HeartLines

TRENDS IN HEART AND VASCULAR DISEASE

A publication from Cardiovascular Consultants of South Florida | www.heartpartners.com | Volume 2 • Issue 3

The Failing Heart

Challenges and therapies in ventricular dysfunction

CARDIOVASCULAR CONSULTANTS OF SOUTH FLORIDA

The Stroke Zone Minimally invasive carotid stenting aids treatment

William R. Alexis, MD, M.P.H

CARDIOVASCULAR CONSULTANTS
OF SOUTH FLORIDA

February is Heart Month

David Tepper, MD, FACC

Cardiovascular Consultants of South Florida presents

HEARTLINES Seminars for February 2008

Howard F. Berlin, MD, FACC

Monday, February 4: Howard Berlin, MD, and Ethan Siev, MD
Location: Hollywood
Vitamin Supplements: Pros and Cons
Understanding the ABCs of Lipid Control

Ethan D. Siev, MD, FACC, FCCP

Kashmira P. Bhadha, MD, FACC

Wednesday, February 6: Michael Braun, MD, and Raul Mitrani, MD
Location: Aventura
How to Prevent a Heart Attack
A Racing Heart: Is It Anxiety or Something More?

Bernard E. Shair, MD, FACC

Michael Braun, MD, FACC

Monday, February 11: William Alexis, MD, and Daniel Norberg, MD
Location: Pembroke Pines
The Stent Controversy
Sodom and Gomorrah: The Lesson of Salt and CHF

Lawrence M. Reiss, MD, FACC

Juan Pastor-Cervantes, MD, FACC

Wednesday, February 13: Raul Mitrani, MD, and Juan Pastor-Cervantes, MD
Location: Hollywood
Arrhythmia: The Beat May Not Go On!
Peripheral Vascular Disease: Not Just Pain in the Legs

Wayne M. Pollak, MD, FACC

John Cogan, MD, FACC

Wednesday, February 20: Kashmira Bhadha, MD, and John Cogan, MD
Location: Pembroke Pines
Women and Heart Disease: Know Your Risk
Syncope: A Funny Word, but No Laughing Matter

Richard H. Pollak, MD, FACC, FACP

Monday, February 25: Ralph Levy, MD, and John Cogan, MD (en Español)
Location: Pembroke Pines
Tuning Up Leaky Valves
Syncope: A Funny Word, but No Laughing Matter

Gary R. Donshik, MD, FCCP

Wednesday, February 27: Susan Fox, DO, Juan Pastor-Cervantes, MD
Location: Aventura
Treating Vein Disease
Peripheral Vascular Disease: Not Just Pain in the Legs

Frank Jay Pearl, MD, FACC, FCCP, FACP

All lectures begin at 6 p.m. A light snack will be served.
RSVP by calling (954) 885-6660.

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Hollywood Office: 1150 N 35th Avenue, Suite 605 (at Memorial Regional Hospital)
Pembroke Pines Office: 603 N Flamingo Road, Suite 355 (at Memorial Hospital West)

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Susan B. Fox, DO, RPVI

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

Welcome

Cardiovascular Consultants of South Florida continues to grow with the addition of two cardiologists in our Aventura office. We are pleased to welcome Richard Pollak, MD, and Gary Donshik, MD, who have practiced in the Aventura area for many years. In advance of their joining our practice, we have added office space, digital X-ray, and nuclear stress testing to our list of offerings.

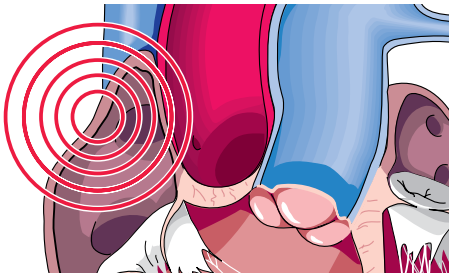
As a group we are focusing our efforts on expanding preventive services to our patients. In the very near future we will open a 64-slice computed tomography (CT) center in Hollywood. This center will allow us to bring cutting-edge technology to our patients and community. It will enable us to screen low- and medium-risk patients for coronary artery disease, perform peripheral vascular disease assessment and calcium scoring, and monitor coronary artery disease progress over time with state-of-the art technology. In addition, we have already embraced advanced lipid testing, but we also plan to focus our attention on diet, nutrition, and exercise.

February is American Heart Month, and we are hosting a series of educational lectures on heart disease prevention for our patients. Please feel free to come and join us to learn how to keep your heart healthy, or recommend the series to friends and loved ones.

We thank all of our sponsors for making this publication possible, and we hope everyone finds this issue informative and interesting.

