HeartLines

TRENDS IN HEART AND VASCULAR DISEASE

A publication from Cardiovascular Consultants of South Florida | www.heartpartners.com | Volume 1 • Issue 2

New Frontiers in Cardiac Imaging

Cardiac CT provides diagnostic utility and clinical applications in cardiovascular disease

CARDIOVASCULAR CONSULTANTS OF SOUTH FLORIDA

Women and Heart Disease | Treatment of Atrial Fibrillation | Diagnosing Sleep Apnea

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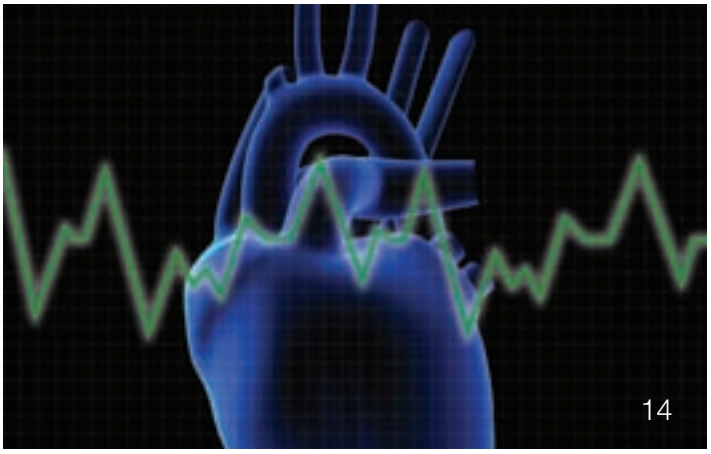

departments

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Welcome

Prior to moving to Florida 12 years ago, I spent the first half of my career working in academic medical centers. These centers of excellence — Albert Einstein College of Medicine and Mount Sinai Medical Center in New York — were exciting and stimulating as I witnessed the evolution of new techniques and therapies and stood side by side with some of the most respected names in medicine. I thought that moving to a private practice setting would be somewhat anticlimactic, as the frenetic push for excellence and the desire to bring new medical techniques and technologies might not be present. I am happy to say I was wrong.

Members of Cardiovascular Consultants of South Florida were the first to perform catheterizations at Memorial Hospital some 25 years ago. Our group was one of the first locally to embrace electronic medical records, allowing us access to a patient's chart 24 hours a day in any part of the world. Our physicians are on the faculty of local medical schools, training the physicians of the future. We participate in clinical trials of pharmaceutical and medical device companies so we can provide the latest devices and drugs available to our patients.

Perhaps of most significance is that our physicians are constantly updating their knowledge by reading, continuing their medical studies, and attending and participating in national and international conferences. They bring this information and these skills back to South Florida, enhancing our abilities in vein and vascular disease, electrophysiology, and clinical medicine. Now, as we enter a new era in cardiac and vascular diagnosis through new modalities of magnetic resonance imaging and computed tomography imaging, we are poised to take the next leap, one that will dramatically improve our ability to fight heart disease.

We thank all the organizations that have "partnered" with us and helped make this publication possible. And thank you to the members of our group who have worked so hard on these outstanding articles.

Judah Friedman, MEd, MBA
Chief Executive Officer

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.

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A publication from

CARDIOVASCULAR CONSULTANTS OF SOUTH FLORIDA

www.heartpartners.com

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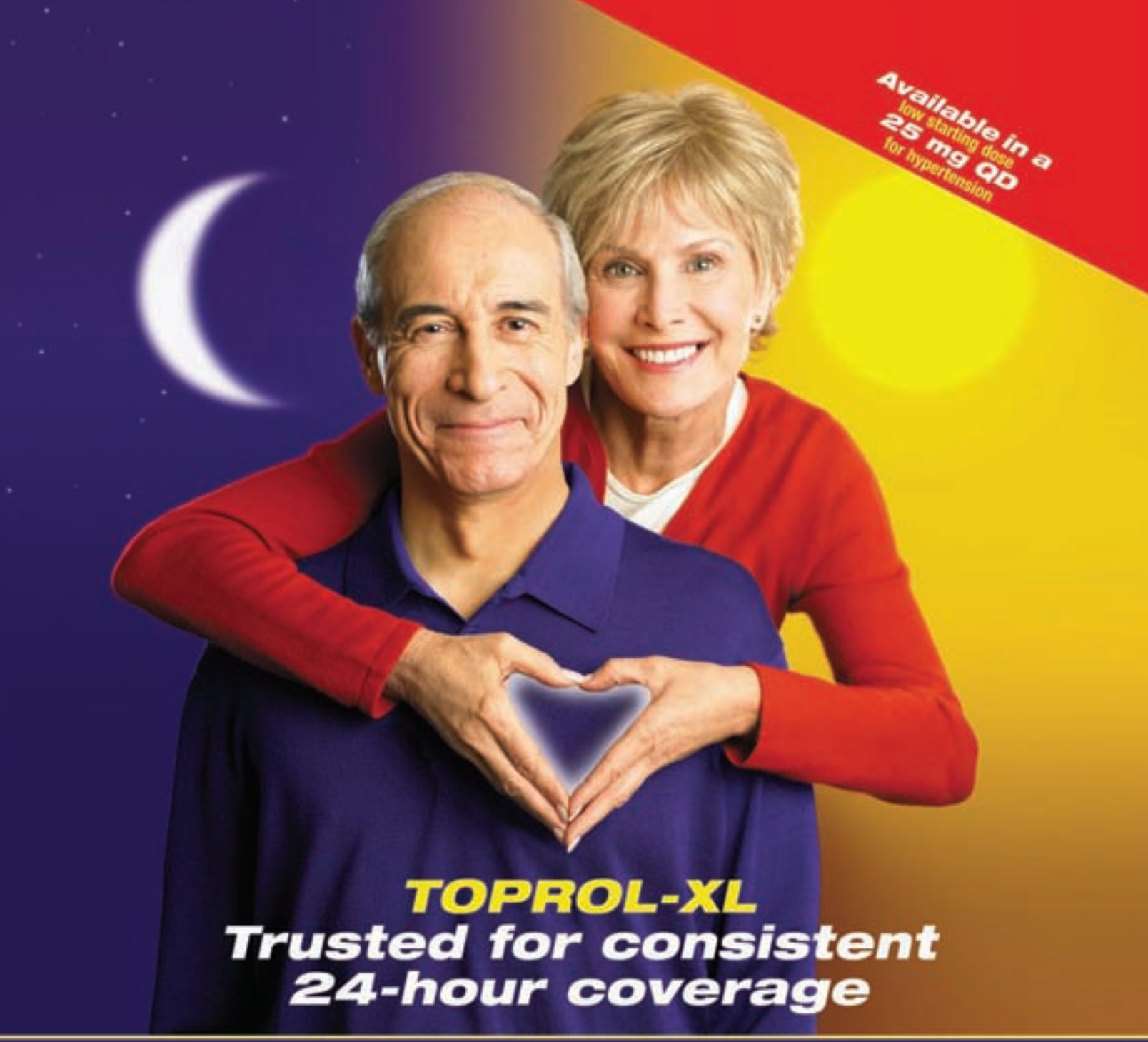

TOPROL-XL is indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

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.

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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, monoamine 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	1.3	0.4
Accident and/or injury	1.4	0.8

Other adverse events with an incidence of > 1% on TOPROL-XL and as common as 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 | 5	1088-05	1088-39
50 mg	Round	A | 50	1090-05	1090-39
100 mg	Round	A | 100	1092-05	1092-39
200 mg	Oval	A | 200	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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AstraZeneca

BY WAYNE M. POLLAK, MD, FACC

New Frontiers in Cardiac Imaging

Cardiac CT provides diagnostic utility and clinical applications in cardiovascular disease

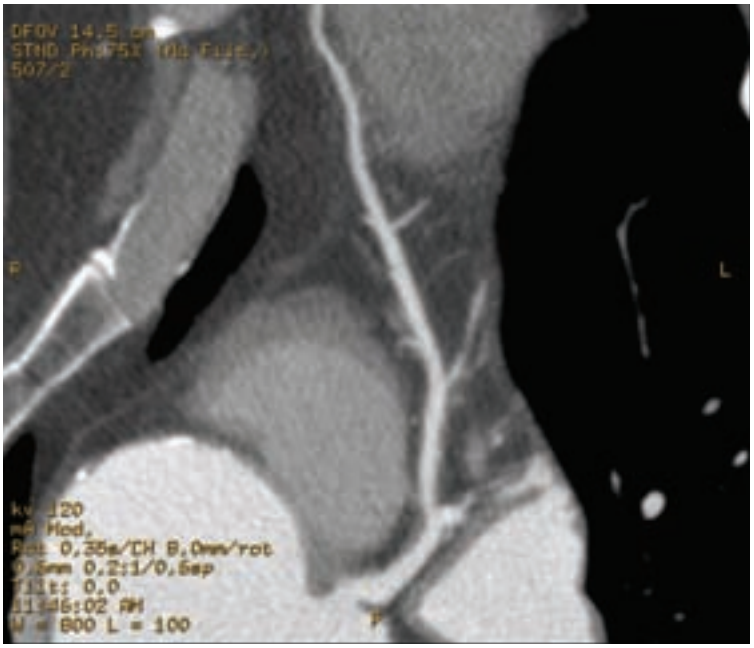
Recent advances in imaging technologies now enable more accurate, noninvasive diagnosis of cardiovascular disease. These advances include echocardiography (newer 3-D and contrast echocardiograms), nuclear cardiac stress testing, cardiac positron emission tomography, cardiac magnetic resonance (CMR), and, recently, cardiac computed tomography (CT). Each of these imaging modalities has strengths and limitations, and each technique offers differing and complementary clinical applications.

