New Frontiers in Cardiac Imaging

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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
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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.

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.

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. 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.

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

Numerous studies utilizing 64-slice CT have demonstrated a consistent negative predictive value of 98% to 99%. 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, and contrast echocardiography. 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. 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.

**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 anastomosis site, 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

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**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 thoracoscopic 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

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.

Wayne M. Pollak, MD, FACC, completed his medical degree at the University of Florida’s College of Medicine. He then completed an internship, a residency, and a fellowship in cardiovascular disease at the University of Miami School of Medicine’s Jackson Memorial Hospital. Dr. Pollak is board certified in internal medicine as well as cardiovascular disease and is certified by the Board of Nuclear Cardiology. He has practiced medicine in Aventura for the past few years. Dr. Pollak’s offices are located in Aventura and Hollywood.

References

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.

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 isovolumic area. Based on prospective and retrospective data, some recommendations for stratification of therapy are now given:

• 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 asymptomatic 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.

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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. 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.
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...
(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.

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.

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.

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 ineffective initiation of these drugs is mandatory due to significant risks of ventricular proarrhythmia/torsades de pointes.

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.

"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."
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 pacemaker. 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.

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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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**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 fetal harm when used at the usual therapeutic dose (0.1%). Therefore, dosing should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

**INDICATIONS AND USAGE**

**Hypertension**

Atacand<sup>®</sup> is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**Heart Failure**

Atacand<sup>®</sup> 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<sup>®</sup> also has an added effect on these outcomes when used with an ACE inhibitor.

**CONTRAINDICATIONS**

Atacand<sup>®</sup> 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 second and third trimesters of pregnancy, including hypotension, neonatal skull hypothesis, anemia, reversible or irreversible renal failure, and death.

Hypoglycemia has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios and fetus are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, if a patient becomes pregnant, physicians should consider the discontinuation of Atacand<sup>®</sup> as soon as possible. (See DOSAGE AND ADMINISTRATION, Clinical Pharmacology, Special Populations.)

**Impaired Renal Function**—As a consequence of reducing the renin-angiotensin system, Atacand<sup>®</sup> should be used with caution in patients with severe renal impairment (creatinine clearance ≤30 mL/min) and in patients with known disturbances of sodium and fluid balance. (See DOSAGE AND ADMINISTRATION, Clinical Pharmacology, Special Populations.)

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 144 weeks at doses of up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration (maximally tolerated doses of Atacand<sup>®</sup> cilexetil provided systemic exposure 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 chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the in vitro mouse lymphoma test. Candesartan (but not its O-deethyl metabolite) was also evaluated in vivo in the mouse microsome test and in vivo 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 test and the hepatocyte unscheduled DNA synthesis assay and the in vitro mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHO chromosomal aberration or CHO gene mutation assay.
ATACAND® (candesartan cilexetil) Tablets

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 2000 mg/kg/day (53 times the maximum daily human dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy/Categories (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 many drugs are excreted in human milk, caution should be exercised when ATACAND is administered to a nursing woman.

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% (833/3952) were 65 years or older, and 4% (153/3952) were 75 years of age or older. In general, older subjects tended to discontinue treatment due to adverse events more frequently than younger subjects. However, after a weighted analysis, there were no apparent differences in responses between the elderly and younger subjects, and other reported clinical experience has not identified age-related differences in responses to candesartan. Therefore, dosing was not altered based on age.

Heart Failure

Of the 759 patients with heart failure in the CHARM program, 43 (5.7%) were age 65 years or older and 179 (23%) were age 75 years or older. In general, treatment with ATACAND was similar to placebo. The most common adverse events in patients with heart failure were edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, and peripheral edema. Other potentially important adverse events in patients with heart failure were death, atrial fibrillation, peripheral edema, and peripheral vascular disease. The most frequent serious adverse events were edema, chest pain, headache, bronchitis, and coughing. In general, the proportion of patients who discontinued ATACAND was similar to placebo and the proportion of patients who discontinued ATACAND due to adverse events was similar to placebo. In addition, the proportion of patients who discontinued ATACAND due to adverse events was similar to placebo in patients with heart failure.

ADVERSE REACTIONS

Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/sessions, including more than 3200 patients treated with ATACAND. Of these patients, 600 were treated for at least 6 months and 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 monotherapy and 3.5% (ie, 28 of 1060) of patients treated with placebo. In placebo-controlled trials, the 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 trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n=2530) than placebo (n=1027) 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, and peripheral edema. Other potentially important adverse events that have been reported with ATACAND include: back pain, dizziness, dyspnea, chest pain, peripheral edema, headache, and cough.

Post-Marketing Experience

Hypertension

The following have been very rarely during post-marketing experience:

Dermatologic: Acne, tachycardia, and myalgia.

Nervous System: Anorexia, asthenia, and depression.

Skin and Appendages: Pruritus and rash.

Laboratory Test Findings

Hypertension

In controlled clinical trials, clinically important changes in standard laboratory tests 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.

Hyponatremia—Hyponatremia was rarely found (19 or 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 g/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were not associated with clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each in these clinical trials.

Potassium—A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was not associated with clinical importance. One patient developed 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 chemistry. 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 g/dL in candesartan-treated patients and 0.3 g/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 in 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 overdosage and at the possible of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

DOSEAGE 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 8 mg once daily. If this does not lower blood pressure to an adequate level, 16 mg once daily is recommended. If blood pressure is not controlled with this dose, additional antihypertensive agents may be added. If blood pressure is controlled with 16 mg once daily, no further dose increases should be given. If blood pressure is not controlled with 16 mg once daily, 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 about 2-week intervals, as tolerated by the patient.