Happy holidays,

Judah Friedman, MEd, MBA
Chief Executive Officer



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BY DANIEL NORBERG, MD, FACC

The Failing Heart

Challenges and therapies in ventricular dysfunction

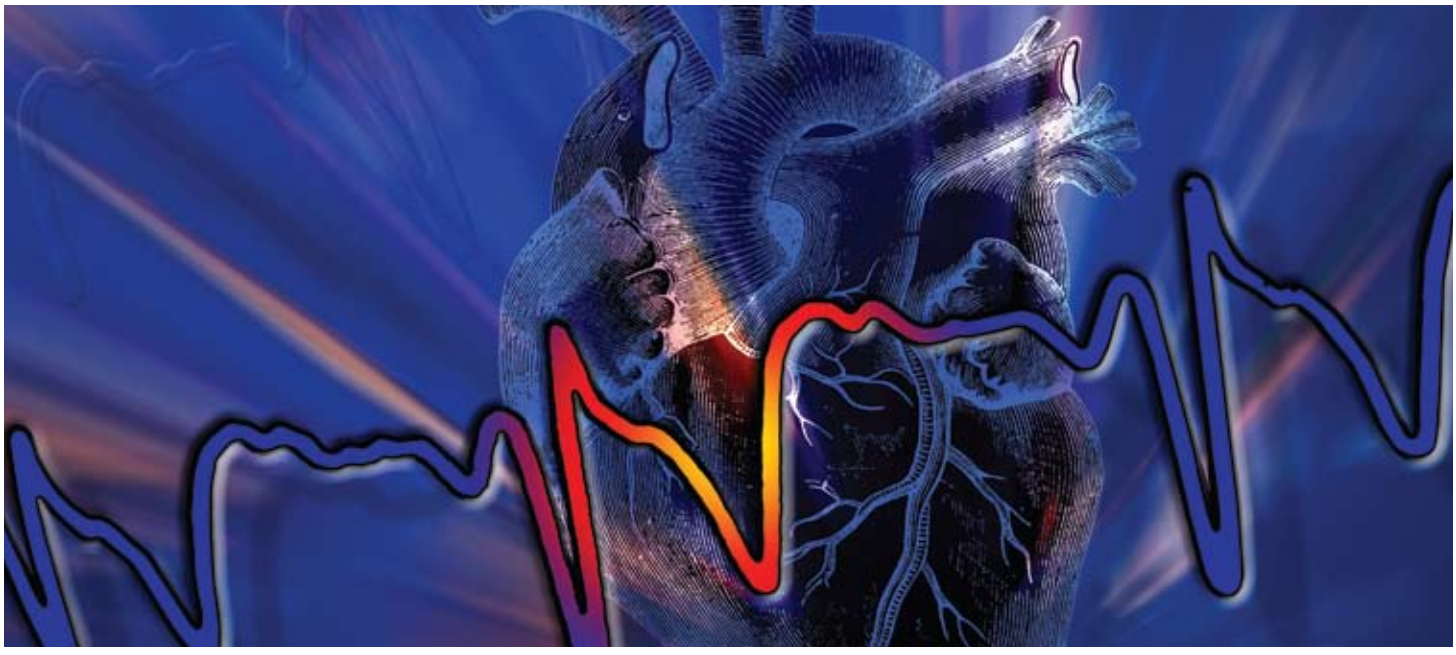
Congestive heart failure (CHF) is a complex clinical syndrome with multiple etiologies. The signs and symptoms of CHF are secondary to the body adapting through various mechanisms to a dysfunctional heart. The congestion of body tissues occurs as the body attempts to maintain a steady state and preserve function.

CHF accounts for millions of hospitalizations per year and is the most common patient discharge diagnosis in the United States. It afflicts 1% to 2% of the U.S. population with the prevalence nearly doubling for each decade of life. Nearly one-third of the presenting CHF population has normal systolic function with the predominance of symptoms secondary to diastolic dysfunction. The treatment of cardiac disease and the population's advancing age contribute to the increases in the incidence and prevalence of CHF. Because intervention and aggressive therapy lead to decreased symptom progression and mortality, early recognition is crucial.

Structural dysfunction

The heart is often described as a sophisticated pump that delivers blood to the body. Cardiac output refers to the dynamic circulation throughout the body per minute and is dependent on the overall function of the heart and many factors controlling cardiac performance. The body can manipulate cardiac output through a complex system of checks and balances. Ultimately, the goal of each organ system (brain, heart, kidneys, etc.) is to preserve perfusion for survival. If the heart is functioning at less than maximum efficiency, organ systems recognize decreased perfusion and send messages to the heart to increases cardiac output. As the heart becomes more dysfunctional, the body, compensating for decreased cardiac output, contributes to further physiologic decompensation and worsened cardiac function. This vicious cycle, although simplistic, illustrates the syndrome of CHF.

There are two components of heart failure involving the impairment of systole (passive phase) and diastole (energy consumption phase) of the cardiac cycle. Systolic dysfunction refers to the heart's decreased ability to contract and provide forward ejection of blood into the circulation. Diastolic dysfunction refers to a decreased ability of the heart to relax and fill with blood prior to contraction. These types of dysfunction may exist separately or together. As much as 30% of the heart failure population has combined systolic and diastolic dysfunction. This combination



complicates the medical therapy and requires close monitoring of responses to treatment modalities.

Left heart failure is the functional decline of the left ventricle and makes up the majority of the population of heart failure patients. As the right heart function declines, signs and symptoms of right heart failure follow. Right and left heart failure occur separately or together. Typically, left heart failure precedes right heart failure. As the poorly functioning left ventricle fails, the blood pressure within the lungs increases. Unable to generate pressures to match that seen within the lungs, the right ventricle fails. Occasionally, right heart failure occurs with normal left ventricular function (pulmonary hypertension, tricuspid, or pulmonic valvular disease). Cardiomyopathy refers to changes in the structure of the heart muscle in response to impaired function.

