiologic significance.

Aggressive Treatment

In addition, treatment modalities have evolved on several fronts. There are now multiple categories of medication to treat CAD aggressively, as well as the hypertension and high cholesterol that exacerbate it. Cardiac catheterization is no longer used just for diagnosis. Percutaneous transluminal coronary angioplasty (PTCA), or balloon angioplasty, can be used to open blocked coronary arteries; and the combined use of stents keeps the opened arteries patent.

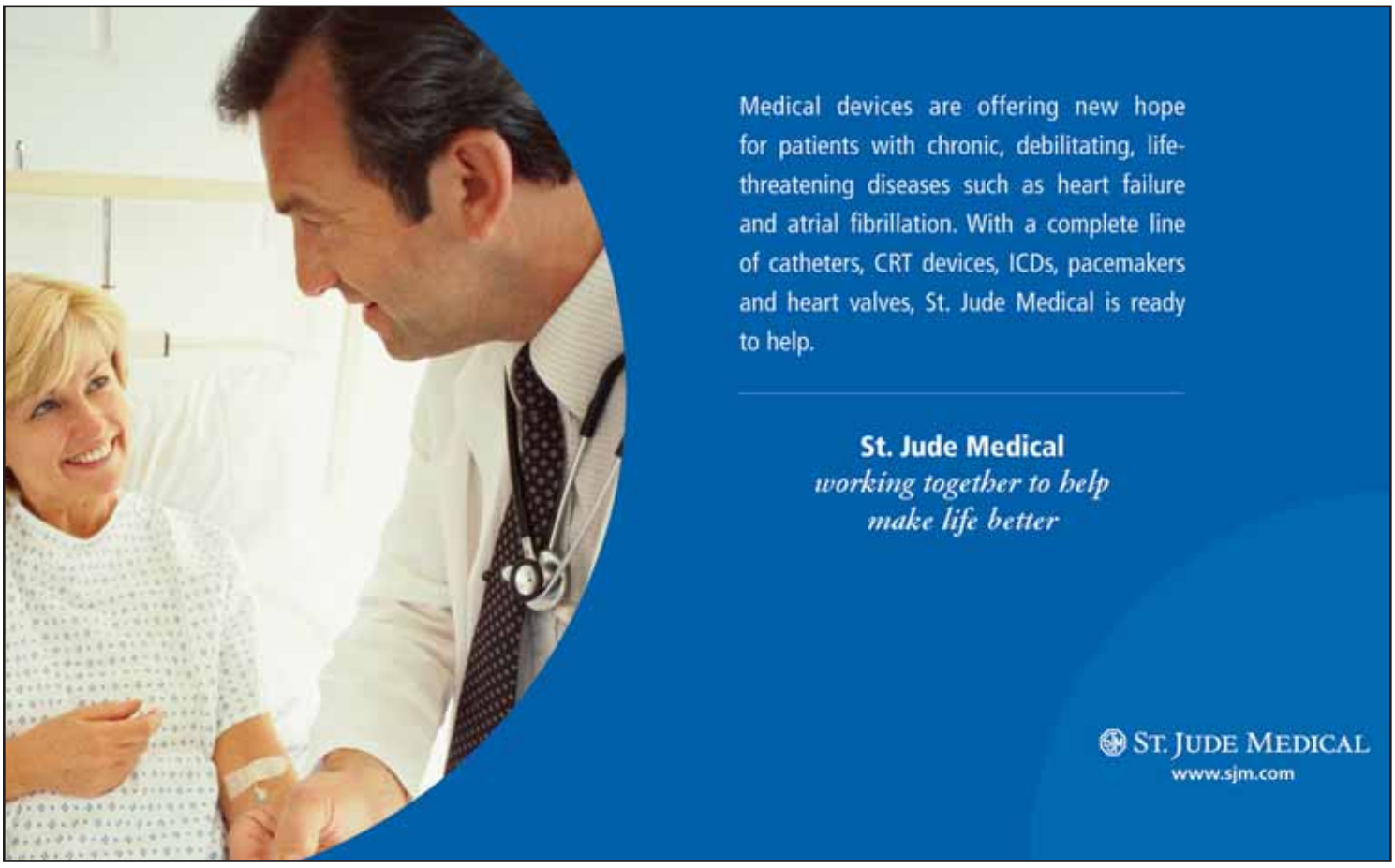


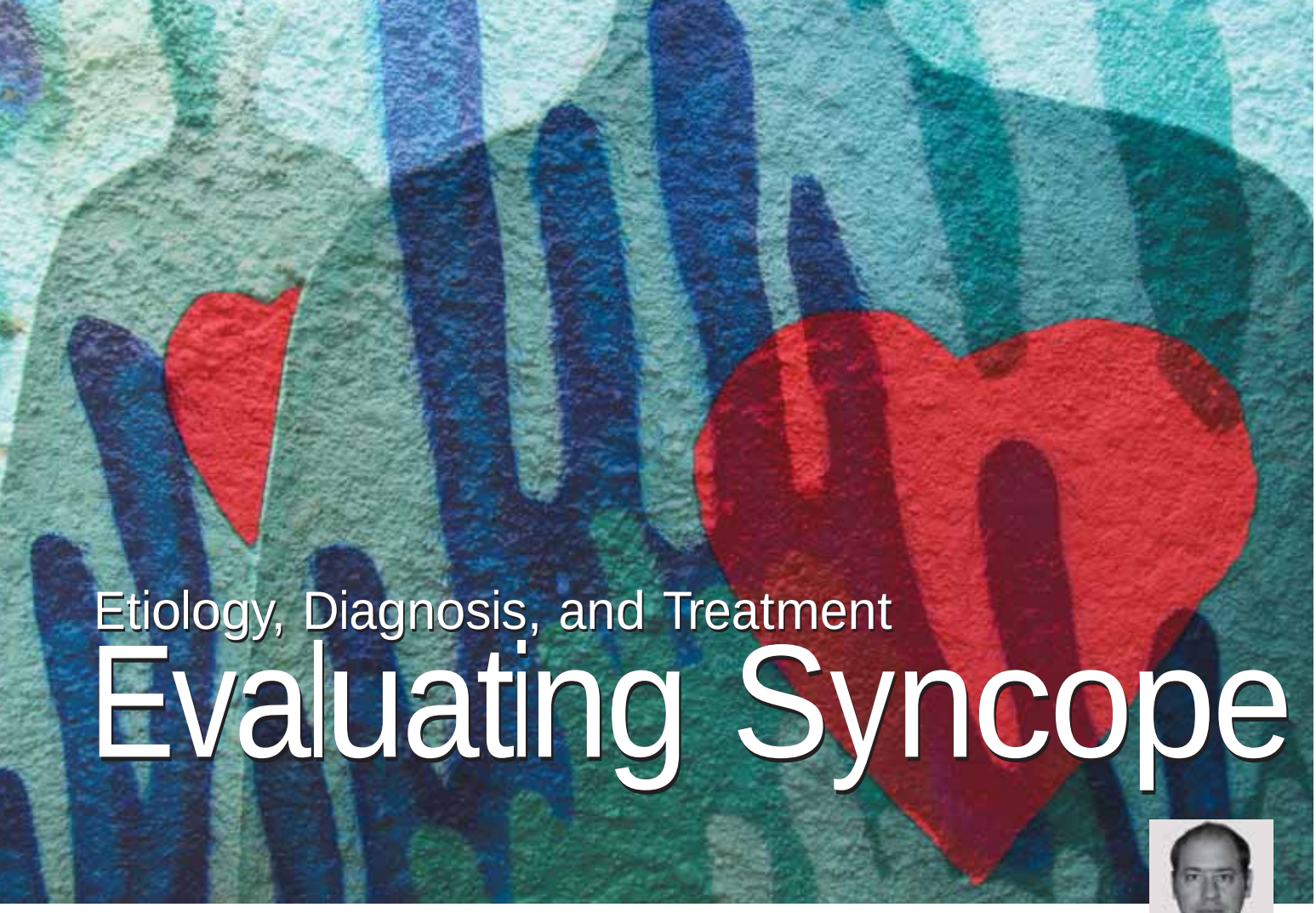
Balloon angioplasty is used to open blocked coronary arteries.