Echocardiography is an effective imaging modality used to define cardiac function. Exercise and pharmacologic nuclear stress testing is the most widely used test for the diagnosis and risk stratification of patients with suspected or known coronary artery disease (CAD). Nonetheless, its accuracy is limited by the common presence of artifacts, resulting in a sensitivity of 88% and specificity of 74% for the detection of obstructive CAD[1].

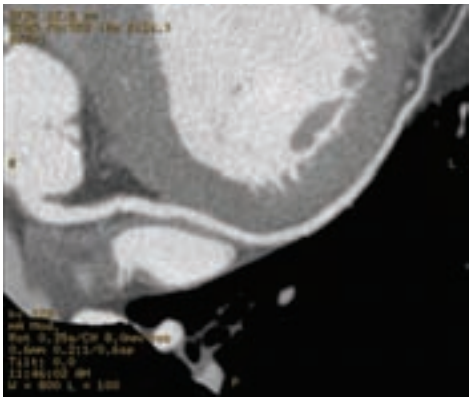
Cardiac MR is excellent for the evaluation of structural heart disease and cardiac function but is a poor study for evaluation of CAD. Cardiac CT has emerged as a robust imaging modality that provides a noninvasive evaluation of coronary arteries and cardiac function. This article reviews the diagnostic utility of cardiac CT and the means by which it is being integrated into clinical practice.

Diagnosing Coronary Artery Disease

In as much as 50% of patients, myocardial infarction or death is the initial presentation of CAD. Despite extensive research and the development of risk-prediction models, traditional risk factors often fail to predict the development of CAD or the occurrence of clinical cardiac events. An imaging modality that identifies such risk in the "vulnerable" patient has the potential to reduce the risk of CAD-related events.



This cardiac CT angiogram (curved multi-planar reformat) demonstrates a 20% stenosis of the left main coronary artery followed by a 40% stenosis of the ostium of the left anterior descending artery with distal luminal irregularities.



This cardiac CT angiogram is a curved multi-planar reformat, demonstrating luminal irregularities (mild atherosclerosis) of the right coronary artery.

Diagnostic Techniques

Coronary artery "calcium scoring," which is performed with a noncontrast CT, is a highly sensitive technique for detecting coronary artery calcium. Calcium scoring, however, has a low specificity for detection of obstructive CAD because it does not provide an angiographic evaluation of CAD[2]. Although calcium scoring correlates well with overall atherosclerosis burden and CAD risk, it does not identify soft, noncalcified plaque, which may be more vulnerable to fissure or rupture and so may pose a greater risk of coronary events[3].

Cardiac CT angiography, however, goes far beyond the quantification of calcified plaque burden obtained from calcium scoring. Cardiac CT, like the traditional invasive, catheter-based angiogram, uses intravenous contrast to fill the lumen of the coronary arteries. The use of multiple detectors (initially 16-slice and now 64-slice CT) and the increased rotation speed of the gantry enable imaging of the entire

length of rapidly moving coronary arteries. Cardiac CT can evaluate narrowing of the arterial lumen, characterize the artery wall, and identify both calcified and noncalcified plaque.

More than 35 studies have demonstrated the high sensitivity and specificity of cardiac CT angiography for the detection of coronary stenosis. A recent study of patients with an intermediate risk of significant CAD demonstrated that cardiac CT detected noncalcified atherosclerotic disease in 30% of subjects, and in 6.2% of patients, a noncalcified plaque was the only lesion[4]. Mollet et al. reported the diagnostic accuracy of 64-slice CT for detecting >50% stenosis compared to the gold standard of cardiac catheterization. The sensitivity and specificity of cardiac CT were found to be 99% and 95%, respectively[5]. Similarly, Leschka et al. demonstrated that 64-slice CT has a sensitivity of 94%, a specificity of 97%, and a negative predictive value of 99% for classifying significant stenosis[6].

Numerous studies utilizing 64-slice CT have demonstrated a consistent negative predictive value of 98% to 99% [6,7]. This evidence strongly demonstrates that cardiac CT can reliably exclude the presence of significant CAD in patients with a low-to-intermediate probability of CAD. It can be used as first-line evaluation of chest pain in such patients and is particularly useful in patients who had equivocal cardiac stress testing. Thus, the high negative predictive power of CT can "rule out" obstructive CAD and help avoid the need for invasive angiography.

Additional Applications of Cardiac CT

Cardiac CT also provides accurate assessment of left ventricular function (ejection fraction, regional wall motion, and infarct identification) when compared to the gold standard, cardiac MR[8], and contrast echocardiography[9]. Cardiac CT is helpful in the evaluation of adult patients with congenital heart disease and provides superior visualization of the anatomy of anomalous coronary arteries compared to invasive coronary angiography. In some centers, cardiac CT is used to define coronary venous anatomy accurately prior to the performance of biventricular lead placement and atrial fibrillation ablation by electrophysiologists.

Appropriate Indications for Cardiac CT

Currently accepted clinical indications are found in Table I (below) and are derived from the consensus statement written by a multidisciplinary task force of cardiology and radiology experts in cardiac CT[10]. The reader is referred to this article for a discussion of other clinical indications that were determined as inappropriate or uncertain indications for cardiac CT at this time. Numerous trials are currently evaluating outcome data and resource utilization in a variety of clinical presentations to clarify appropriate indications further. The use of cardiac CT in the emergency room for the evaluation of acute chest pain to exclude pulmonary embolus, aortic dissection, and obstructive CAD (coined the "triple rule-out") is also currently under investigation. It is important to emphasize that cardiac CT as a screening test is currently not recommended because of radiation exposure and contrast administration.

Table 1 — Appropriate Indications for the Use of Cardiac CT

For the Detection of CAD:

- Chest pain syndrome in a patient with an intermediate pre-test probability of CAD and an uninterpretable EKG or patient unable to exercise
- Chest pain syndrome and an uninterpretable or equivocal stress test
- Acute chest pain in a patient with intermediate pre-test probability of CAD, no EKG changes, and negative serial cardiac enzymes
- Suspected coronary anomalies in the symptomatic patient
- New onset heart failure to evaluate coronary arteries and etiology of cardiomyopathy

For Evaluation of Cardiac Structures:

- Assessment of complex congenital heart disease
- Cardiac masses (thrombus or suspected tumor) and pericardial conditions when transthoracic or transesophageal echo provided limited images
- Pulmonary vein anatomy prior to radiofrequency ablation for atrial fibrillation
- Coronary vein mapping prior to placement of biventricular pacemaker

ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging. J Am Coll Cardiol 2006;*48 (7). October 3, 2006.*

Patient Selection, Limitations, and Clinical Challenges

Current limitations for the evaluation of native coronary arteries include administration of contrast and radiation exposure, the need to reduce the patient's heart rate with beta-blockers prior to imaging, and decreased resolution in obese patients and those with significant coronary calcium. Patients with heart rates greater than 70 beats per minute have reduced sensitivity and specificity due to motion artifact. The presence of extensive amounts of calcium may reduce the ability to estimate the severity of a stenosis and thus reduce accuracy for the detection of obstructive CAD.

Coronary artery bypass grafts are imaged with excellent quality because of their larger caliber, relative lack of motion, and lack of calcification. Although current studies achieve near 100% accuracy for bypass graft evaluation, including the distal anastamosis site[11], evaluation of the native coronary artery distally can prove challenging. The metal present in the struts of a stent can sometimes produce artifacts that make its evaluation by cardiac CT a clinical challenge.

Economics

Medicare recently assigned temporary current procedural terminology (CPT) codes for cardiac CT for the purpose of tracking this new technology. Local

coverage determinations (LCD) for reimbursement vary widely throughout the country, and at present, reimbursement is provided in more than half of states. Currently, Florida Medicare is giving limited reimbursement under such codes and final LCD is expected to complete in 2007. The completion of clinical trials demonstrating improved patient outcomes will likely be required to gain widespread acceptance by insurance carriers.