Common etiologies

There are many etiologies of cardiomyopathy and cardiac dysfunction. Common etiologies include ischemic (coronary artery disease, myocardial infarction), hypertension, postviral syndrome, restrictive (i.e., amyloidosis), hypertophic, valvular dysfunction, pulmonary hypertension, metabolic (thyroid disorders, mineral deficiencies, alcohol), and idiopathic. These disease processes lead to decreased cardiac performance and circulatory system changes. These changes become evident in a patient's decreased general well-being and physical condition. The presentation and progression of CHF progress are variable, and the signs and symptoms are related to conditioning and the severity of the failing heart chambers.

In left heart dysfunction, there are symptoms of dyspnea with exercise and/or at rest, orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased functional capacity, anorexia, and nocturia. Signs include weight gain, evidence of increased pulmonary markings on a chest roentgenogram, interstitial pulmonary edema and pleural effusion, hypoxia, and pericardial effusion. Symptoms of right heart failure may include some shortness of breath or fatigue. The signs of right ventricular failure include lower extremity edema, change in abdominal girth associated with ascites, jugular venous distention, and weight gain. Once heart failure is suspected, diagnostic testing is necessary to determine the etiology and severity of heart failure.

Evaluation via left heart catheterization is necessary to rule out the possibility of coronary artery disease, measure left heart pressures, and evaluate left ventricular function. Right heart catheterization measures the pressure within the right side of the heart and pulmonary arteries and estimates the left ventricular filling pressure. If suspected, incorporation of endomyocardial biopsy with right heart catheterization can identify a myocardial disorder. Stress testing with cardiac imaging allows for evaluation of ischemia, cardiac perfusion, and cardiac function. Transthoracic echocardiogram is useful in the evaluation of left and right ventricular function, wall motion abnormalities, and valvular dysfunction.

When there is insufficient data from transthoracic echocardiography, a transesophageal echocardiogram provides a clearer view of the heart. Once cardiomyopathy is diagnosed and the etiology investigated, initiation of therapy for CHF is essential.

Patient, help thyself

The most important component to the success in the treatment of heart failure is the compliance of the patient with his or her diet, fluid restriction, exercise, and medical therapy. Patient education and involvement in the treatment protocols are crucial. Changes in diet are necessary and essential. Patients with heart failure need to be aware of sodium consumption — namely the use of table salt and natural sodium contents in the foods consumed. It is important to understand that wherever salt goes, water will follow. Increased salt consumption in conjunction with increased fluid consumption leads to fluid retention. The typical low-sodium diet consists of less than 2 grams per day.

Fluid restriction makes up the second component of patient involvement in decreasing fluid retention. Thirst increases as the heart fails and occurs in response to decreased cardiac output and the body thinking it is depleted of fluid. Frequently, there is too much fluid in the circulatory system, which leads to increased work for the heart, edema, pulmonary edema, and/or pleural effusion, ascites, or pericardial effusion.

“The most important component to the success in the treatment of heart failure is the compliance of the patient with his or her diet, fluid restriction, exercise, and medical therapy.”

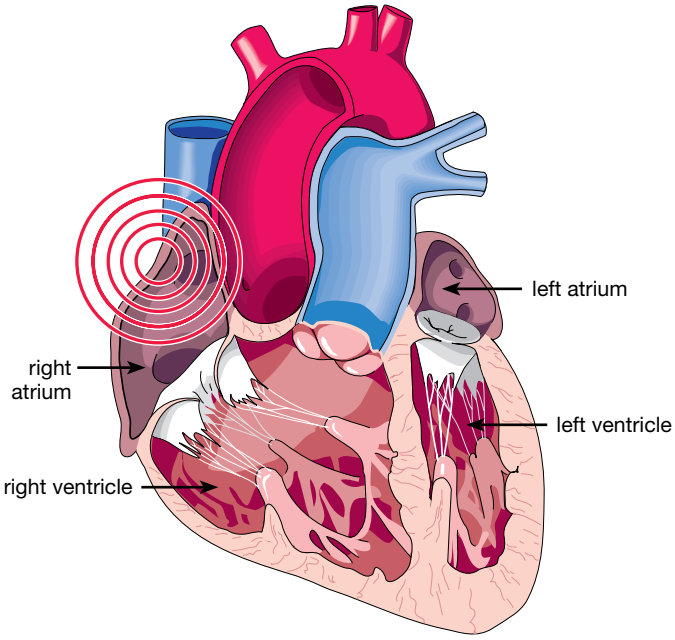
Medication therapies

Medications have become the hallmark for treatment of CHF. Current aggressive medical regiments increase functional capacity, decrease mortality, and increase the well-being of the patient. Currently, medical therapy encompasses afterload reducers, preload reducers, ionotropic agents, chronotropic agents, and peptides. These various medications together provide the greatest amount of symptom relief and improved longevity. The treatment of systolic dysfunction is well studied and provides important guidelines in regard to medical therapy. Therapy for diastolic dysfunction is anecdotal and based in theory.