From the surgical standpoint, aorto-coronary bypass surgery has now matured to the point that the routine bypass patient is discharged from the hospital within five to seven days. Moreover, in the coming decade, there is an excellent chance gene therapy will become available.

Given all the current options, it is important to identify any coronary problem so it can be found and treated before it finds us. ■

Frank J. Pearl, MD, FACC, FCCP, FACP, earned his medical degree from Jefferson Medical College, Philadelphia, in 1974. An internship and residency were completed at University of Miami, Jackson Memorial Hospital. Dr. Pearl completed his fellowship in cardiology at Jefferson Medical College and Temple University Health Sciences Center. He is board certified in internal medicine, cardiovascular disease, and critical care medicine. He is a Voluntary Associate Professor of Medicine at the University of Miami and a Clinical Assistant Professor of Medicine at Nova Southeastern University.





Etiology, Diagnosis, and Treatment

Evaluating Syncope

BY JOHN COGAN, MD

Syncope, or the transient loss of consciousness and postural tone with spontaneous recovery, is one of the most common reasons for emergency room visits (3.5%), and one-third of those patients are admitted to the hospital.

There are many causes of syncope. Some of them are benign, while others may represent a malignant arrhythmia capable of causing sudden death. Even benign causes of syncope can produce injury, substantial anxiety, and disability.

According to the Framingham Heart Study data and pooled data from five other studies, the most common causes for syncope are neurocardiogenic ("vasovagal," 18%), cardiac (18%), neurologic (10%), orthostatic (8%), "situational" (5%), and medication induced (3%).

Syncope Etiology

The etiology of syncope depends on the patient's age. In the younger population, neurocardiogenic syncope (NCS), situational, and psychiatric causes are the most common and are usually benign. Causes for cardiac syncope in younger patients that are infrequent but important to diagnose since they are potentially life threatening include the long QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, arrhythmogenic right ventricular dysplasia, and hypertrophic cardiomyopathy.

NCS is less prevalent in the older population than in the younger set, although carotid hypersensitivity, a form of neurally mediated syncope, becomes more common. Orthostatic hypotension, medication-induced syncope, cardiac syncope, or multifactorial etiologies also become more prevalent in the elderly.

The most common causes of cardiac syncope include tachyarrhythmias (ventricular fibrillation/tachycardia, torsades de pointes, hypotensive supraventricular tachycardia) and bradyarrhythmias (heart block, sick sinus syndrome, carotid hypersensitivity). Conditions associated with these arrhythmias include VT/VF post myocardial infarction, hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome, Brugada syndrome, anomalous coronary arteries, and right ventricular dysplasia.

The mortality related to syncope is clearly related to its etiology. NCS has the same mortality as the general population, whereas cardiac, neurologic, or even unknown causes for syncope have a greater mortality at one or two years than age-matched population. From several studies, it is clear that cardiac causes for

syncope are associated with a 20% to 30% mortality in one year if left untreated. Patients with syncope in the setting of moderate to severely depressed ejection fraction have a mortality rate as high as 40% in one year. It is now recommended to refer this subgroup of patients for evaluation for a defibrillator implantation.

Diagnosis

Finding the etiology of syncope is challenging. The diagnostic work-up begins with a careful history and physical examination, with all the details on frequency and circumstances on each event (including prodromal symptoms and precipitating factors), the complete family history, past medical history, and history from witnesses of these episodes. The physical exam can reveal clues on the etiology of syncope, including heart murmurs and neurologic signs.

A 12-lead electrocardiogram (ECG) should be performed routinely in almost all cases of syncope (with careful attention to rhythm, QT duration, bundle branch blocks, and evidence of ischemia or hypertrophy). An echocardiogram should be performed in patients in whom there exists any question as to whether he or she has structural heart disease.

> "There are many causes of syncope. Some of them are benign, while others may represent a malignant arrhythmia capable of causing sudden death."

Diagnostic tools for the work-up syncope may include tilt table testing (TTT), Holter monitor, event recorder, echocardiogram, and an electrophysiologic study (EPS). Further work-up (for example, magnetic resonance imaging [MRI] or electroencephalogram [EEG] in neurologic cases) is often necessary if the initial history and physical examination point to other diagnoses.

The work-up and treatment of patients with syncope depends on the initial assessment and impression.

Patients with suspected NCS would likely require TTT. It is the best method for confirming the diagnosis of neurocardiogenic syncope. Indications for TTT include unexplained recurrent syncope in patients with normal hearts or a single episode associated with injury or in settings that pose a high risk of injury (for example, while driving a car). It is also indicated for patients with organic heart disease in whom other causes of syncope are ruled out or patients with a clear history of NCS in whom the test may alter the treatment.

Other indications include trying to differentiate convulsive syncope from epilepsy, assessment of recurrent falls, or recurrent near-syncope. A positive test is one that reproduces the patient's symptoms with a hypotensive/bradycardic episode. TTT can also help distinguish other etiologies for syncope, including postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia, and autonomic insufficiency.

In cases where bradyarrhythmias or tachyarrhythmias are suspected, Holter and event monitors can be diagnostic. A relatively new modality of event monitor is the implantable loop recorder (ILR). It is a small recording device that is implanted in the subcutaneous tissue in the chest. It can store up to 45 minutes of retrospective ECG recording (without noisy channels, as often seen in the Holter monitors or event recorders), and the battery lasts for up to 18 months. It can record automatically (triggered by a slow or fast heart rate) or be activated by the patient with a small remote control after a syncopal spell. In cases where the usual work-up has revealed no diagnosis, the ILR yields 25% to 40% of diagnoses in eight to 10 months.

The EPS is of relatively low yield in patients with normal hearts and normal electrocardiograms but is often helpful in patients with depressed ejection fraction, a history of coronary artery disease, or some ECG abnormalities. In cases where the EPS shows a clear abnormality, treatment is often provided, including ablation (in cases of supraventricular tachycardia or selected ventricular tachycardias) and pacemaker and defibrillator implantation.

Treatment

Treatment for syncope depends on the etiology. Patients with diagnosed NCS are often treated with lifestyle modification (hydration, exercises, salt repletion, learning about their own triggers, and prodromal symptoms, etc.) without the need for medications. In patients who fail lifestyle modifications, medications are indicated. There are several medications used for NCS but only limited randomized controlled data.

Beta-blockers are the traditional first-line agents and have been used successfully for many years. Five of seven different trials regarding beta-blocker use in NCS showed no benefit, however. There are many methodological limitations and patient-selection problems with these trials.

Fludrocortisone appeared effective in uncontrolled studies. In a randomized trial, it was compared to atenolol and showed no significant difference (although no placebo was used).

Vasoconstrictors were evaluated as well. Midodrine (a direct alpha-1 agonist) was studied in a randomized, double-blind, crossover study for one month. Results showed patients had less syncope than with placebo. It was also compared to salt and fluid therapy for six months, where midodrine was superior. An uncontrolled study of methylphenidate suggested it may be an alternative. Etilefrine was no better than placebo in a randomized trial.

Selective serotonin-reuptake inhibitors (SSRIs) were proposed as a potential therapy, and in one randomized trial, 82% of patients on paroxetine were free of syncope at 25 months compared to 53% on placebo ($P<.001$). These medications may become first-line therapy if results are duplicated.

Cardiac pacing has been proposed as a treatment for NCS for many years, especially using the rate-drop response algorithm. Initial trials showed benefit, but they had no comparison group (patients received a pacemaker or no therapy), so the benefit may have been a placebo effect of the pacemaker. Later, two published trials compared patients with pacemakers either turned on or off (to avoid the placebo effect). These trials showed no benefit for pacemakers.

At present, pacers are not recommended as first-line therapy. Pacemakers, however, are often used in patients who have little



A 12-lead electrocardiogram should be performed routinely in almost all cases of syncope.

or no prodrome or who fail other therapy and experience profound bradycardia or asystole during their syncope. In these patients, cardiac pacing may alleviate symptoms and provide time for patients to take evasive action (for example, to lie down).