Conclusion

Cardiac CT has a wide range of clinical applications and has demonstrated the ability to detect the presence of calcified and noncalcified plaque, as well as luminal stenosis within coronary arteries. With a consistent negative predictive power of >98%, it may become the initial test for the symptomatic, low-to-intermediate-risk patient in order to exclude obstructive CAD. Cardiac CT offers great promise in the management of coronary artery disease, but it must be used in the context of other imaging modalities and in the appropriate clinical setting. ■

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References

1. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging. *J Am Coll Cardiol 2003*;42:1318–33.
2. ACC/AHA consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol 2000*;36:326–40.
3. Hecht HS, Budoff MJ, Berman DS, et al. Coronary artery calcium scanning: clinical paradigms for cardiac risk assessment and treatment. *Am Heart J 2006*;151:1139–46.
4. Hausleiter J, Meyer T, Hadamitzky M, et al. Prevalence of noncalcified coronary plaques by 64-slice CT in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol 2006*;48:312–18.
5. Mollet NR, Cademartiri F, van Mieghem C, et al. High-resolution spiral CT coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation 2005*;112:2318–23
6. Leschka S, Alkadhi H, Plass A, et al. Accuracy of MDCT coronary angiography with 64-slice technology: first experience. *Eur Heart J 2005*;26:1482–87.
7. Leber AW, Knez A von Ziegler F, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice CT: A comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol 2005*;46:147–54.
8. Yamamuro M, Tadamura E, Kubo S, et al. Cardiac functional analysis with multi-detector row CT and segmental reconstruction algorithm: Comparison with echocardiography, SPECT, and MR imaging. *Radiology 2005*;234:381–90.
9. Lessick J, Mutlak D, Rispler S, et al. Comparison of multi-detector CT versus echocardiography for assessing regional left ventricular function. A*m J Cardiol 2005*;96:1011–15.
10. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR appropriateness criteria for cardiac CT and cardiac magnetic resonance imaging. *J Am Coll Cardiol 2006*;48(7). Oct. 3, 2006.
11. Ropers D, Pflederer T, Rixe J, et al. Improved accuracy of noninvasive coronary angiography in patients after bypass surgery using 64-slice spiral CT. American Heart Association Scientific Sessions. Nov. 13-16, 2005 Poster 2651.

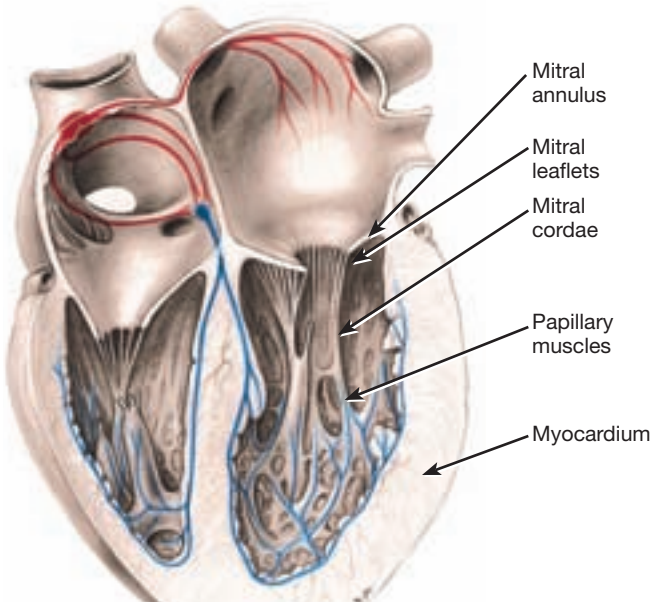
BY RALPH M. LEVY, MD, FACC

Valvular Disease Series

The shifting paradigm in mitral regurgitation

The mitral valve (MV) is a complex organ. Anatomically, it consists of two leaflets (anterior and posterior) attaching via tendinous cords and two major papillary muscles (anterolateral and posteromedial) to the left ventricular wall. It is supported by connective tissue (the annulus, which is part of the cardiac fibrous skeleton) and has close relationships to the aortic valve and the left atrium. The failure of the MV to close in its appropriate anatomical plane leads to valvular insufficiency.

Mitral regurgitation (MR), when significant, causes a series of hormonal and hemodynamic events, which rapidly or slowly (depending on the etiology of the MR) lead to left ventricular failure, congestive heart failure, and death. New insights into the pathophysiology and natural history of MR have led to a sea of change in the way in which physicians approach the treatment of the disease. For instance, it is now known that patients with MR have a 20% survival rate at four years when severely symptomatic (class III-IV of the New York Heart Association [NYHA]) and a 65% survival rate at 10 years when asymptomatic or minimally symptomatic (this is in excess of expected mortality for age). Once symptomatic, patients with MR also have a significant rate of sudden cardiac death.



The mitral valve consists of two leaflets attached via tendinous cords (mitral chordae) and two major papillary muscles to the left ventricular wall (myocardium), supported by connective tissue (mitral annulus).

Medications Do Not Suffice

Conventional wisdom indicates that surgery is too risky and the outcomes too poor to justify intervention, thereby mandating medical therapy. Unfortunately, medical therapy, as far as the evidence goes, is ineffective in delaying the progression of MR. Once MR occurs and becomes at least moderate, compensatory mechanisms using Frank-Starling Law develop, resulting in left ventricular (LV) hypertrophy and neurohormonal activation. It is also now known that the degree of MR depends on the effective regurgitant orifice (ERO), the degree of left atrium compliance, the gradient for the MR, and the closing force effected on the leaflets. Eliminating or decreasing MR is not enough to alter the disease progression. It is also necessary to reverse ventricular remodeling, attenuate the neurohormonal activation, and improve hemodynamics.

Remarkably, afterload is not particularly increased in MR, which likely explains why a recent study of angiotensin-converting enzyme inhibitors in patients with chronic MR did not show any benefit (including delaying progression to surgery) at seven years. There is some recent evidence that beta-blockers may improve survival but only in patients after MV repair. With the advent of MV repair and improved operative techniques, surgery is now the therapy of choice for patients with significant MR. MV repair is now performed for prolapse of the anterior or posterior leaflets with similar results and has proven to be of low risk and durable.

For NYHA class I or II patients, the expected surgical mortality is zero percent for patients 75 years of age and younger and 3.6% for patients 75 years of age and older. The most important insight gained by cardiologists recently is that we should identify and operate on patients earlier in their diseases, as the operative mortality rises to 2.5% in NYHA class III-IV patients 75 years of age and younger and 12.7% in patients 75 years of age and older. The obvious lesson is to operate before it is too late.

Evaluating the Severity

The current evaluation of MR depends on the usual culprits, such as the history and physical exam, but MR is not always detectable this way. For example, there are patients with ischemic MR whose murmurs are barely auscultable. Another group of patients with functional, usually ischemic, MR is detectable only during stress echocardiography.

For most patients, however, the quantification of MR is performed by echocardiography. MR was quantified as mild, moderate, or severe by estimating the area of regurgitation into the left atrium as visualized by color flow mapping. This

approach was generally unreliable. Major changes here include the fact that color Doppler is now utilized for actual quantification of severity, including the quantification of the ERO and regurgitant volume based on the principle of proximal isosystolic area. Based on prospective and retrospective data, some recommendations for stratification of therapy are now given:

> As of this year, of more than 3,500 major randomized studies in clinical cardiology, only 16 are properly conducted studies for valvular therapy.

- In asymptomatic patients, if the LV ejection fraction is more than 60%, there is normal exercise tolerance (VO2 or oxygen consumption per unit of time), there is normal brain natriuretic peptide (insensitive but reasonably specific), and the ERO is more than 40 mm2, observation is suggested.
- In asymptomatic patients with an ERO of more than 40 mm2 and BNP activation, early surgery is considered.
- In patients with ischemic MR, intervention is suggested if the ERO is more than 20 mm2.

Surgery is also suggested in symptomatic patients with severe MR (probably moderate MR as well, if LV dysfunction is present). If the ejection fraction is less than 60%, the LV is already dysfunctional in the setting of severe MR (remember that the LV ejection fraction is falsely elevated by the fact that the LV is emptying in part into a low-resistance chamber, the left atrium) and surgery should be considered.

A Complex Medical Issue

Of course, many other considerations are included in the decision-making process — the age of the patient (particularly 75 years of age and older), comorbidities (diabetes, chronic kidney disease, arteriosclerotic heart disease, chronic obstructive pulmonary disease, etc.), level of activity, severity of LV dysfunction (MV surgery in patients with severe LV dysfunction is controversial and beyond the scope of this review), the quality and experience of the surgical team, and, most important, the mechanism of MR. Patients whose MR is due to heavy mitral annular calcification (MAC), MV endocarditis, or ischemia benefit from different types of intervention. They include preferential repair for MAC-induced MR, mostly MV replacement for infectious endocarditis (30% rate of repair in healed endocarditis) and only after full debridement is accomplished, and a multiplicity of techniques for ischemic MR (from restrictive and remodeling annuloplasty to stented tissue prostheses).

A Promising Procedure

A very interesting technique — one Raul D. Mitrani, MD, and John Cogan, MD, have used in conjunction with the clinicians at Cardio Consultants of South Florida — is the use of biventricular pacing in patients with MR in the setting of ventricular dysynchrony (i.e., left bundle branch block). Although this has been studied in patients with dilated cardiomyopathies (EF less than 35%, QRS more than 130 ms, NYHA class III-IV on optimal medical treatment), the results so far are encouraging, with evidence of reverse remodeling, decreased MR, significant improvement in symptoms, and decreased mortality. The rate of responders is about 70%, although the data on patients with ischemic MR are sketchy.