Currently, the uses of angiotensin-converting enzyme inhibitors (ACE inhibitors) or the combination of hydralazine and isosorbide dinitrate are effective afterload-reducing medications. Angiotensin receptor blockers are approved for treatment of CHF; ACE inhibitor therapy, however, remains the treatment of choice. Studies have shown the use of afterload-reducing medications slows disease progression, decreases symptom progression, and decreases mortality. These medications are available in an intravenous and oral form. Intravenous milrinone and dobutamine also are effective afterload-reducing medications, but they are not beneficial for long-term therapy. The use of afterload-reduction medication >>

requires careful observation when used in combination with preload reduction medication.

The normal heart can increase contraction based on the amount of stretch that occurs in diastole or ventricular relaxation. In the dysfunctional heart, however, this reflex does not respond appropriately, and the pressures within the heart increase. This increased pressure transmits into the lungs and venous system, causing edema. To decrease the filling volumes and pressures, medications such as long-acting nitroglycerin and diuretics are used to decrease preload.



The sinus node is found in the right atrium, where the electrical pulse that makes the heart beat begins. An irregularity in these pulses, such as when the heart beats faster or slower than normal, is known as an arrhythmia.

It is important to mention that a certain amount of elevation in preload is needed in the dysfunctional heart, especially when there is diastolic dysfunction. Decreasing preload through diet, fluid restriction, and sodium restriction are important in the management of CHF. Overall, the control of afterload and preload is a delicate balance in a failing heart.

For some time, medications to slow the heart rate were used, primarily in the treatment of diastolic dysfunction and heart failure, to increase ventricular filling time and relaxation. Beta-blockers are beneficial in the treatment of left ventricular systolic dysfunction, diastolic dysfunction, and heart failure. The use of beta-receptor blocker therapy in heart failure revolves around the theory that, as the heart fails, the levels of catecholamine increase in the circulation.

Elevated catecholamine levels lead to increased heart rate and force of heart contraction, leading to an increase in cardiac output. Chronic elevations of catecholamines in the bloodstream are toxic to the heart muscle and can cause further worsening of function. The use of beta-receptor blocker therapy decreases the response of the heart to the elevated catecholamine levels. Studies have shown that the use of this medication, in conjunction with current medical therapy for CHF, increases functional capacity, decreases the need for hospitalizations, and decreases mortality. Despite negative chronotropic effect, the use of calcium channel blocker therapy has no role in the treatment of systolic dysfunction secondary to negative ionotropic effect. The negative ionotropic effect has shown some benefit in increasing diastolic filling times and improving symptoms associated with diastolic dysfunction.

With the exception of digoxin, intravenous medications in this class require a monitored environment, such as a hospital or special heart failure clinic. Digoxin therapy has no advantage for isolated diastolic dysfunction and could have a deleterious effect in patients. Direct physician and nursing observation is necessary with close monitoring of heart rate, heart rhythm, and blood pressure. Currently, intravenous ionotropic medications, such as dobutamine, milrinone, and dopamine, are short-term therapy secondary to the poor outcomes realized with prolonged infusion.

Overall, these medications are effective in the improvement of cardiac function and well-being of the patient when used in short-term support. Despite improvements in a patient's functional capacity on milrinone and dobutamine, long-term follow-up studies suggest decreased patient longevity on these medications. Digoxin is the only oral medication proven safe for long-term ionotropic support. The use of intravenous ionotropic therapy has fallen out of favor in the face of newer peptide therapy.

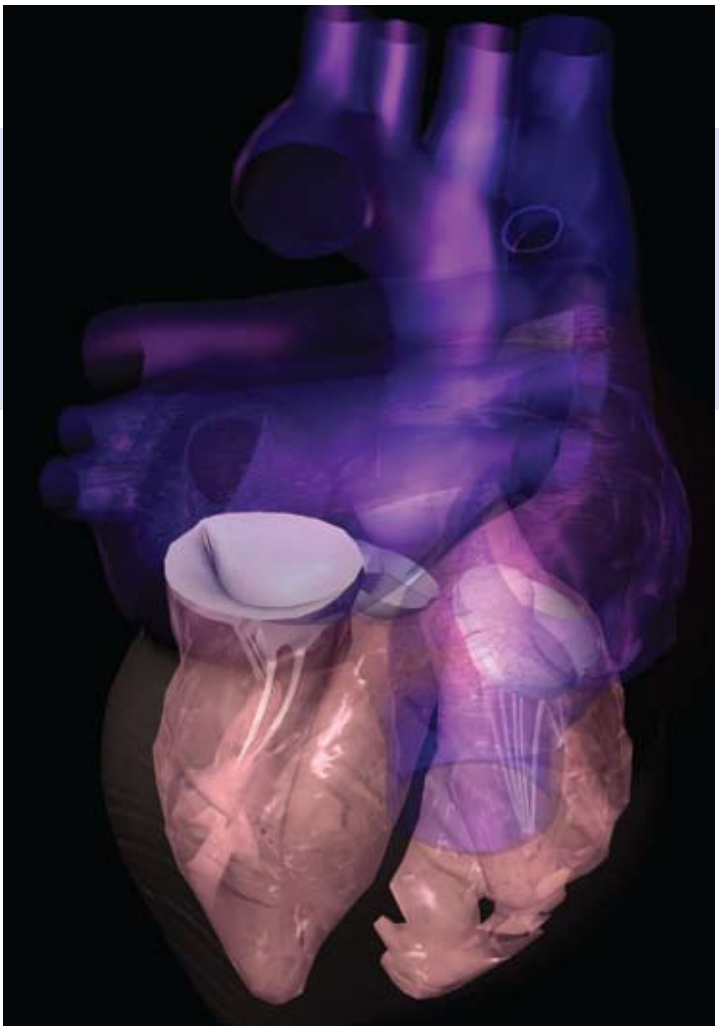
> "Patients with CHF due to diminished systolic function are at increased risk for dying suddenly from ventricular arrhythmias."