Patients with other causes of cardiac syncope should be treated based on the precise etiology. Patients with the long QT syndrome are treatable with beta-blockers, pacemakers, and/or defibrillators. Patients with the Brugada syndrome often require a defibrillator in the setting of syncope.

Patients with syncope and the Wolff-Parkinson-White syndrome or other supraventricular arrhythmias should be referred for EPS and ablation. Patients with hypertrophic cardiomyopathy and syncope may need beta-blockers and a defibrillator. Patients with bradyarrhythmias or carotid hypersensitivity (a group of neurally mediated syncope that benefits of pacing) need a pacemaker. Patients with low ejection fraction and syncope should also be referred for electrophysiology evaluation.

In summary, patients presenting with syncope need a detailed history and physical examination and an ECG to categorize the event, followed by the appropriate tests to get the correct diagnosis and begin treatment. ■

John Cogan, MD, earned his medical degree from Universidad Peruana Cayetano Heredia in Lima, Peru. He completed his internal medicine residency at University of Texas Southwestern Medical School in Dallas, Texas, where he was appointed chief medical resident. Dr. Cogan's training includes all facets of diagnosis and treatment of heart rhythm disorders, including radiofrequency ablation of complex cardiac arrhythmias and implantation of pacers, defibrillators, and biventricular cardiac devices.

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HeartLines Fact

AstraZeneca, a major international pharmaceutical company engaged in the research, development, manufacture, and marketing of prescription pharmaceuticals and the supply of health care services, recently chose Cardiovascular Consultants of South Florida as one of eight Centers of Excellence in the United States.

According to the American Heart Association, cardiovascular diseases are still "America's number-one killer." In fact, 73 million people in the United States have some form of cardiovascular disease, and Americans will spend more than $400 billion in 2006 on medical and disability costs related to these diseases. These numbers point to the ever-increasing need for high-quality cardiovascular care concentrating on treatment and prevention.

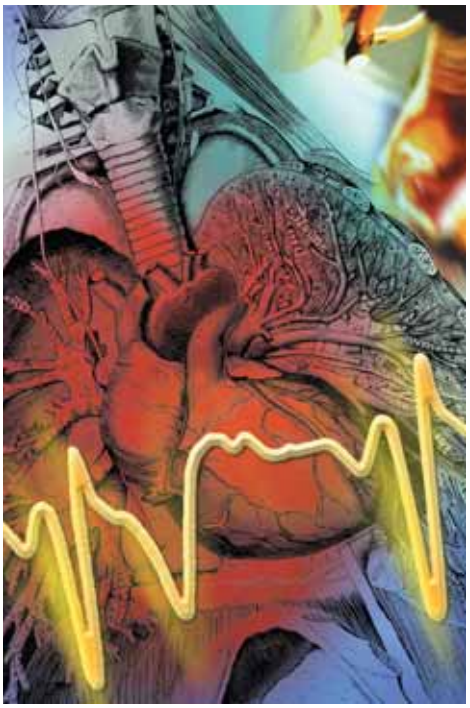
The cardiologists at Cardiovascular Consultants of South Florida (CCSF) know these numbers by heart. CCSF is one of the largest cardiovascular groups in Florida. Each day, these physicians and the highly skilled staff that supports them dedicate themselves to providing the best medical care to patients.

Quality Care through Clinical Research

One of the primary ways CCSF guarantees its patients the most innovative, progressive cardiovascular care is through its enthusiastic support of and participation in clinical research. By taking part in clinical studies sponsored by pharmaceutical and medical device companies, the practice helps push medicine forward and brings the most advanced drugs available in the marketplace to patients.

CCSF has conducted invasive and non-invasive, Phase II, III, and IV, inpatient and outpatient clinical trials. The group takes pride in its research record, especially in the fact that it often succeeds in surpassing enrollment goals for studies in areas such as hyperlipidemia, arrhythmias, hypertension, myocardial infarctions, and congestive heart failure.

Patients who participate in the CCSF trials receive investigational products at no cost. All clinical research trials at CCSF strictly follow established protocols to maintain quality control and patient safety.



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CCSF's easily accessible office locations in Hollywood, Pembroke Pines, Aventura, and Weston are staffed with skilled and compassionate full-time technologists, nurses, and other support personnel. The offices are equipped with state-of-the-art equipment, such as new digital single photon emission computed tomography (SPECT) cameras for highly sophisticated nuclear imaging and new digital ultrasound equipment for accurate imaging of the heart and blood vessels. These factors make it possible for CCSF to provide the most comprehensive cardiac and vascular evaluation and treatment available in South Florida. ■

Proper Application of Pacer Technology



BY RAUL D. MITRANI, MD, FACC



The concept for bradycardia pacemakers originated in the 1950s. Initial units were bulky, required frequent battery changes, and had no programmability. Until the 1980s, single-chamber ventricular pacing was the predominant mode; and even through the early 1990s, dual-chamber atrioventricular (AV) pacers had limited programmability and functionality.

The modern pacemaker generator now weighs 25 to 35 grams. It is capable of fully programmable dual chamber and biventricular pacing and rates response to activity. It also has transtelephonic capability for telemetry of all pacing parameters downloadable to the Internet, incorporates algorithms to respond to changes in intrinsic rhythms, and can store details of patients' arrhythmic events. Because of the complexities of types of pacers, programmed parameters, and drug interactions with these cardiac devices, cardiac electrophysiologists have become the predominant specialists managing and implanting these devices.

The initial pacers (single and dual chamber) were designed to provide right ventricular (RV) pacing in the event of asystole, generally due to AV block. In the early days of pacing, most patients presented with high-degree AV block. At present in the United States, however, approximately two-thirds of patients requiring pacing have an indication of sick sinus syndrome or one of its variants. These patients generally require atrial pacing backup, which the dual-chamber pacers can reliably provide.

However, standard dual-chamber pacers with traditional programming of the DDD mode are designed to provide backup RV pacing. Therefore, the DDD pacing mode may inadvertently stimulate the RV, which can lead to desynchronization of ventricular function.

Complications

The problem with inadvertent RV pacing is often exacerbated by rate-slowing drugs (beta-blockers, calcium blockers, digoxin), which are often used in patients with sick sinus syndrome because these patients also tend to have atrial fibrillation. These drugs are used appropriately to slow the heart rate during paroxysms of atrial fibrillation; however, these drugs also prolong the patient's intrinsic AV conduction (PR interval). In this scenario, a prolonged PR interval is more likely to lead to more RV pacing.

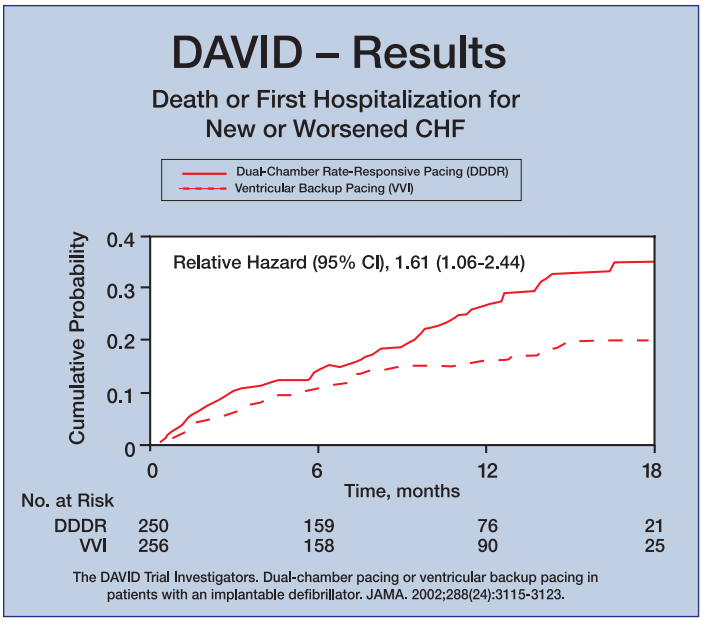
Another common problem involves the use of rate-responsive pacing (DDDR). The premise of DDDR includes pacing the atria and ventricle at a faster rate (driven by the pacer sensor) in order to provide appropriate heart-rate response during activity. This faster atrial rate causes a physiologic delay in patients' intrinsic AV conduction (PR interval). The pacer AV interval stays the same or actually shortens during DDDR, which again would lead to inadvertent RV pacing. Unfortunately, many patients have inappropriate DDDR, which leads to RV pacing.