As one can see, MR is a complex medical issue. The approach to treatment depends on careful evaluation of the etiology, clinical consequences, and prognosis. It requires close coordination with the surgeons and relies on accurate estimation of severity, for which a variety of advanced echocardiographic and transesophageal echocardiography techniques are required. It is always evolving and exciting, and the future of therapy will include the development of percutaneous techniques for valve repair, which are currently undergoing clinical trial evaluation. Proof of efficacy is always required, and on this point, the cardiology literature is sorely lacking. As of this year, of more than 3,500 major randomized studies in clinical cardiology, only 16 are properly conducted studies for valvular therapy. ■

***Ralph M. Levy, MD, FACC**, earned his medical degree from the University of Rosario's Medical School in Bogota, Colombia, in 1983. He then completed an internship and a residency in internal medicine from SUNY Health Sciences Center in Brooklyn, New York, and a cardiology fellowship at Mount Sinai Medical Center in New York City. He is board certified in internal medicine, cardiovascular disease, and critical care medicine. Dr. Levy established the intraoperative TEE program at Memorial Regional Hospital. He has served as chief of the department of cardiology at MRH and is currently the chief of the section of cardiology at Memorial West Hospital. Dr. Levy's offices are located in Hollywood, Weston, and Pembroke Pines.*

BY KASHMIRA P. BHADHA, MD, FACC

An Equal Opportunity Killer

For women, heart disease is a deadlier risk than many realize

Heart disease is often thought of as a man's problem, but heart disease (cardiovascular disease) is the leading cause of death in women. During the last 25 years, the death rate from heart disease for men has steadily decreased, but the rate for women is increasing. When a large group of women took a Gallup survey, most thought they were likely to die from some form of cancer, probably breast cancer. In reality, one out of every three women (and two out of three women 65 years of age and older) will die from heart disease.

The Gender Difference

Coronary heart disease (CHD) is often overlooked or misdiagnosed in women. Although men often have severe chest and arm pain, women's symptoms are often different and, therefore, overlooked. Women may have shortness of breath, nausea, vomiting, cold sweats, fatigue or weakness, feelings of anxiety, loss of appetite, and pain in the upper back, jaw, or neck.

Most women who are admitted to a hospital with a heart attack or cardiac arrest are not aware of their risk or were not diagnosed previously by their physicians as having heart problems. Women have a higher risk of death after a heart attack and are more likely to suffer a second attack. Even in the hospital, women have a higher rate of death after coronary bypass surgery and have more complications following angioplasty.

Women who come to the emergency room with chest pain are treated less aggressively than men. They are less likely to get an electrocardiogram or a blood test for cardiac enzyme measurement (to determine whether they have had an attack) and are less likely to be seen by a cardiologist. They are, however, more likely to receive pain killers (like codeine) or anti-anxiety medications (like Xanax® or Valium®).

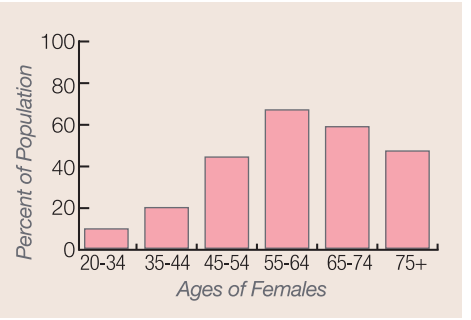
Factors that Increase Risk

A woman's age, hormonal status, diabetes, hypertension, smoking, overweight status, sedentary lifestyle, lipid abnormalities, and family history of heart disease at a young age are important risk factors for CHD in women.

It is important for women to get a complete cholesterol test, which includes a breakdown of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. A low level of HDL is more predictive of coronary risk in women. Triglycerides appear to influence coronary risk mainly in older women. Every woman 20 years of age and older should have a fasting lipid measurement. A more detailed test (such as the Berkeley Heart Profile), which includes lipoprotein(a) and apolipoprotein B and A-1 is recommended if the standard lipid profile (cholesterol test) is normal in women 60 years of age and younger with CHD. Lipoprotein(a) is a useful determinant of CHD in women 66 years of age and younger.

Women are usually diagnosed with CHD at an older age, about five to 10 years after menopause. CHD is unusual in premenopausal women who do not have any other risk factors. A complete hysterectomy, however, both with or without hormone replacement, carries an increased risk of CHD. Lower levels of estrogen cause an increase in LDL cholesterol, total cholesterol, and triglycerides but a decrease in HDL cholesterol.

Cigarette smoking is associated with 50% of heart-related ailments (heart attack, angina, sudden death, etc.) in women.



Prevalence of cardiovascular disease in women

Coronary risk is increased even in women who may smoke only one or two cigarettes a day. Compared with nonsmokers, the probability of a heart attack is increased 600% in women and 300% in men, but it is never too late to stop smoking. Most of the increased risk from smoking is eliminated within two to three years after quitting.

Central obesity (a waist-hip ratio of > 0.9 or a waist circumference of more than 35 inches) is more predictive of risk than the total body weight or simple body mass index in women.

In a future issue of this magazine, diagnostic tests, treatment options, and CHD risk-reduction techniques currently available will be discussed. ■

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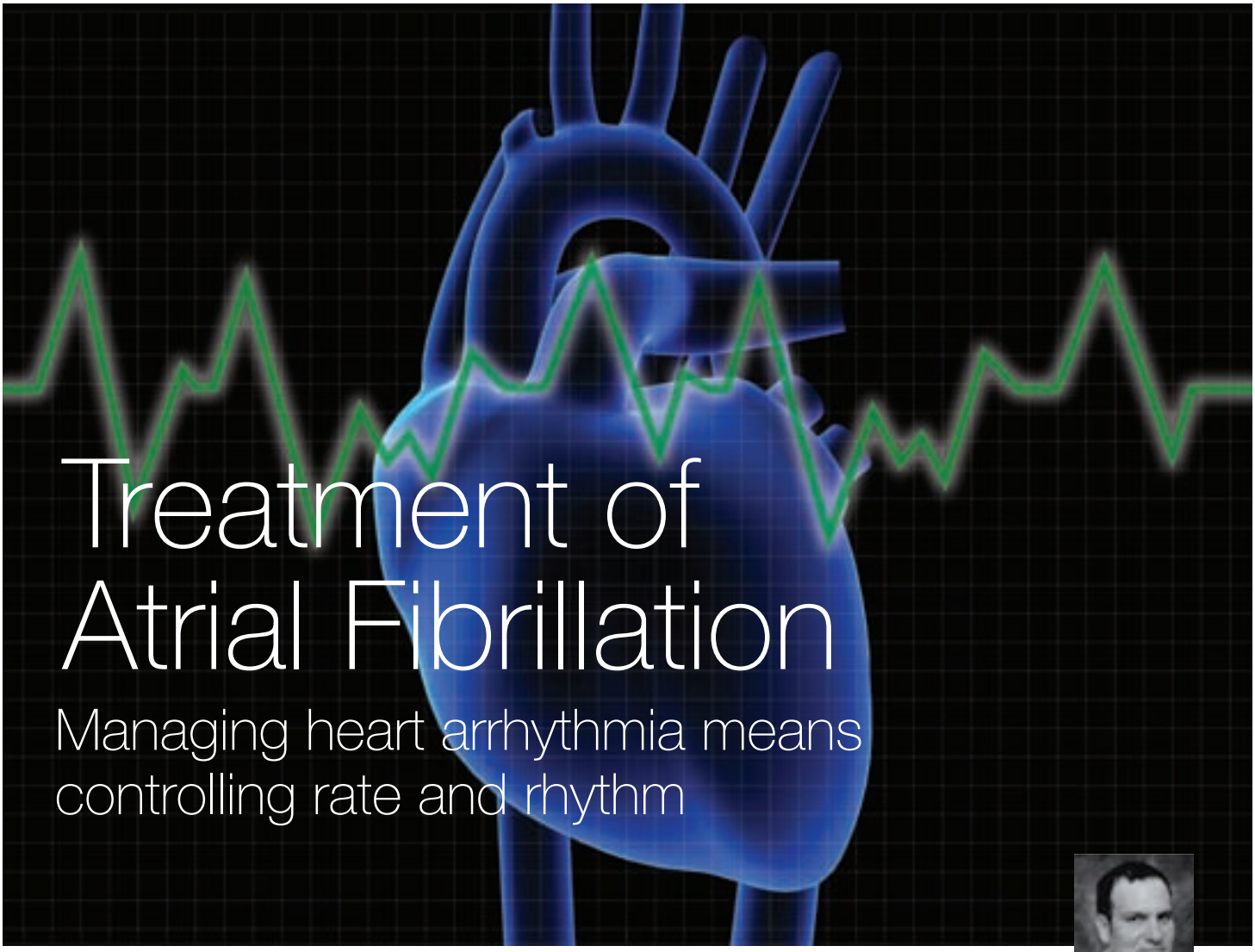


Treatment of Atrial Fibrillation

Managing heart arrhythmia means controlling rate and rhythm

BY RAUL MITRANI, MD

Atrial fibrillation (AF) is the most common arrhythmia in the United States, affecting 2.4 million people. The incidence of AF increases with age; it is estimated that by 80 years of age 8% of patients have or have had an episode of AF.

AF is a disease associated with increased morbidity and mortality. Patients with AF are at risk for thromboembolic events and worsening cardiac function that could lead to congestive heart failure. Many patients have fatigue, tiredness, or other symptoms associated with loss of mechanical atrial function. AF is an independent risk factor for mortality in patients with congestive heart failure. Therefore, AF is a major clinical problem.

This review focuses on current therapies of AF and incorporates recommendations from the 2006 American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee (ACC/AHA/ESC) Practice Guidelines for the Management of Patients with Atrial Fibrillation published in August 2006. In particular, the discussion will focus on management issues in heart rate control, prevention of thromboembolic complications, and rhythm control to normal sinus rhythm.