Human B-type natriuretic peptide is secreted by the heart as part of the body's normal response to heart failure. The intravenous use of nesiritide is helpful in decreasing dyspnea symptoms of CHF by decreasing preload and reducing pulmonary capillary wedge. The medication is only approved for use in a monitored hospital setting. To date, this drug has never been shown in a controlled trial to reduce mortality in CHF patients.

Patients with CHF due to diminished systolic function are at increased risk for dying suddenly from ventricular arrhythmias. It has now been demonstrated that implantable defibrillators can reduce sudden cardiac death and overall mortality in patients with CHF and decreased ejection fraction. Furthermore, in patients with wide QRS complexes and decreased ejection fraction, the use of biventricular pacing to resynchronize left ventricular function has been shown to improve symptoms of CHF and overall cardiac function in a majority of patients indicated for this procedure.

More drastic measures

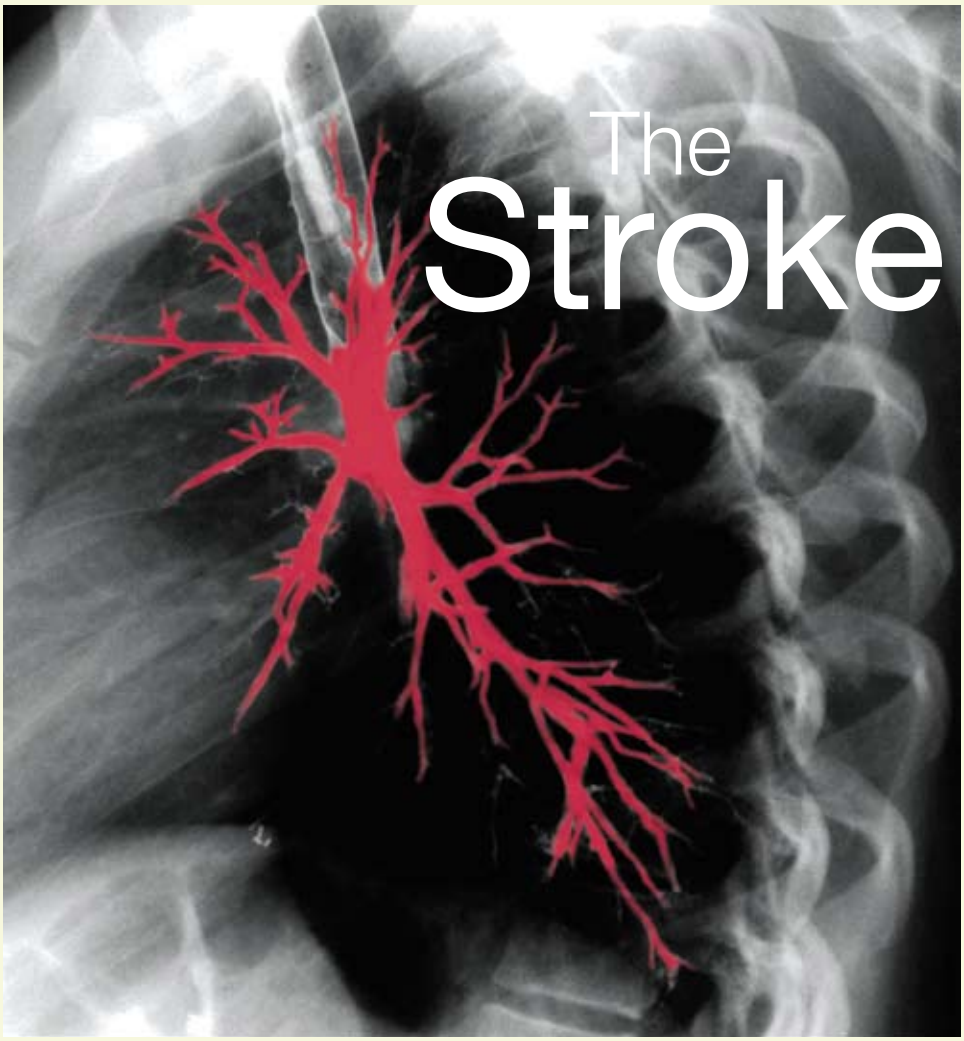
In the event that the patient remains unresponsive to medical therapy, mechanical and surgical support are available. The uses of an intra-aortic balloon pump and a biventricular assist device are available in the short term and experimentally in the long-term



treatment of CHF. Currently, the intra-aortic balloon pump temporarily assists the heart in an aggressive effort to treat heart failure unresponsive to medical therapy alone. The use of a biventricular assist device is as a bridge to cardiac transplantation in a patient who fits the strict criteria.