The concept of inappropriate RV pacing was developed only over the past five years. Based on various studies, it is now recognized that RV pacing leads to abnormal electrical activation of the left ventricle (LV) similar to patients having an intrinsic left bundle branch block (LBBB). In certain patients, this condition desynchronizes LV systolic function, leading to left ventricular dysfunction and congestive heart failure. In fact, biventricular pacing was developed in order to resynchronize LV systolic function in patients with congestive heart failure (CHF), low ejection fraction, and LV dyssynchrony due to LBBB or abnormal electrical activation.

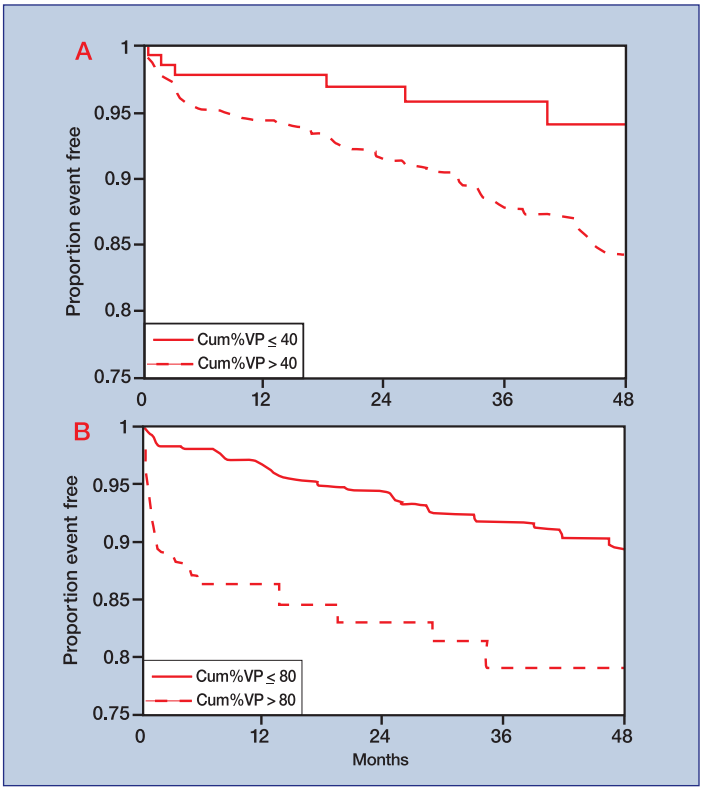
The DAVID Study (see Figure 1) followed patients with implantable defibrillators designed to compare backup VVI pacing at 40 to aggressive DDDR pacing at 70. The hypothesis was that DDDR pacing at 70 would lead to less ventricular tachycardia, better quality of life, and better outcomes. To the authors' surprise and as shown in the graph, the patients with VVI pacing at 40 fared better. The reason is that DDDR pacing led to LV desynchronization and worsening CHF, despite the fact that these patients were paced at faster heart rates than patients treated with VVI pacing at backup rate 40.

The percent of RV pacing was examined and compared with outcomes of CHF in the MOST trial (Circulation. 2003;107 :2932). As shown in Figure 2, those patients with DDD pacing (Figure 2A) or VVI pacing (Figure 2B) with ventricular pacing

FIGURE 1



FIGURES 2A & 2B



less than 40% or less than 80%, respectively, had lower incidence of hospitalization for heart failure compared with patients with higher percentages of ventricular pacing.

Inappropriate RV pacing has also led to higher incidence of atrial fibrillation. This condition can lead to higher incidence of thromboembolic complications.

Improved Patient Outcomes

Current strategies to prevent pacing-induced desynchronization involve programming DDD mode with excessively long AV intervals. This type of programming can lead to other problems, including pacemaker mediated tachycardia. DDI pacing mode may be used in this setting as long as the patient does not have any form of second- or third-degree AV block.

patient's intrinsic AV conduction, intraventricular conduction defects, and hemodynamic function.

The appropriate pacer algorithm (DDD, DDI, AAI with back-up DDD, search AV hysteresis algorithms) can make a significant difference in long-term cardiac function and quality of life. Follow-up of these patients involves assessment of frequency of pacing in the different cardiac chambers and determining whether the various programming parameters (rate, AV interval, VV interval, etc.) are optimal for the patient's overall hemodynamic function. Fortunately, proper pacer programming and follow-up leads to improved patient outcomes. ■

> "The initial evaluation of patients considered for pacing therapy should include evaluation of the patient's underlying rhythm, heart function, symptoms, and indication for the pacer."

Recently, some pacer companies have developed complex algorithms involving AAI pacing (atrial pacing only) with back-up DDD pacing, should the patient go into advanced AV block. The purpose of all these algorithms is to provide appropriate atrial pacing backup response and allow for PR interval, which, in the presence of normal QRS width, is preferable to having the RV pacing.

In sum, there are new paradigms in pacer selection, programming, and follow-up in patients requiring pacer therapy. The initial evaluation of patients considered for pacing therapy should include evaluation of the patient's underlying rhythm, heart function, symptoms, and indication for the pacer. It should be determined whether the patient requires placement of an LV lead for cardiac resynchronization and whether a backup defibrillator as part of the pacer system should be used. Programming of these devices is often quite complex and needs to consider the

Raul D. Mitrani, MD, FACC, completed his internship and residency at Case Western Reserve University following graduation from Columbia College and medical school at Columbia University College of Physicians and Surgeons. He then completed his cardiovascular fellowship at Indiana University and cardiac electrophysiology fellowships at Indiana and Case Western Universities. He is a Diplomate and is board certified in cardiovascular disease and clinical cardiac electrophysiology. He has authored 17 book chapters, 35 refereed journal articles, and 37 refereed abstracts. Dr. Mitrani has served as a consultant for many local hospitals and is a past associate professor of medicine at the University of Miami School of Medicine and director of the Arrhythmia and Pacemaker Center, Jackson Memorial Hospital. Currently, he serves as Director of Electrophysiology for Memorial Regional Hospital and Director of Cardiovascular Consultants of South Florida's cardiac electrophysiology practice. He is also Director of Florida Arrhythmia and Syncope Center at CCSF.

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Safety and effectiveness in pediatric patients have not been established. Greater sensitivity of some older individuals (eg, ≥75 years) with heart failure must be considered.

ATACAND is indicated for the treatment of heart failure (NYHA Class II-IV) in patients with left-ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. (See Clinical Trials.) ATACAND also has an added effect on these outcomes when used with an ACE inhibitor.

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

In heart failure patients receiving ATACAND, hypotension, increases in serum creatinine, and hyperkalemia have occurred. Caution should be observed for hypotension when initiating therapy. Evaluation of patients with heart failure should always include assessment of renal function and volume status. Monitoring of blood pressure, serum creatinine, and serum potassium is recommended during dose escalation and periodically thereafter.

During concomitant use of ATACAND and lithium, careful monitoring of serum lithium levels is recommended.

The adverse-event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued ATACAND for adverse events vs 16.1% of placebo patients.

Please see brief summary of full Prescribing Information, including boxed WARNING regarding use in pregnancy, adjacent to this ad.

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Once-A-Day Tablets

Atacand®

candesartan cilexetil

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TABLETS

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

BRIEF SUMMARY

Before prescribing, please see full Prescribing Information for ATACAND (candesartan cilexetil).

INDICATIONS AND USAGE

Hypertension

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

Heart Failure

ATACAND is indicated for the treatment of heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. (See Clinical Trials.) ATACAND also has an added effect on these outcomes when used with an ACE inhibitor.

CONTRAINDICATIONS

ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with ATACAND during pregnancy. When pregnancy is detected, ATACAND should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Oral doses ≥10 mg of candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10-mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m² basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m² basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m² basis) were administered to pregnant mice.