Definitions

AF is an atrial arrhythmia characterized by rapid, uncoordinated atrial activity or mechanical function.

Persistent AF is AF that persists unless active medical measures are employed to electrically or pharmacologically cardiovert the patient back to normal sinus rhythm. Generally, AF duration greater than seven days is classified as persistent.

Paroxysmal AF is AF that starts and stops spontaneously.

Lone AF is AF in a patient without valvular heart disease, coronary artery disease, congestive heart failure, cardiomyopathy, or a history of diabetes mellitus, hypertension, prior cerebral vascular accident (CVA), or thromboembolic event.

Initial Evaluation

Although most patients with AF have chronic heart disease that causes AF, there are patients with reversible causes. These include excess alcohol intake, recent cardiothoracic surgery, hyperthyroidism, pulmonary embolus and other pulmonary diseases, Wolff-Parkinson-White Syndrome, and some metabolic disorders. For

these patients, treatment of the underlying disorders can eliminate the AF. Therefore, identification of reversible causes should be part of the initial evaluation.

It is important to classify patients according to the presence or absence of other heart disease. Additionally, patients should be classified according to whether the episode is the first, whether the AF is paroxysmal or persistent, and to what extent the AF causes symptoms. The initial evaluation also involves documentation by electrocardiogram of the AF. In general, initial evaluation includes a comprehensive history and physical exam, measurement of thyroid function, and an echocardiogram.

Additional monitoring with event recorders or Holter monitors is recommended to quantify the AF, characterize the ventricular response and rate, and correlate symptoms to arrhythmias. Stress testing or other ischemia workup is indicated only in patients who have other conditions mandating such testing. Diagnostic electrophysiology studies are usually not indicated unless there are concurrent arrhythmias (atrial flutter, supraventricular tachycardia) or to guide primary ablation therapy.

Management of AF

Treatment of AF involves three objectives:

- Prevention of thromboembolism
- Ventricular rate control
- Restoration and maintenance of normal sinus rhythm (rhythm control)

Prevention of Thromboembolism

Antithrombotic therapy (warfarin) to prevent thromboembolism is recommended for most patients with AF, except those with lone AF or those with anticoagulation contraindications. Warfarin is recommended for all patients with moderate risk factors, including advanced age (65 years of age and older), hypertension, history of congestive heart failure, impaired left ventricular systolic function (ejection fraction <35%), diabetes mellitus, or past history of transient ischemic attack (TIA)/CVA or other thromboembolism. In the absence of mechanical heart valves, the target international normalized ratio (INR) is 2.0 to 3.0. There is no difference in anticoagulation strategies in patients with paroxysmal versus persistent AF.

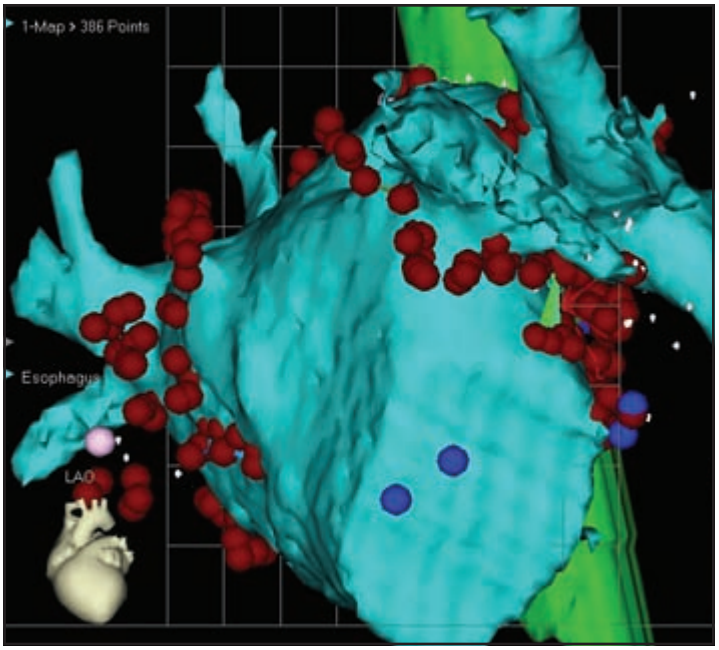
As per the recent ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation, aspirin therapy may be substituted for warfarin in select lower-risk patients, depending on the risk/benefit ratio. Additionally, in patients younger than 60 years of age with lone AF, warfarin therapy is not recommended.

Newer anticoagulants to replace warfarin are currently undergoing trials in the United States.

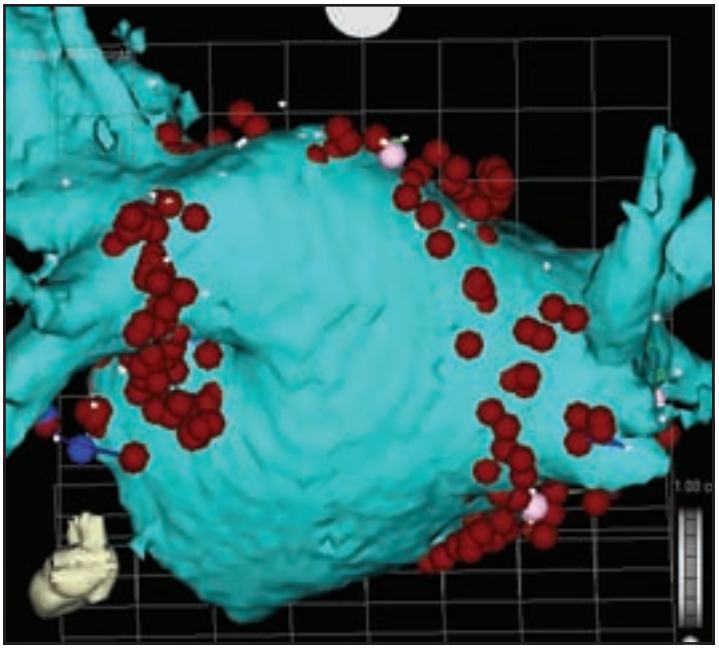
Rate Control

Acute control of ventricular response in patients with AF and rapid response is often achieved with beta-blockers, calcium channel blockers (diltiazem, verapamil), or digoxin. The choice of agents to control ventricular response depends on comorbidities. For patients with chronic obstructive pulmonary disease, beta-blockers are avoided. For patients with congestive heart failure, beta-blockers and calcium channel blockers are used with caution. Digoxin is usually not effective as a single agent but is used as a second- or third-line agent. Intravenous amiodarone is often useful to control heart rate in patients with AF when other measures are unsuccessful or contraindicated.

Chronic rate control is very much achievable with the same medications, either as solo agents or in combination



Anterior (above) and posterior (below) views of CT scan-guided reconstruction of the left atrium during atrial fibrillation ablation. The tree-like branch structures emanating from the left atrium represent the pulmonary veins. The red dots represent ablation lesions encircling the pulmonary veins. In one view, the bright green structure represents the esophagus, which sits right behind the left atrium.



(beta-blockers, nondihydropyridine calcium blocker, digoxin). During office visits, the adequacy of rate control should be assessed at rest and during exercise. Many elderly patients with underlying sick sinus syndrome may develop symptomatic bradyarrhythmias as a consequence of rate control treatment. In this scenario, a pacer is implanted to prevent bradyarrhythmias and to allow for treatment of AF.

The deleterious effects of having rapid rates to AF include fatigue, palpitations, and shortness of breath. A tachycardia-induced cardiomyopathy may develop, leading to congestive heart failure. In patients with already compromised left ventricular systolic or diastolic function, the presence of AF with rapid rates leads to worsening of the congestive heart failure. There are occasional patients who have persistent rapid rates despite medical therapy; in these patients, it is reasonable to perform an atrioventricular-nodal ablation and implant a pacer.

Maintenance of Normal Sinus Rhythm

As discussed above, treatment of any precipitating or reversible causes of AF is the initial recommendation. In most patients, no cause is identified. Therefore, an antiarrhythmic drug is often recommended. Many antiarrhythmic drugs are associated with side effects, toxicities, and potential for ventricular proarrhythmia. Therefore, these drugs are usually carefully chosen and, in many cases, initiated under a monitored setting.

> “With improvements in technology and operator experience, it is expected that radiofrequency ablation will be used to cure an ever-expanding population of patients with AF.”

Rhythm Control

Rhythm control in patients with AF refers to a strategy of converting a patient in persistent AF to normal sinus rhythm and to one of using drugs or nonpharmacologic techniques to maintain normal sinus rhythm in patients with either persistent or paroxysmal AF. Rhythm control is preferred in many patients with AF due to the presence of symptoms of fatigue, malaise, shortness of breath, and palpitations, even if they have adequate rate control. Additionally, it is thought that converting and maintaining normal sinus rhythm is beneficial in the long term, although studies done to date have not supported this notion.

Cardioversion of AF

Cardioversion of AF to normal sinus rhythm involves a two-step process. The first step is to ensure that such cardioversion does not place patients at undue risk of thromboembolic complications. Cardioversion is thought to involve acceptably low risk of thromboembolic complications in many but not all patients with AF lasting less than 24 to 48 hours or in patients who have documented therapeutic INRs>2.1 for more than four weeks. In other patients, a transesophageal echocardiogram should be performed to rule out left atrial appendage thrombus prior to cardioversion. After cardioversion to normal sinus rhythm, patients should receive adequate anticoagulation for at least four weeks and, in many instances, for a considerably longer duration of time, depending on other clinical factors.