Overall, important strides have been made toward improving functional capacity, decreasing symptoms, and decreasing mortality of patients with heart failure. The overlap of systolic and diastolic ventricular dysfunction continues to pose challenges to CHF management. ■

***Daniel Norberg, MD, FACC**, earned his undergraduate degree from the University of Miami in Florida and his medical degree from the University of Florida College of Medicine in Gainesville. He completed an internship and a residency at the University of Miami's Jackson Memorial Medical Center in 1994 and a fellowship from the University of Florida's Shands Medical Center, also in Gainesville, in 1997. He is board certified in internal medicine, cardiovascular disease, and nuclear cardiology. His interests are preventive cardiology, congestive heart disease, coronary artery disease, congenital heart disease, cardiology of pregnancy, and valvular heart disease. Dr. Norberg's office is in Pembroke Pines.*



The Stroke Zone

Minimally invasive carotid stenting aids treatment

BY JUAN PASTOR-CERVANTES, MD, FACC

My interest in extracranial carotid disease spans nearly 10 years, and it began at a time when carotid endarterectomy (CEA) indication for patients with symptomatic lesions showed a clear benefit over conventional medical therapy. Since that time, minimally invasive therapies like carotid stenting have emerged as viable alternatives for patients who are deemed at high risk for surgery or poor candidates for CEA, which is considered the standard of care[1].

Stroke is the most common life threatening neurologic disease and the third leading cause of death in the United States, exceeded only by heart disease and cancer. It is responsible for one of every 15 deaths. Despite being more often disabling than lethal, 167,660 deaths were attributed to stroke in 2000[2]. That same year, the American Heart Association estimated that there were 500,000 initial strokes, 200,000 stroke recurrences, and 4,700,000 stroke survivors in the United States, many of whom required chronic care[3]. It is estimated that by 2015, the elderly population (>65 years) will increase to 14% of the population, up from 2.3% in 1900. This growth in the elderly population will be a source of continuing disability from stroke unless vigorous and effective preventive measures are implemented more aggressively.

Stroke prevalence

Overall, the annual age-adjusted (ages 35 to 94 years) total initial completed stroke event rates were 5.9/1,000 in men and 4.9/1,000 in women — a 20% excess rate is observed in men. The annual age-adjusted incidence of isolated transient ischemic attack also increases with age and was 1.2/1,000 in men and 0.71/1,000 in women[4].

Stroke registries and prospective population studies indicate that there is a disproportionate rate of ischemic stroke occurrence after awakening between 6 a.m. and noon[5]. An increased rate of intracerebral hemorrhage was reported in men who drink, possibly reflecting binge drinking on the weekend[6].

More than three million Americans have symptomatic cerebrovascular disease. Its prevalence is much higher in blacks (2.6%) than in whites (1.6%) for patients between the ages of 25 and 74[7].

The short-term, intermediate, and long-term adjusted mortality rates were investigated in the Department of Veterans Affairs care system in veterans who had experienced initial hemorrhagic or ischemic strokes. These investigators found a 30-day mortality rate of 7.4% and 18.8% for ischemic and hemorrhagic strokes, respectively. The adjusted 90-day mortality rate for ischemic stroke was 11.4%, and, for one year, 19.1%. The adjusted mortality rate for 30-day survivors of a hemorrhagic stroke was 5.6% for 30 to 90 days and 7.3% for three months to one year[8].

The frequency of completed strokes by type was nearly identical in men and women. Atherothrombotic brain infarction (including infarction secondary to large vessel atherothrombosis, lacunar infarction, and infarct of undetermined cause) accounted for more than 61.5% of strokes in men and 60% in women.

Extracranial large artery disease accounted for approximately 10% to 20% of cases of cerebral infarction. Intracranial hemorrhage accounted for 14% of completed strokes in men and 13.4% in women.

Risk factors for stroke

A number of modifiable atherogenic stroke risk factors were identified from The Framingham Study and other prospective epidemiological studies. These risk factors include elevated blood pressure, diabetes mellitus, obesity, hyperlipidemia, elevated blood homocysteine levels, impaired left ventricular systolic function, coronary artery disease, atrial fibrillation, left ventricular hypertrophy, migraine, intracranial aneurysms, sleep apnea, cigarette smoking, oral contraceptive use, and alcohol consumption.

Extracranial carotid artery disease

Carotid atherosclerosis develops in areas of low vessel wall shear stress, most commonly the carotid bulb.

The earliest lesion of atherosclerosis is the fatty streak, which is an infiltration of monocyte-derived macrophages and T-lymphocytes in the arterial wall. Fatty streaks occur early in life, involving the aorta in the first decade of life and the coronary and extracranial carotid arteries in the second decade. The fatty streaks start as an infiltration of low-density lipoprotein (LDL) cholesterol in the arterial wall, followed by its oxidation. The process continues when macrophages secrete chemokines and mitogens that induce smooth muscle cell proliferation. This progression may lead to plaque growth and eventual narrowing of the vessel lumen.

In the carotid bifurcation, atherosclerosis is most severe in the posterior wall of the carotid bulb, where there is low shear stress and greater turbulence. Disturbed laminar flow in the carotid bulb may lead to high adhesion molecule expression of endothelin, among other changes. Most myocardial infarctions are associated with thrombosis in plaques with inflammatory cell content and large necrotic lipid cores, so-called unstable plaques. This mechanism has not been established as clearly in the carotid artery, although recent evidence suggests that occlusion of the extracranial carotid artery bifurcation has a similar pathophysiology[9,10].