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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.

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.
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 rehiles 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.

The surgical options available for sleep apnea are somewhat disappointing. The most common operation performed is a palatopharyngouvaloplasty, 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.
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.
CRESTOR, rosvastatin calcium, is a cholesterol-lowering medicine. It is used to lower cholesterol in patients who have had a heart attack or other heart problems, and in those who have high cholesterol or triglycerides and are at risk for heart disease. CRESTOR reduces the risk of having a heart attack or stroke. It is also used to lower cholesterol and triglycerides in people who have heart disease or other risk factors for heart disease. CRESTOR is also used to lower cholesterol in people who have not had a heart attack or other heart problems.

**INDICATIONS AND USAGE**
CRESTOR is indicated as an adjunct to diet to reduce the risk of heart attack, stroke, revascularization, or unstable angina in patients with coronary artery disease, and to reduce the risk of stroke in patients with previous stroke or transient ischemic attack. It is indicated as an adjunct to diet to lower blood cholesterol and triglyceride levels in patients with primary hypercholesterolemia (type IIa) or mixed dyslipidemia (type IIb), and in patients with homozygous familial hypercholesterolemia who are intolerant of niacin and other lipid-lowering medications. CRESTOR is indicated to treat elevated cholesterol levels in patients with homozygous familial hypercholesterolemia (type IIe) as an adjunct to a diet and one or more other lipid-lowering medications.

**CONTRAINDICATIONS**
CRESTOR is contraindicated in patients with a hypersensitivity to rosvastatin calcium or any other component of the product. It is contraindicated in patients with active liver disease or unexplained persistent elevation of liver enzymes. CRESTOR is also contraindicated in patients with moderate or severe hepatic impairment. CRESTOR is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤30 mL/min). CRESTOR is contraindicated in patients with a history of myopathies or rhabdomyolysis, or in patients with liver disease or unexplained persistent elevation of liver enzymes.

**ADVERSE REACTIONS**
In clinical trials, the most common adverse reactions reported with CRESTOR were myalgia, arthralgia, and headache. Other common adverse reactions included upper respiratory tract infection, back pain, and pharyngitis. Niacin and other lipid-lowering medications have been associated with myositis, myoglobinuria, rhabdomyolysis, and death. CRESTOR is contraindicated in patients with a history of myopathy or rhabdomyolysis, or in patients with liver disease or unexplained persistent elevation of liver enzymes.

**PRECAUTIONS**
Drug Interactions
drug interactions with CRESTOR may increase the risk of myopathy or rhabdomyolysis.

**DOSAGES AND ADMINISTRATION**
CRESTOR is usually taken once daily, preferably at bedtime. Patients should be advised to take the medication with or without food. The recommended starting dose of CRESTOR is 5 mg. The dose may be increased to 10 mg after 1 to 2 weeks if necessary and tolerated. The maximum recommended dose is 20 mg once daily. CRESTOR should be taken at the same time each day.

**ADVERSE EVENTS**
Adverse events reported with CRESTOR were generally mild to moderate in severity and did not require discontinuation of therapy. The frequency of adverse events was similar across placebo-treated and rosvastatin calcium-treated patients. No specific adverse events were reported as being more common in patients who received rosvastatin calcium compared to placebo. The most common adverse events reported in clinical trials were myalgia, arthralgia, and headache. Other adverse events reported with CRESTOR include upper respiratory tract infection, back pain, and pharyngitis.

**CLINICAL ADVERSE EXPERIENCES**
Adverse experiences, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosvastatin are shown in Table 1. Discontinuations due to adverse events in these studies are reported in ≥0.1% of patients in placebo-controlled clinical studies. The adverse reactions are categorized by body system based on clinical trials of rosvastatin calcium at doses up to 20 mg. Adverse events are included only if they were considered to be at least possibly drug-related by the investigator.

**Table 1. Adverse Events in Placebo-Controlled Studies**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>CRESTOR 5 mg</th>
<th>CRESTOR 10 mg</th>
<th>CRESTOR 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>0.6%</td>
<td>0.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>0.3%</td>
<td>0.6%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of patients treated with rosvastatin in clinical studies. The adverse reactions are not included in the adverse reactions listed above, as they occur less frequently. These are included in the following sections: Lipid abnormalities, Metabolic and Endocrine Disorders, Gastrointestinal Disorders, Dermatological Disorders, and Others. The following adverse events were reported in clinical studies of rosvastatin calcium at doses up to 20 mg: abdominal pain, back pain, chest pain, flatulence, pain, purpura, and rash.
As an adjunct to diet

POWERED...for success

For your broad range of high-risk patients

In 2 separate studies in high-risk patients with diabetes or CAD
More LDL-C reduction than twice the dose of atorvastatin1,2
- 82% of patients with diabetes reached LDL-C goal with a low 10-mg dose without titration3

Established HDL-C efficacy3,4
- CRESTOR 5 mg to 40 mg increased HDL-C between 8% and 14% (vs 3% with placebo) in patients with primary hypercholesterolemia4

Safety in line with other leading statins**
- In preapproval clinical trials and postmarketing experience, CRESTOR has demonstrated a safety profile in line with other leading statins**

Important Safety Information
- CRESTOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, Apo B, 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, semianually) 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%)**
- 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.