The actual process of cardioversion is often accomplished by electrical cardioversion using DC energy between 50 and 360 joules. Biphasic shocks are more effective than the older-style monophasic shocks. Chemical cardioversion is often accomplished successfully in a lower percentage of patients using drugs such as amiodarone, ibutilide, procainamide, or others. In general, rate-slowing drugs, such as beta-blockers, calcium blockers, and digoxin, do not directly induce cardioversion from AF to normal sinus rhythm.

Class I antiarrhythmic drugs, especially flecainide and propafenone, are generally contraindicated in patients with coronary artery disease but are recommended agents in patients with lone AF or patients with hypertension without left ventricular hypertrophy and otherwise no significant heart disease. Amiodarone is considered the most effective drug, but significant long-term side effects and toxicities limit its use to patients with heart failure or coronary artery disease. Sotalol and dofetilide are also used in coronary artery disease and heart failure (dofetilide), but inpatient initiation of these drugs is mandatory due to significant risks of ventricular proarrhythmia/torsades de pontes.

Rate vs. Rhythm Control

Studies to date do not support a routine strategy of rhythm control rather than rate control in patients with minimally symptomatic or asymptomatic AF. The AFFIRM trial examined more than 4,000 patients with AF who randomized to a strategy of either rate or rhythm control. There was no advantage to rhythm control compared with rate control. In this trial, only 65% of patients in the rhythm control arm were in normal sinus rhythm (NSR) and approximately 35% of patients in the rate control arm were in NSR. Post hoc retrospective analysis showed that patients in NSR (in either the rhythm control or the rate control arms) actually did better in terms of survival compared with patients in AF. Therefore, the data suggests that we still have imperfect and somewhat risky therapies for rhythm control which may counterbalance the benefit of being in NSR. In current clinical practice, rhythm control is advisable for patients who are symptomatic or have other clinical sequelae with AF.

Radiofrequency Ablation for AF

The initial use of radiofrequency (RF) ablation for patients with AF was restricted to ablation of the AV node to cause heart block and placement of a permanent pacer. This strategy was and, to some extent, is still used in patients with AF with rapid ventricular response refractory to medication. This strategy, however, neither eliminated the underlying AF nor reduced the need for anticoagulation therapy to prevent thromboembolism.

As discussed above, antiarrhythmic drugs have limited efficacy at maintaining NSR and are associated with potential side effects and toxicities. Therefore, RF ablation has gained popularity as a technique to actually cure patients of AF. Because most patients have AF initiating in the left atrium in or around the pulmonary veins, the technique of RF ablation usually involves electrical isolation of the pulmonary veins vs. encircling lesions around the pulmonary veins.

As shown in the figure on page 15, RF lesions were placed around the ostia of the right and left-sided pulmonary veins. Other lesion sets in the right or left atrium are sometimes necessary to achieve success. The long-term success rate of this approach is between 70% and 90%, depending on the patient population. Early recurrences of AF or atrial flutter in the first 3 months post ablation does not necessarily predict long-term failure.

The use of RF ablation to cure AF should only be performed in experienced centers, because the potential for serious complications may approach 5% to 6%. These complications include cardiac perforation or tamponade, pulmonary vein stenosis, and thromboembolic complications, such as myocardial infarction or cerebral infarct. Rare complications such as atrioesophageal fistula formation can lead to death.

Nevertheless, in carefully selected patients with symptomatic AF refractory to at least one antiarrhythmic drug, the use of RF ablation to cure AF is a reasonable therapy that offers patients the opportunity to live free of the symptoms of AF and the use of drugs and anticoagulants.

Conclusions

AF is associated with major morbidity and increased risk of mortality. Treatment algorithms are geared toward rate control, rhythm control, and prevention of thromboembolic complications. There is no clear mortality or quality of life advantage to rhythm control vs. rate control in patients with minimal to no symptoms of AF. However, in symptomatic patients with AF, a strategy of rhythm control is often necessary. The use of antiarrhythmic drugs is limited by side effects, potential toxicities, and inefficacies of the drug. RF ablation as a curative procedure is gaining acceptance as a second-line therapy. With improvements in technology and operator experience, it is expected that RF ablation will be used to cure an ever-expanding population of patients with AF. ■

***Raul Mitrani, MD**, earned his bachelor's degree from Columbia College and his medical degree from Columbia University College of Physicians and Surgeons. He completed an internship and a residency at Case Western Reserve University. He then completed a fellowship in cardiovascular diseases and cardiac electrophysiology at Indiana University. Dr. Mitrani is also a diplomat and 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, as well as an associate professor of medicine at the University of Miami School of Medicine and director of the Arrhythmia and Pacemaker Center at Jackson Memorial Hospital. He currently works as director of electrophysiology for Memorial Regional Hospital and director of Cardiovascular Consultants of South Florida's cardiac electrophysiology practice. Dr. Mitrani's offices are located in Hollywood and Aventura.*

Suggested Reading

1. Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. *J Am Coll Cardiol 2006*; 48:854–906.

2. AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *NEJM 2002*; 347:1825–33.

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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

Atacand®
candesartan cilexetil

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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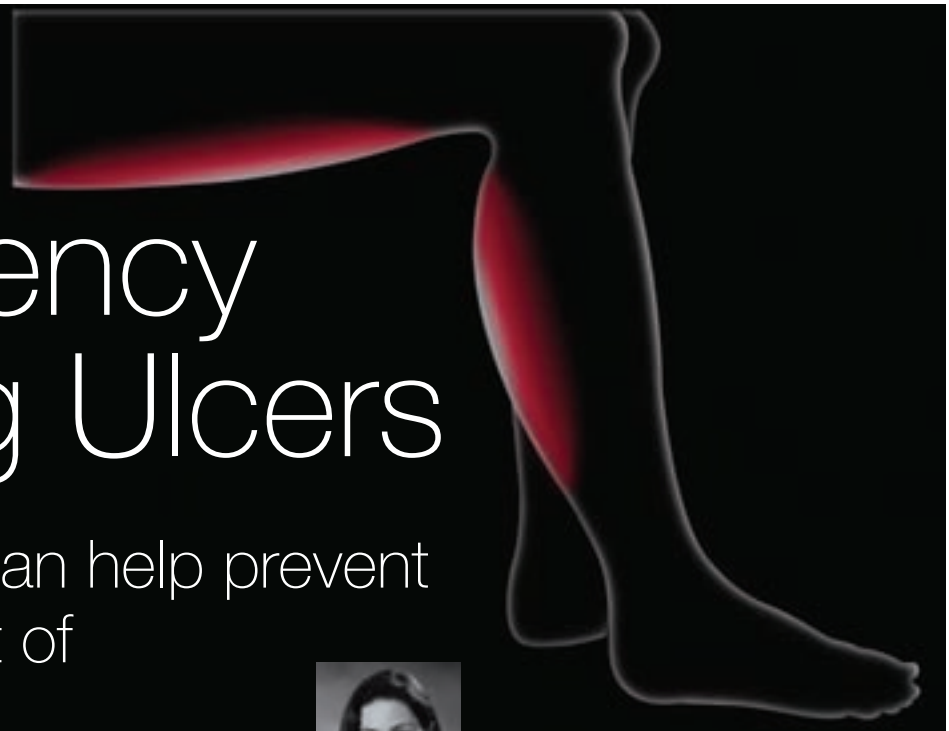
Rev. 05/05

AstraZeneca

Venous Insufficiency and Leg Ulcers



Early treatment can help prevent the development of venous ulcers

BY SUSAN FOX, DO

Venous stasis ulcers are the most common form of leg ulcerations. As much as 80% of lower extremity ulcers are due to venous disease. Venous disease exists in 25% of the U.S. population as a whole. Vein disease affects 70% of all women and 40% of all men. More than one million Americans have venous stasis ulcers, and more than 100,000 people are totally disabled as a result. One-quarter of patients have their first ulcers by 40 years of age and three-quarters by 60 years of age.

The average cost to treat a venous ulcer is approximately $10,000, resulting in a huge burden on the U.S. health care system — $2.5 billion to $3 billion each year. Between three and four million workdays are lost annually. As much as 70% of venous ulcers recur within the first six months to a year of healing. It is important to diagnose venous insufficiency early in its course and treat it appropriately before the patient develops an ulcer.

Those at Risk

Several epidemiological studies have been performed to determine who develops venous insufficiency. Older age, heredity, obesity, a history of phlebitis or leg trauma, surgery, or crush injuries are major risk factors. Debate exists over whether professions that require people to work on their feet for the majority of the day (i.e., nurses, hairdressers, teachers) help contribute to venous insufficiency.

The majority of ulcers are due to chronic venous insufficiency. When a person is standing upright, blood returning to the heart from the lower extremities must travel against gravity. As one walks, calf muscles contract, compressing the deep veins and propelling blood upward. Normally, semilunar valves in the veins prevent the backflow of blood. However, valvular failure and muscle weakness can lead to the backflow of blood. This retrograde flow of blood leads to pooling of blood in the veins and venous hypertension.