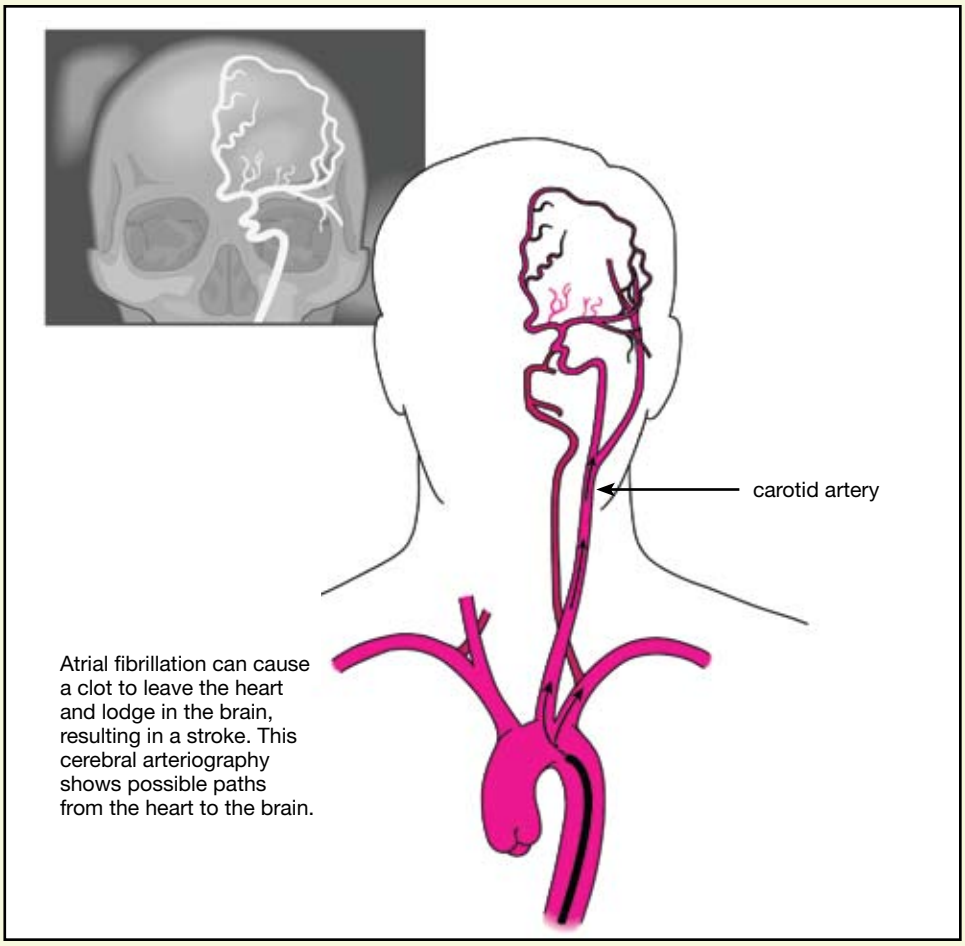
> “Stroke is the most common life threatening neurologic disease and the third leading cause of death in the United States, exceeded only by heart disease and cancer.”

Approach to the patient

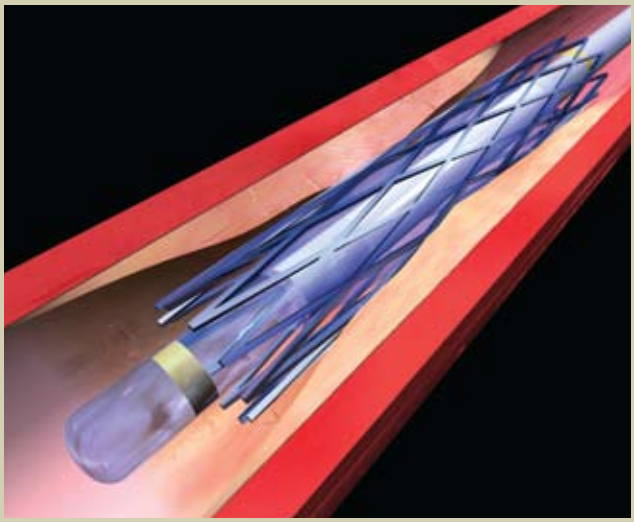
The first and most important approach to the patient with carotid atherosclerosis is to initiate strategies to modify vascular risk factors and stabilize and prevent the progression of carotid atherosclerotic plaque. Therefore, aggressive blood pressure reduction in hypertensive patients is essential. Management of hyperlipidemia, obesity, diabetes, obesity control, smoking cessation counseling, and lifestyle-changing strategies are all of extreme importance.

The second approach is the initiation of antithrombotic therapy. Strong evidence supports the use of antiplatelet therapy for secondary stroke prevention. All available anti-platelet agents have demonstrated benefits in reducing recurrent stroke rates. The choice between aspirin, clopidogrel, ticlopidine, or a combination and modified-release dipyridamole will depend on the patient's risk-factor profile, side effects, and cost.