Hypotension in Volume- and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given ATACAND commonly have some reduction in blood pressure. In patients with symptomatic hypotension this may require temporarily reducing the dose of ATACAND, or diuretic, or both, and volume repletion. In the CHARM program, hypotension was reported in 18.8% of patients on candesartan versus 9.8% of patients on placebo. The incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients. Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

PRECAUTIONS

General

Impaired Hepatic Function— Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations.)

Impaired Renal Function— As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

ATACAND® (candesartan cilexetil) Tablets

In heart failure patients treated with ATACAND, increases in serum creatinine may occur. Dosage reduction or discontinuation of the diuretic or ATACAND, and volume repletion may be required. In the CHARM program, the incidence of abnormal renal function (e.g., creatinine increase) was 12.5% in patients treated with candesartan versus 6.3% in patients treated with placebo. The incidence of abnormal renal function (eg, creatinine increase) leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients. Evaluation of patients with heart failure should always include assessment of renal function and volume status. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

Hyperkalemia

In heart failure patients treated with ATACAND, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM program, the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo. The incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients. During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

Information for Patients

Pregnancy— Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III). Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Lithium— Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with ATACAND, so careful monitoring of serum lithium levels is recommended during concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy Categories C (first trimester) *and D* (second and third trimesters)—See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Hypertension

Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

Heart Failure

Of the 7599 patients with heart failure in the CHARM program, 4343 (57%) were age 65 years or older and 1736 (23%) were 75 years or older. In patients ≥75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with ATACAND or placebo compared with patients <75 years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with ATACAND than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

ADVERSE REACTIONS

Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (ie, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (ie, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (ie, 57 of 2350) of patients treated with ATACAND and 3.4% (ie, 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n=2350) than placebo (n=1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Heart Failure

The adverse event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued ATACAND for adverse events vs. 16.1% of placebo patients.

Post-Marketing Experience:

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: renal impairment, renal failure.

Skin and Appendages Disorders: Pruritis and urticaria.

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Laboratory Test Findings

Hypertension

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND.

Creatinine, Blood Urea Nitrogen— Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia— Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit— Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium— A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests— Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

Heart Failure

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan-treated patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.

OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Candesartan cannot be removed by hemodialysis.

Treatment: To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

DOSAGE AND ADMINISTRATION

Hypertension

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ATACAND.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (eg, patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food.

If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

Heart Failure

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

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BY JUDAH FRIEDMAN, CEO, CARDIOVASCULAR CONSULTANTS OF SOUTH FLORIDA
EDITED BY MIKE SEGAL, ESQ., BROAD AND CASSEL

Know the Law

Examining Critical Regulations Governing Medical Practices

When I talk with physicians about health care regulations, their eyes roll back into their sockets and they immediately tune me out. Health care is one of the most regulated industries in our economy. Physicians spend years in medical school, residencies, and fellowship programs training to provide quality medical care to their patients. They spend little time thinking about the practical aspects of running a practice and, in most cases, no time on the myriad federal and state regulations governing the practice of medicine.

Medicare provides a template for coding the services that each of you provide to your patients. Medicare sends out bulletins every month, notifying you of changes in the regulations. It is essential that you read these bulletins so you are coding properly for your services. If you find there is not enough time, subscribe to a national service or contract with a local consultant.

OSHA Standards

A number of pieces of legislation that have passed in the last 35 years have had major impacts on medical practices. In 1970, the federal government enacted the Occupational Safety and Health Act (OSH Act). This program was established to ensure every man and woman in the nation is working in safe, healthful conditions.

The Occupational Safety and Health Administration (OSHA) sets strict standards for medical practices. As an example, all employees who have patient contact must receive certification stating they have the required knowledge to handle blood and other pathogens safely. OSHA has the right to enter a facility without prior warning, and if it finds the standards are below "national consensus standards," it can shut the facility down.

Anti-Kickback and Stark Laws

It is also critical for you to have a familiarity with the federal Anti-kickback and Stark laws, as well the Florida Patient Self-Referral law. The federal Anti-kickback law has existed since 1972. Initially a criminal law, it is extremely expansive, prohibiting the payment or acceptance of kickbacks (bribes) of any kind in exchange for referrals.

In 1987, the law was modified to include civil penalties, including fines and a Medicare "death penalty" — termination from the Medicare (and Medicaid) program. To address complaints that the statute was too broad in scope, the government also modified the law to include exceptions, or "safe harbors" — safety nets that allow health care providers comfort that potentially violative transactions will comply with the law. A problem is that many transactions only meet some — but not all — the safe harbors.

In 1992, Congress enacted the Stark law in honor of the congressman who sponsored the bill. Stark prohibits any physician and members of his or her family from referring certain defined ancillary services (known as designated health services, or DHS) that are reimbursable under Medicare or Medicaid to a business in which he or she has a financial interest. There are many exceptions to that rule (such as the exception for certain group practices) and voluminous regulations interpreting the law.

The Anti-kickback and Stark laws differ greatly in many aspects, including their applications. While the Anti-kickback law has many shades of gray, the Stark law is black and white — either the law is satisfied or it is not.

Baby Stark

In 1992, Florida enacted its own version of the Stark law — the Florida Patient



Ensure you understand the laws and their consequences. At the end of the day, you are held responsible, not your office manager.

Self-Referral law, often referred to as "Baby Stark." Similar to the Stark law's prohibition on referrals, Baby Stark contains a general prohibition against a physician referring to an entity in which he or she owns an interest. In addition, like the Stark law, Baby Stark contains many exceptions to the general rule, including an exception for referrals within group practices.

The laws also differ in many aspects, however. DHS is defined differently in Baby Stark. Although the Stark law includes 11 services within its definition of DHS, Baby Stark only consists of four general categories of DHS. Also, Baby Stark applies to DHS where the service is not reimbursable by Medicare or Medicaid.

Finally, whereas the Stark law limits physician ownership of an entity to which the physician refers, Baby Stark restricts physician ownership of a medically related entity, even where no DHS is involved. With Baby Stark, unless a physician meets certain requirements, such ownership is prohibited.

Lesson Learned

The lesson here is for you to ensure you understand the laws and their consequences. At the end of the day, you are held responsible, not your office manager.

And for those who believe "this too shall pass," I hate to burst your bubble. Taking all three parts of Medicare together, it is projected that the total Medicare debt for the current generation will reach $29.2 trillion; and future generations will add $32.5 trillion to this obligation. Clearly, the federal government will look for as many ways as possible to reduce this debt, either by increasing taxes or reducing costs. No doubt the easiest path is to reduce costs by eliminating fraud and abuse and promoting more efficiency through Medicare HMOs. ■

Judah Friedman, CEO of Cardiovascular Consultants of South Florida (CCSF), has had a long and distinguished career in health care administration. Prior to joining CCSF, Mr. Friedman served as academic administrator at Albert Einstein College of Medicine, Jacobi Hosptial, and Mount Sinai Medical Center in New York. Thereafter, he spent three years developing a multispecialty medical practice in Boca Raton. Mr. Friedman was instrumental in the growth of CCSF as well as in developing new programs, such as the first freestanding cardiac catheterization in South Florida, and in implementing an electronic medical records program that allows physicians instant access to patient charts and improves the data quality. In 2003, Mr. Friedman was named Best Practice Administrator at the 14th Annual Medical Business Awards presented by Florida Medical Business.