These elevated venous pressures communicate to the superficial veins and cause the veins to stretch, creating superficial varices. The elevated pressures cause even the thin-walled capillaries (small veins) to stretch, leaving gaps between the cell walls. As the single-layer-cell walled capillaries stretch, water, proteins (causing fibrin cuffs), and red blood cells leak through these gaps, causing leg edema, tissue changes, and discoloration around the ankles.

Progression

Venous disease is broken down into three stages. Stage one is edema in the anterior shin and ankles with starburst spider vein formations around the medial ankle. Stage two is discoloration from hemosiderin (an iron pigment in the blood) staining with swelling of the lower extremity. Gradually, skin hardening, called lipodermatosclerosis, occurs, often containing thin white atrophic scars and small painful foci primarily on the medial ankle or posterior foot. The exact step leading from venous hypertension to ulceration is unknown. In stage three, an ulcer develops primarily in the medial ankle, but as much as 20% may occur in other areas.

Venous ulcers are often located around the medial malleolus in an area referred to as the gaiter area. Skin around the ulcer tends to be swollen and pigmented. Venous ulcers are often larger than arterial ulcers. Patients should undergo baseline arterial testing with and without exercise to rule out concomitant arterial disease. Also, a venous color duplex ultrasound is needed. A venous insufficiency study is important to determine the exact location of valvular incompetence and any possible arteriovenous shunts or thrombosis. Invasive phlebography is rarely if ever used now to diagnose venous disease.

The traditional, conservative modality used to treat venous ulcerations is compression therapy (Unna boots, Dyna-Flex™, Profor, multilayer compression bandages, compression hose, or soft casting). As long as the arterial supply to the lower extremity is intact, multilayer compression bandages or medical-strength compression hose are applied to the lower extremity to decrease lower extremity edema.

> "70% of venous ulcers recur; however, new treatment options are available to treat venous disease definitely, especially if caught early."

Leg elevation, moisturizing the lower extremity, and good foot care also play key roles. Having patients sleep with their legs elevated 4 to 6 inches reduces the majority of edema by morning. Before getting out of bed, the person should immediately apply medical grade compression hose. The compression hose keep the edema out of the extremity and allow nutrients in the body to heal the damaged tissue. Calf-pumping exercises, in addition to the compression therapy, enhance venous return and facilitate ulcer healing. Even after the ulcer is healed, patients need to continue to wear compression hose on their legs. Patients who are compliant with wearing compression hose have increased ulcer healing rates and decreased recurrence rates.

Beyond Vein Stripping

Because 70% of venous ulcers recur, patients with symptoms of venous insufficiency (leg pain, swelling, discoloration, malleolar flare, and tissue damage) with or without leg ulceration should be evaluated for one of the new treatment options to treat their venous disease definitively. This early treatment can help prevent development of venous ulcers or their recurrence.

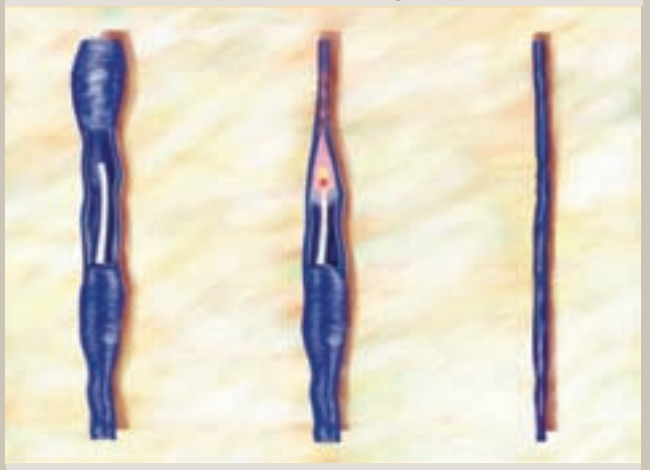
The conventional treatment for chronic venous disease was vein stripping. Now, newer treatment options are available, such as endovenous laser and radiofrequency ablation of the veins. These newer, minimally invasive treatment modalities result in less postoperative pain, fewer wound infections, fewer scars, fewer missed varices, fewer recurrences, fewer nerve injuries, and fewer days off work than vein-stripping surgery. Recovery takes just a few days. The radiofrequency ablation has a success rate of 90% at two years, and the endovenous laser has success rates ranging from 96% to 100% at two years. The procedures close off the superficial incompetent vein(s) and are usually performed in the office under local anesthetic.

Whether the venous disease is due to superficial or deep venous insufficiency, new treatment options are available. Studies have shown that intensive treatment of superficial venous disease, both varicose and spider veins, can improve deep venous flow. In one study, more than 80% of deep venous blood flow improved (resolving venous insufficiency and shrinking vein size) after aggressive treatment of the superficial veins. This improvement in blood flow assists in the healing of venous stasis ulcers and decreases their recurrence. Aggressively treating venous disease helps prevent venous ulcerations that are a huge health care burden. ■

New Horizons in Treatment of Venous Leg Ulcers

ELVeS™ is one of the newer options for treating venous leg ulcers. This endovenous laser treatment is minimally invasive and results in less postoperative pain, fewer wound infections, fewer scars, fewer missed varices, fewer recurrences, fewer nerve injuries, and fewer days off work than vein-stripping surgery.

ELVeS™
(Endo Laser Vein System)



Varicose vein before treatment; ELVeS laser and catheter inserted into vein	Laser beam heats interior of varicose vein; vein scars down and collapses as catheter is withdrawn	ELVeS catheter is removed; vein remains closed and shrinks over time

Susan B. Fox, DO, *is board certified in vascular medicine and received her medical degree from Nova Southeastern College of Osteopathic Medicine in Fort Lauderdale, Florida, and completed a residency in internal medicine and a fellowship in vascular medicine at The Cleveland Clinic in Ohio. Before moving to Florida, she practiced as a vein and vascular expert at University Hospitals of Cleveland in Ohio and was on the teaching faculty at Case Western Reserve University in Cleveland, Ohio. Dr. Fox sees patients in Hollywood, Pembroke Pines, and Aventura.*

BY ETHAN DANIEL SIEV, MD, FACC, FCCP

In Search of Good Night's Sleep

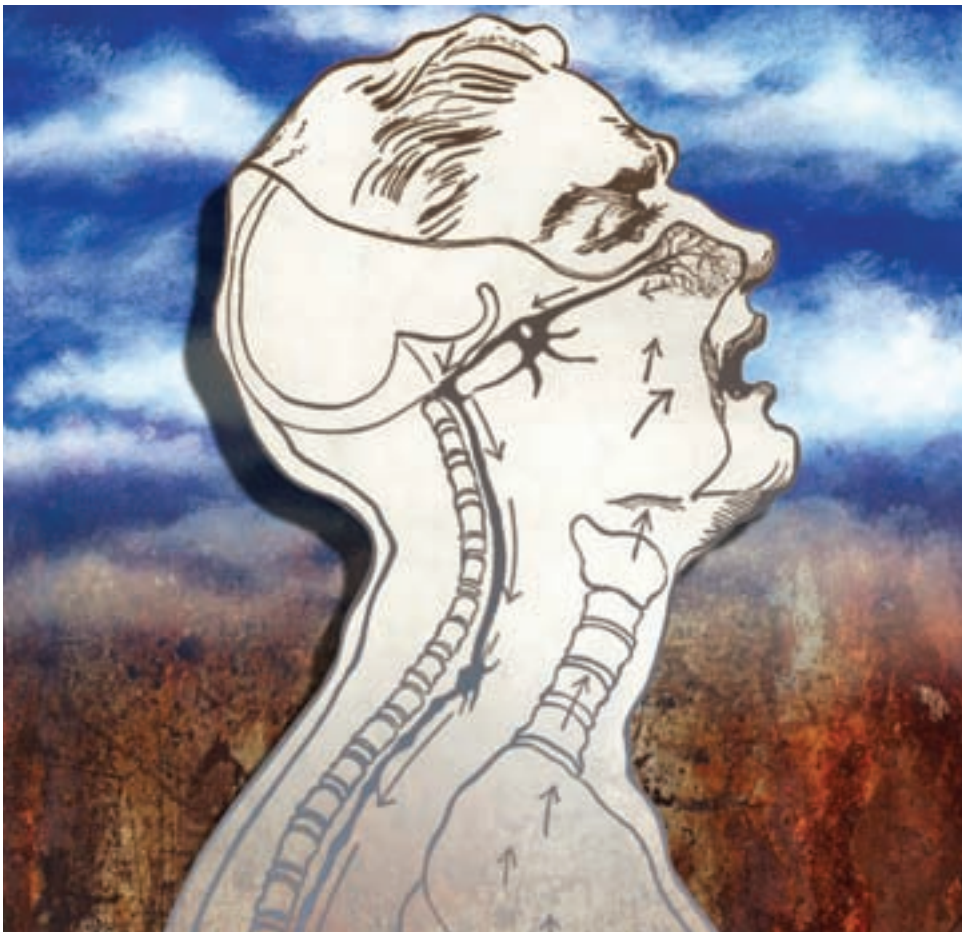
Sleep apnea can lead to serious medical consequences

Two types of sleep apnea can affect the adult population — obstructive sleep apnea and central sleep apnea.