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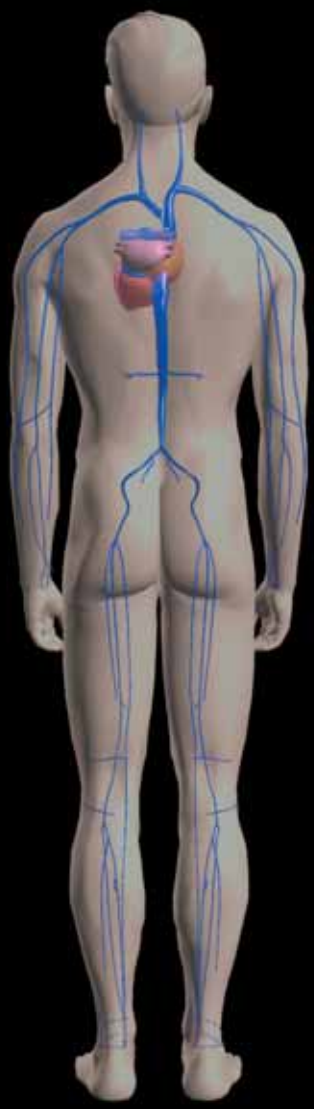
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New Treatment Options for Venous Disease

Evaluating Varicose Veins and Venous Insufficiency

Venous disease affects an estimated 80 million Americans and ranges from spider veins to increasing degrees of venous insufficiency (VI). In one U.S. health survey, varicose veins were found to be the seventh most common reason for medical referral. By the approximate age of 60, 72% of women and 40% of men are affected by VI.[1]



BY SUSAN B. FOX, DO

Saphenofemoral incompetence causing reflux in the greater saphenous vein is the most common cause of VI. If left untreated, approximately half of the patients will develop venous hypertension and symptoms of chronic VI.[2] With progressive degrees of reflux, patients can develop leg pain, swelling, venous hemorrhage, venous eczema, stasis dermatitis, atrophie blanche, lipodermatosclerosis, and ulcerations. Venous stasis ulcers are the most common cause of lower extremity ulceration in the world.

Diagnosing Venous Insufficiency

Since VI is a common problem, it is important to notice the signs and symptoms associated with the condition. A thorough history and physical, as well as looking for leg swelling, varicose veins, venous stasis changes, hemosiderin deposition, and venous eczema are important. Clinical tests are sometimes used to diagnose VI. These tests, however, are relatively insensitive and unreliable. The gold standard is a duplex ultrasound called a valvular incompetency study.

Conservative Treatment

If the pedal pulses are normal, patients should receive a prescription for medical-grade, graduated compression hose and encouragement to elevate their legs. They should moisturize their legs and maintain good foot care to prevent skin breakdown, infections, and ulcer development.

Definitive Treatment

Conventional therapy for VI is ligation of the saphenofemoral junction, with or without vein stripping. High ligation with vein stripping is more successful than high ligation alone. Ligation plus stripping has an immediate success rate of 86% but a patient satisfaction rate of only 62%.[3] Even when performed by a surgeon skilled in treating venous disease, there is still a high rate of recurrence.

The most common complications of vein stripping involve those associated with general anesthesia. Other complications include postoperative pain, saphenous nerve injuries, infections,

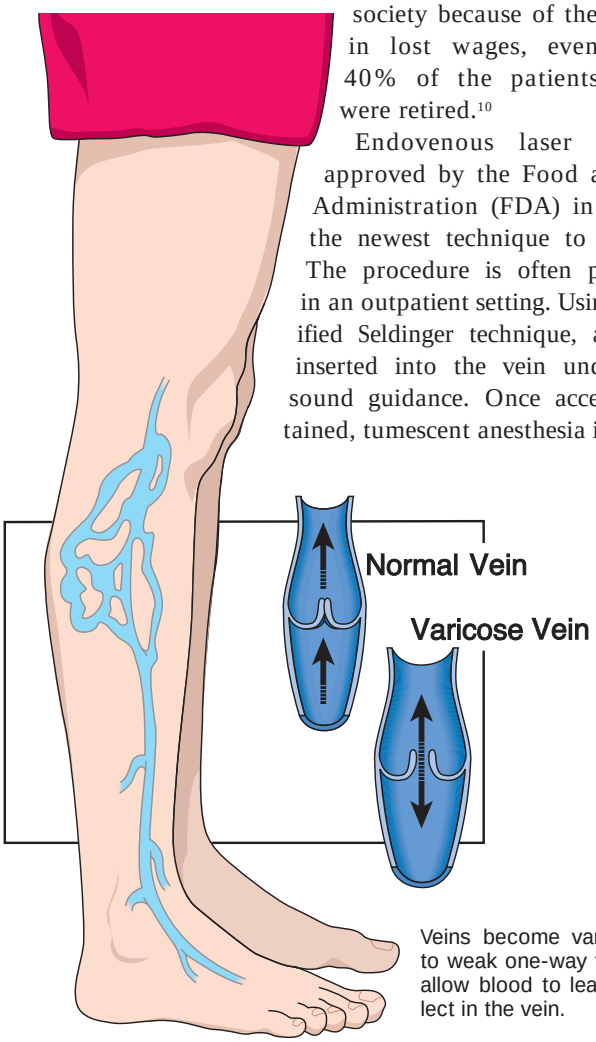
neovascularization, hematomas, and thromboses. Neovascular reconnection that occurs in about half of these patients and persistently abnormal venous physiology are considered the primary causes of recurrence.[4] Postoperative morbidity of vein stripping is high. As a result, newer, less invasive treatments are becoming the standard of care. These include VNUS closure and endovenous laser vein ablation.

VNUS closure, approved in the United States in 1999, involves threading a radiofrequency catheter into the vein under ultrasound guidance. The probe contacts the venous endothelium, heating it to 85˚C and causing the vein to seal shut. Tumescent anesthesia injected between the skin and the vein limits surrounding tissue damage.

The procedure can be performed on veins 2 mm to 12 mm in diameter. It has a 92% to 98% success rate and a 10% recurrence rate at two years.[5, 6, 7] Two other studies by vein specialists reported success rates of only 68% and 73%, however.[8, 9] The procedure is frequently performed in the operating room.

Drawbacks and complications include the relative size limitations, some neovascularization, potential nerve injuries, infections, skin burns, thromboses, and hematomas. Recovery time is short, and people can return to their regular activities within a few days. The average time off work was 6.5 days with VNUS and 15.6 days with stripping. Patients had less pain and were more satisfied with VNUS closure than vein stripping. Even though the procedure costs more, it appears cost-saving to society because of the decrease in lost wages, even though 40% of the patients studied were retired.[10]

Endovenous laser ablation, approved by the Food and Drug Administration (FDA) in 2002, is the newest technique to treat VI. The procedure is often performed in an outpatient setting. Using a modified Seldinger technique, a laser is inserted into the vein under ultrasound guidance. Once access is obtained, tumescent anesthesia is injected between the skin and the vein. The tumescent anesthesia numbs the area, contracts the vein around the catheter, and dissipates heat from the laser. The entire procedure takes 45 minutes. Patients usually have only mild bruising and a temporary pulling sensation along the course of the vein.



Veins become varicose due to weak one-way valves that allow blood to leak and collect in the vein.

Complications include minor skin burns, hematomas, infections, nerve injuries, and thromboses. The benefits are that the procedure is performed under local anesthesia, there is no limitation to the size of veins that are treatable, and recovery is short, so people can return to work almost immediately. Several reports have documented a success rate of 94% to 100%, with a two-year recurrence at less than 4%.[11,12,13,14] As many as 99.8% of patients surveyed were satisfied with their results and would refer a friend for endovenous laser ablation.[15] ■

After earning her medical degree from Nova Southeastern College of Osteopathic Medicine, Susan B. Fox, DO, completed her residency in internal medicine and her fellowship in vascular medicine at The Cleveland Clinic in Cleveland, Ohio. Before moving to Florida, she practiced as a vein and vascular expert at University Hospitals of Cleveland and was on the teaching faculty at Case Western Reserve University. Dr. Fox specializes in the nonsurgical treatment of varicose and spider veins using state-of-the-art, minimally invasive therapy for large varicose veins and venous insufficiency. Dr. Fox was featured on several news programs and in articles and has lectured extensively on varicose veins.

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BY HOWARD F. BERLIN, MD, FACC

Heart Failure Guidelines

Update Offers Effective Treatments

A new updated version of the ACC/AHA Clinical Performance Measures for Adults With Chronic Heart Failure was released in September 2005. This third release since 1995 was called for due to the magnitude of new data since the last guideline in 2001. The guideline is available in its entirety at www.acc.org.

This article highlights some of the important data presented in this latest review.

Justification

The new guidelines develop a staging system similar to that used in cancer staging. It is not meant to replace the New York Heart Association functional classification that is a symptoms guide. The new staging system recognizes that heart failure is a result of structural changes and that symptoms can vary during a short period of time, but the underlying structural changes usually remain unchanged.

Neurohormonal System

Left ventricular dysfunction begins with some injury to or stress on the myocardium, resulting in failure of inflow (diastolic dysfunction) or outflow (systolic dysfunction). There is usually a change in the geometry and structure of the left ventricular that follows. The left ventricular chamber dilates and/or hypertrophies and becomes more spherical, which is termed cardiac remodeling.

It is apparent that the activation of the neurohormonal system plays an important role in these changes. Patients with heart failure have elevated circulating or tissue levels of epinephrine, angiotensin II, aldosterone, endothelin, vasopressin, and cytokines that are regulated by the neurohormonal system. Treatment of heart failure has improved immensely with the use of drugs that interfere with the neurohormonal system — angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone antagonists.

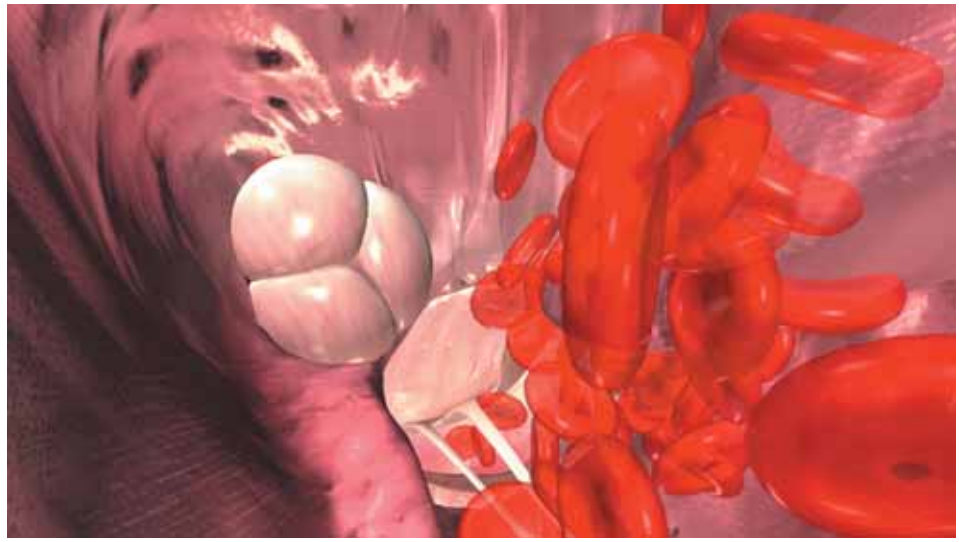
Staging and Interventions

The guidelines recognize that heart failure is usually progressive once there are structural changes in the myocardium. The most effective treatment is to prevent the initial structural changes. Stage A addresses the category of patients who have only risk factors (hypertension, hyperlipidemia, diabetes mellitus, a family history of heart failure, obesity, atherosclerotic cardiovascular disease, or metabolic syndrome) but no structural heart disease. Aggressive risk factor intervention is suggested at this stage, with the use of ACE inhibitors encouraged in appropriate patients.

Stage B patients have structural changes (myocardial infarction, left ventricular hypertrophy, low ejection fraction, or asymptomatic valvular disease) but are without symptoms of heart failure.

Drugs at this stage should include ACE inhibitors or ARBs, beta-blockers, and devices in selected patients. Devices (implanted cardioverter/defibrillator) should be considered in patients with an ejection fraction of less than 35%. Consider cardiac resynchronous therapy (BiV ICD) for symptomatic heart failure despite stable optimal medical therapy with a QRS greater than 120 ms and an ejection fraction of less than 35%.

Stage C patients have the structural changes of Stage B patients but also have or have had symptoms of heart failure. ACE inhibitors and/or ARBs should be used in all appropriate patients. Beta-blockers are to be initiated and, specifically, should be one of the currently approved drugs — metoprolol succinate (not metoprolol tartrate), carvedilol, or bisoprolol. In selected patients, aldosterone antagonists (spironolactone and eplerenone), ARBs,



This anterior view of the left chamber of the heart shows the mitral and aortic valves with blood cells. Left ventricular dysfunction begins with some injury to or stress on the myocardium, resulting in failure of inflow or outflow.

Brief Suggestions and Concepts

1. Do not delay the use of beta-blocker therapy despite the inability to achieve the desired level of ACE inhibitor or ARB doses.
2. If coronary artery ischemia is suspected, cardiac catheterization should be undertaken early in an attempt to revascularize an ischemic ventricle.
3. Screen for sleep apnea if suspected in obese individuals.
4. Keep in mind hemochromatosis, HIV, rheumatologic diseases, amyloid, and pheochromocytoma as less frequent but treatable causes of heart failure.
5. Avoid the combination of an ACE inhibitor, ARB, and aldosterone antagonist because of the risk of hyperkalemia.
6. Digoxin is not to be used in patients with sinus rhythm, low ejection fraction, and no heart-failure symptoms. Digoxin did reduce hospitalizations in patients with a reduced ejection fraction and symptoms of heart failure.
7. Calcium channel blockers with negative inotropic effects may be harmful in patients with low ejection fractions and symptoms of heart failure post myocardial infarction.
8. Avoid nonsteroidal anti-inflammatory agents.
9. Add a nitrate/hydralazine combination if the patient is symptomatic on ACE inhibitor and beta-blocker or if drug intolerant, hypotensive, or renal insufficient.
10. Do not use an aldosterone antagonist if creatinine is greater or equal to 2.5 mg/dL in men and 2.0 mg/dL in women or if potassium is greater than 5.0.
11. Long-term infusion of an inotrope may be harmful except as palliation for end-stage heart failure.
12. Nutritional supplements are not indicated for the treatment of heart failure at any stage.

digitalis, or hydralazine/nitrates should be initiated. Devices in select patients as mentioned above should also be utilized.

Stage D patients have refractory heart failure requiring specialized interventions. These patients require a decision on compassionate end-of-life care. Extraordinary measures may include heart transplant, chronic inotropes, mechanical support, experimental surgery, or experimental drug therapy.

The most effective treatment of heart failure is in prevention because heart failure is usually a progressive disorder. Physicians must be steadfast in their treatment of risk factors to achieve published guidelines.

Heart-failure patients are growing in numbers, with a current direct and indirect cost of $27.9 billion per year. Only $3 billion per year are for drug costs. There are more than 550,000 new patients per year diagnosed with heart failure, and the current affected population tops five million.

I hope many of you will take the time to read the new guidelines or at least keep a copy of the pocket version to use in your treatment of heart-failure patients. ■

Howard F. Berlin, MD, FACC, earned his medical degree from Jefferson Medical College in 1975. He completed his internship and residency at Abington Memorial Hospital, Philadelphia, and a cardiology fellowship at the University of Miami, Jackson Memorial Hospital. Dr. Berlin was honored by the Hobert Amory Hare Honor Medical Society, Jefferson Medical College. He is board certified in internal medicine and cardiovascular disease.

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BY DANIEL G. NORBERG, MD, FACC

The Future of Medical Care

Electronic Medical Records Benefit Both Patient and Physician

Imagine a world where your patients' medical information was readily available to send to health care providers anywhere in the world, was updated continuously, and was safely stored and securely managed on a mainframe computer.

Electronic medical records (EMRs) are here and provide significant benefits to both physicians and patients. EMR is a term used to describe computer-based patient medical records. As more medical service providers convert to "paperless," electronic systems, medical information could follow patients through patient-consented, secure Internet access.

Accurate and Accessible

EMR allows rapid access and transferring of medical information. Consider the possibility that your patient becomes ill while out of town or while his or her regular physician is not on call. With EMRs, the treating physician is able to access the relevant medical record and obtain important information for patient care. The use of EMRs facilitates quality and efficiency of patient care.

The system links multiple offices, allowing access to patient data at any provider location. There are no charts to transport, store, or maintain. Complete medical data is available anywhere in the network and is continuously updated.