Obstructive Sleep Apnea

Obstructive sleep apnea is a treatable form of disordered breathing in which the upper airway closes repeatedly during sleep. It is frequently linked with obesity and excessive tissue in the oral pharynx. The syndrome is frequently associated with cardiovascular risk factors and represents a substantial risk for cardiovascular morbidity and mortality. Frequently, the patient will complain of somnolence and fatigue. The patient is not actually aware of the nighttime arousal or disordered sleep patterns, but the spouse will frequently report episodes of loud snoring alternating with episodes of absence of breathing.

Obstructive sleep apnea is associated with pulmonary hypertension, congestive heart failure, and stroke. During the episodes of apnea, there is a fall in oxygen saturation with a decrease in oxygen delivery to the tissues, which leads to cellular dysfunction in the brain, heart, and other organs. In addition, there is an increase in endothelial dysfunction, which can lead to vasoconstriction, inflammation, and thrombosis. The increase in pulmonary vasoconstriction causes an increase in pulmonary blood pressure, leading in time to pulmonary hypertension. This interaction increases the afterload on the right ventricle and eventually results in cor pulmonale. Possible mechanisms leading to stroke include acute hemodynamic changes during episodes of apnea, decreased cerebral blood flow, hypercoagulability, paradoxical embolism, progressive arteriosclerosis, and hypoxia-related cerebral ischemia.



In addition, episodes of hypoxia lead to partial arousal from sleep with increased adrenergic tone and increased systemic vascular resistance. There is also an increase in the intrathoracic pressure, which puts excess pressure on the right and left ventricles as well as the pulmonary vasculature.

Central Sleep Apnea

Central sleep apnea occurs in the setting of congestive heart failure. It can affect 25% to 40% of patients with congestive heart failure. The mechanism is considered a cyclic hyperventilation and decrease in the partial pressure of arterial carbon dioxide below the apnea threshold. At that point, the hypoxic respiratory drive is suppressed and the patient becomes apneic. The condition causes tissue hypoxia, arousal from sleep, and activation of the sympathetic nervous system similar to the mechanisms of obstructive sleep apnea. There is also a mixed version of the disease, which represents combinations of obstructive and central apneic episodes.

The prevalence and severity of central sleep apnea seems to connect directly to the severity of the congestive heart failure.

The mortality in this condition is frequently connected to the arrhythmias induced by the hypoxic or apneic episodes. Arrhythmias are frequently sinus bradycardia, sinus arrest, long periods of asystole, sinoatrial block, premature atrial contractions, atrial fibrillation, ventricular premature beats with bigeminy and trigeminy, and ventricular tachycardia. Because there has been an improvement in both pharmacologic and device therapy for heart failure over time, the morbidity and mortality of central sleep apnea appear to have improved.

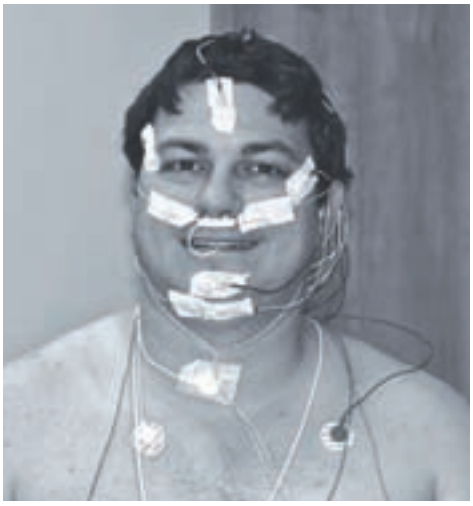
Diagnosis

The first steps in diagnosis are obviously a complete history and physical exam accompanied by careful questioning of the patient's spouse or family members and anyone else who might have observed the patient sleeping and can report on the patient's episodes of apnea or heavy snoring. The primary diagnostic test is a sleep study, or polysomnography. Episodes of apnea lasting longer than 10 seconds are qualified as obstructive if respiratory efforts were present and as central apnea if respiratory efforts were absent. Partial airway closure, resulting from a decrease in airflow of more than 30% for at least 10 seconds and associated with oxygen desaturation of 4% or more from the baseline, is called hypopnea.

An index of apnea to hypopnea, as well as the number of arousals per hour of sleep, are calculated to determine whether the study is positive or negative. A diagnosis of sleep apnea is made if the apnea-to-hypopnea index is greater than 15 events per hour, and a diagnosis of central sleep apnea is determined if more than 50% of the events are not accompanied by respiratory efforts or abdominal musculature motion.

Treatment

The mainstay of treatment is continuous positive airway pressure (CPAP). Recent trials have shown a markedly improved patient tolerance to the CPAP mask, with only a 15% discontinuation during the course of two years of follow-up. In obstructive sleep apnea, the application of positive airway pressure relieves the obstruction in the upper airway, forcing oxygen-containing air through the obstructed area and preventing airway collapse. In central sleep apnea, the CPAP continues to force air in under pressure, even when the respiratory muscles ceased to function. The major drawback is the difficulty tolerating the mask, usually in patients who find it uncomfortable or develop a sense of claustrophobia.



A man shows how a continuous positive airway pressure (CPAP) mask is worn during sleep. It is hooked to a machine that blows air into the throat at the appropriate pressure level.

The surgical options available for sleep apnea are somewhat disappointing. The most common operation performed is a palatopharyngouvuloplasty, during which the excess tissue in the upper airway is surgically removed. The postoperative course is painful, and healing is slow. Frequently, the obstruction recurs, either because of postoperative swelling or later on because of scar tissue formation. Tracheostomy is another option for obese patients who cannot tolerate the CPAP mask. Other novel approaches, such as phrenic nerve with diaphragmatic pacing, are sometimes recommended but are in disfavor.

The morbidity and mortality of central sleep apnea have improved drastically with the improvement of treatment of the underlying congestive heart failure. Optimal treatment with angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, digoxin, and diuretics has reduced the incidence and the severity of the central sleep apnea. Several new approaches to the treatment of sleep apnea have actually reflected the new approaches to the treatment of the underlying congestive heart failure.

Biventricular pacing has helped reduce the frequency and the severity of the apneic episodes in several small uncontrolled trials. This treatment is awaiting a large, randomized study. Atrial pacing was also tested with similar results. Implantable defibrillators, with or without the biventricular pacing, appear to have reduced the mortality rate (probably on the basis of sudden cardiac death but possibly by treating the arrhythmias induced by the hypoxic or apneic episodes).

In Summation

Clearly, the first step to diagnosis and treatment of either the obstructive or central version of sleep apnea is recognition of the possibility that the syndrome exists. Patients who are complaining of morning headaches, daytime somnolence, altered states of consciousness, tremors, or disorientation could be developing this syndrome. Patients who have recently developed much more difficult-to-control systemic hypertension or whose congestive heart failure has become more uncontrolled could be developing sleep apnea.

Sometimes, even a subtle complaint, such as increasing fatigue, in the patient who has worsening peripheral edema or dyspnea on exertion could be the earliest sign that sleep apnea is developing. Even before the referral is made for polysomnography, aggressive treatment of the patient's underlying congestive heart failure could frequently improve the symptoms associated with sleep apnea. For patients with advanced class III or class IV congestive heart failure, a referral for a biventricular pacemaker or defibrillator may be useful in treating not only the congestive heart failure but also the underlying central sleep apnea. ■

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INSIDE CCSF

Introducing New Faces ...

William R. Alexis, MD, MPH

Dr. Alexis received his medical degree and completed an internship and a residency in internal medicine at Boston University Medical Center. He also received his master's degree in public health from Boston University. He completed a fellowship in cardiovascular disease and a fellowship in interventional cardiology at the University of Pennsylvania Health System from 2002 to 2006. Dr. Alexis practices clinical cardiology and vascular and endovascular medicine. He also performs interventions for the group. His primary office is in Pembroke Pines.

Wayne M. Pollak, MD, FACC

Dr. Pollak completed his medical degree at the University of Florida College of Medicine. He then completed an internship, a residency, and a fellowship in cardiovascular disease at the University of Miami School of Medicine/ Jackson Memorial Hospital. Dr. Pollak is board certified in cardiovascular disease and certified by the Board of Nuclear Cardiology. Dr. Pollak has practiced in Aventura for the past few years and has his primary office there.

... and New Places

Aventura Office

Cardiovascular Consultants of South Florida recently moved into the new Aventura Medical Office Building on the grounds of Aventura Hospital. The new office is located at 21097 NE 27th Court, Suite 320 (third floor). The office building is connected by a bridge on the second floor to a new parking garage that was built to service the building. The new 6,000-square-foot office is extremely attractive, with granite counter tops, marble floors, and a large, comfortable waiting room. It has five physician consultation rooms, nine examination rooms, ultrasound, echocardiography, nuclear medicine, and laboratory drawing. Wayne Pollak, MD; Michael Braun, MD; Ethan Siev, MD; Lawrence Reiss, MD; and Raul Mitrani, MD, have office hours in the new suite. ■

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 1.3-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 314 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 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 ≥80 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 90 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 90 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 clastogenic 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 18 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 25 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 39%, 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 appraised 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 postpartum 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	1.8
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. Uitterlinden 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;257:537-548. **2.** Jukema JW, Lorn AH, Dunselman PHJM, et al, on behalf of the RADIANT study investigators. LDL-C/HDL-C ratio in patients with coronary artery disease and low HDL-C: the RADIANT 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;94:393-406. **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, ZA-CRS-01.

AstraZeneca

As an adjunct to diet

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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, Apo8, 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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