In addition to maintaining a current list of patient medications and medical problems, it automatically checks for drug interactions and allergies. Accurate and accessible EMRs greatly assist in providing quality and affordable medical care.

Improving Efficiency

Economically, EMRs improve efficiency through several methods. A paperless system is environmentally friendly and decreases the long-term cost of producing and maintaining charted medical records. Since the information is complete, there is a decrease in duplication of services and needless overutilization of resources.

Scheduling is completely automated and linked to the patients through a phone reminder system. Billing cost and confusion are decreased through electronic claims submissions to insurance companies and patients. Maintaining records electronically allows for instant availability of entire records from hard-drive storage, which is continuously backed up to protect information loss.

Electronic transmission of medical data is performed in a secure environment. The EMR system information is secured through 128-bit encryption. Encryption is the conversion of data into a form that is not easily understood by unauthorized individuals. The EMR system complies with the Health Insurance Portability and Accountability Act (HIPAA) and only allows access by health care professionals with secure provider access. Medical professionals maintain and update patient medical records in one integrated system. The EMR system is capable of generating timely clinical notes, printing prescriptions, linking laboratory information, updating medications, storing procedure/operative reports, and preliminarily evaluating and comparing electrocardiograms. Reports generated at outside facilities or hospitals and previous patient medical information are easily scanned, stored, and maintained through one system.

The future of medical care is available electronically at Cardiovascular Consultants of South Florida, where electronic medical records are in place. Our computers are linked to local hospitals, insurance providers, and laboratories and provide facsimile support for referring physicians and pharmacies. We have invested significant time, effort, and capital to create a paperless electronic medical information system that offers the most up-to-date tools for excellence in patient care. We believe accurate and accessible medical records are essential to providing quality medical care to our patients. ■



A paperless system is environmentally friendly and decreases the long-term cost of producing and maintaining charted medical records.

Daniel G. Norberg, MD, FACC, earned his medical degree from the University of Florida College of Medicine in 1991 and completed his internship and residency at the University of Miami School of Medicine, Jackson Memorial Hospital. He completed a fellowship at the University of Florida College of Medicine, Shands Hospital Medical Center. A Diplomate of the American Board of Internal Medicine in cardiovascular disease, Dr. Norberg is certified in nuclear cardiology.

BRIEF SUMMARY: For full Prescribing Information, see package insert.

INDICATIONS AND USAGE CRESTOR is indicated: 1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); 2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV); 3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **CONTRAINDICATIONS** CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes). **Pregnancy and Lactation** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus. **WARNINGS Liver Enzymes** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. **It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS). **Myopathy/Rhabdomyolysis Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency. Consequently: 1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism. 2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. 3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION). 4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions).** 5. **The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General).** 6. **Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).** **PRECAUTIONS General** Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE). Administration of rosuvastatin 20 mg to patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION). The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.) **Information for Patients** Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions). **Laboratory Tests** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing. **Drug Interactions Cyclosporine:** When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION). **Warfarin:** Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants. **Gemfibrozil:** Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION). **Endocrine Function** Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks



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by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures ≤60 times the human exposure at 40 mg/day based on AUC comparisons) following treatment up to one year, did not reveal retinal findings. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses. In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses. Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test. In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class. **Pregnancy** ***Pregnancy Category X*** See CONTRAINDICATIONS. Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus. In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/day based on AUC comparisons). In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times human exposure at 40 mg/day based on body surface area comparisons. In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed. Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to human exposure at 40 mg/day based on AUC or body surface comparison, respectively). **Nursing Mothers** It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman. **Pediatric Use** The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age. **Geriatric Use** Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.) The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly. **ADVERSE REACTIONS** Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea. **Clinical Adverse Experiences** Adverse experiences, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosuvastatin are shown in Table 1; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

Table 1. Adverse Events in Placebo-Controlled Studies

Adverse event	Rosuvastatin N=744	Placebo N=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in ≥2% of these patients. **Body as a Whole:** *Abdominal pain, accidental injury, chest pain, infection, pain,* pelvic pain, and neck pain. **Cardiovascular System:** *Hypertension,* angina pectoris, vasodilatation, and palpitation. **Digestive System:** *Constipation, gastroenteritis,* vomiting, flatulence, periodontal abscess, and gastritis. **Endocrine:** Diabetes mellitus. **Hemic and Lymphatic System:** Anemia and ecchymosis. **Metabolic and Nutritional Disorders:** *Peripheral edema.* **Musculoskeletal System:** *Arthritis,* arthralgia, and pathological fracture. **Nervous System:** *Dizziness, insomnia, hypertonia, paresthesia, depression,* anxiety, vertigo, and neuralgia. **Respiratory System:** *Bronchitis, cough increased,* dyspnea, pneumonia, and asthma. **Skin and Appendages:** *Rash* and pruritus. **Laboratory Abnormalities:** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.) Other abnormal laboratory values reported were elevated creatinine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities. Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis. **Postmarketing Experience** In addition to the events reported above, as with other drugs in this class, the following event has been reported during post-marketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice. **OVERDOSAGE** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin. **DOSAGE AND ADMINISTRATION** The patient should be placed on a standard cholesterol-lowering diet before receiving CRESTOR and should continue on this diet during treatment. CRESTOR can be administered as a single dose at any time of day, with or without food. **Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)** The dose range for CRESTOR is 5 to 40 mg once daily. Therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. **The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy. Homozygous Familial Hypercholesterolemia** The recommended starting dose of CRESTOR is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. CRESTOR should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels. **Dosage in Asian Patients** Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General). **Dosage in Patients Taking Cyclosporine** In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Concomitant Lipid-Lowering Therapy** The effect of CRESTOR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Dosage in Patients With Renal Insufficiency** No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Rx only

References: 1. Wolffenbuttel BHR, Franken AAM, Vincent HH, on behalf of the Dutch CORALL study group. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes – CORALL study. *J Intern Med.* 2005;257:531-539. **2.** Jukema JW, Liem AH, Durselman PHJM, et al, on behalf of the RADAR study investigators. LDL-C/HDL-C ratio in patients with coronary artery disease and low HDL-C: the RADAR study [poster]. Presented at: 74th European Atherosclerosis Society Congress; April 17-20, 2004; Seville, Spain. **3.** Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160. **4.** Prescribing Information for CRESTOR. AstraZeneca, Wilmington, DE. **5.** Shepherd J, Hunninghake DB, Stein EA, et al. Safety of rosuvastatin. *Am J Cardiol.* 2004;94:982-988. **6.** Rosuvastatin Information Web site. Rosuvastatin Clinical Information-Postmarketing Experience, Safety Information. Available at: http://www.rosuvastatininformation.com. Accessed July 19, 2005. **7.** Data on file, DA-CRS-01.

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As an adjunct to diet

POWERED...for success

For your broad range of high-risk patients



In 2 separate studies in high-risk patients with diabetes or CAD

More LDL-C reduction than *twice* the dose of atorvastatin[1,2]

- 82% of patients with diabetes reached LDL-C goal with a low 10-mg dose without titration[1]

Established HDL-C efficacy[3,4]

- CRESTOR 5 mg to 40 mg increased HDL-C between 8% and 14% (vs 3% with placebo) in patients with primary hypercholesterolemia[4]

Safety in line with other leading statins[4-6]

- In preapproval clinical trials and postmarketing experience, CRESTOR has demonstrated a safety profile in line with other leading statins[4-6]

Important Safety Information

- CRESTOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non–HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- CRESTOR is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases, in women who are or may become pregnant, and in nursing mothers
- It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter
- The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20-mg dose. Patients initiating statin therapy or switching from another statin should begin treatment with CRESTOR at the appropriate starting dose
- Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with CRESTOR and with other drugs in this class. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Therapy with CRESTOR should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected
- Adverse reactions were usually mild and transient; the most frequent adverse events thought to be related to CRESTOR were myalgia (3.3%), constipation (1.4%), asthenia (1.3%), abdominal pain (1.3%), and nausea (1.3%)[4,7]
- The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined; long-term outcome studies are currently under way

Please see brief summary of full Prescribing Information on reverse side of this advertisement.

CRESTOR®
rosuvastatin calcium

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