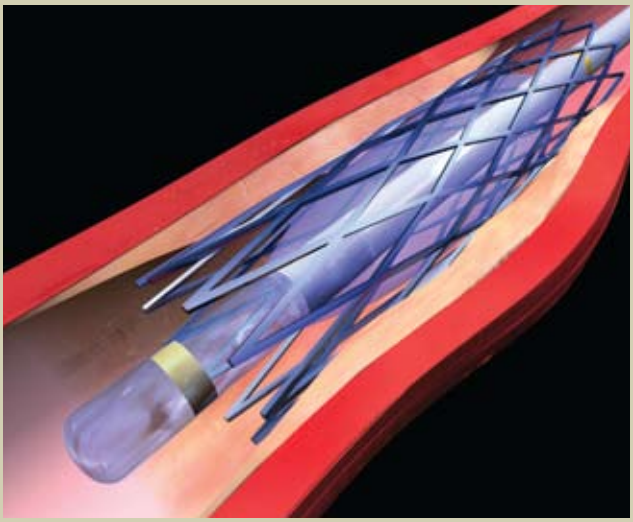
Warfarin is not superior to aspirin in reducing recurrence of noncardioembolic >>



Atrial fibrillation can cause a clot to leave the heart and lodge in the brain, resulting in a stroke. This cerebral arteriography shows possible paths from the heart to the brain.



The balloon catheter carrying the stent is positioned in the narrowed section of the artery, and the balloon is inflated, expanding the stent.



The vascular stent is fully extended via the inflation of the balloon catheter, widening the lumen of the artery.

ischemic events and probably should not be used routinely in this population because of its potential hemorrhagic complications[11]. A possible exception is the intraluminal thrombus in the internal carotid artery (ICA). These patients are managed preferably with anticoagulation for a few weeks, followed by CEA[12].

The third approach is the removal of the atherosclerotic plaque through surgery or an endovascular procedure, known as carotid artery stenting, or CAS (see photos above).

Carotid artery revascularization

Surgical treatment for carotid stenoses was introduced in the early 1950s. Prospective observational data suggested benefit for surgery over medical therapy, but large prospective randomized trials investigating the effect of CEA on stroke reduction were not completed until the late 1980s and early 1990s.

Studies such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[13], the European Carotid Surgery Trial (ECST), and the Asymptomatic Carotid Atherosclerosis Study (ACAS) confirmed the short- and long-term superiority of surgery over medical management in symptomatic and asymptomatic patients with significant carotid stenosis.

The CEA studies excluded patients who were at high risk for this surgery. Thus, patients were excluded if they had previous ipsilateral endarterectomy, intracranial stenosis that was more severe than the surgically accessible lesion, unstable angina pectoris, recent myocardial infarction, recent contralateral CEA, progressive neurologic dysfunction, recent surgical procedure, long-term anticoagulation therapy, and surgically inaccessible lesions[14].

Cardiovascular complications of surgery, such as myocardial infarction and congestive heart failure, are well recognized, and a significant number of patients were reported to have transient myocardial ischemia and occult infarction associated with adverse cardiac events[15].

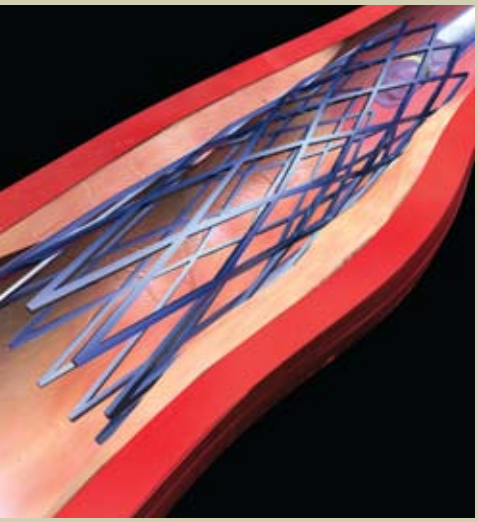
CEA has significant surgical complications not always reported (as was the case with the ESCT study) but should be acknowledged. In the NASCET, perioperative wound complications (9.3%) and cranial nerve damage (8.6%) emphasized the adverse events associated with an open surgical procedure[16]. Medical complications were common (8.1%), largely of cardiovascular origin (7.1%), including myocardial infarction (1.2%) and congestive heart failure (1.2%)[16].

The mission to develop safer, percutaneous solutions to carotid arterial stenosis was pioneered in 1977 by Mathias and colleagues, who performed the first balloon angioplasty to the carotid artery bifurcation[17].

In 1986, Rabkin[18] reported the use of primitive nitinol stents in the carotid artery, and Theron[19] began pivotal work with distal balloon protection during carotid bifurcation angioplasty. In 1994, Roubin and his group at the University of Alabama began routine carotid stenting under rigorous institutional protocols[20]. Later, the use of distal protection devices was recognized as an integral part of carotid artery dilatation and stenting[21]. The high technical success rate noted in the early works and the progress made over the years have led to an exponential growth in the number of cases around the world[22].

The state of carotid stenting

The indications for intervention with carotid stenting are similar to those of carotid surgery with respect to symptomatic status and severity of carotid stenosis. This approach to patient management is based on documented, prospective outcome



After the vascular stent is fully extended, the balloon catheter is removed, leaving the expanded stent to hold the artery lumen open.

assessment from many experienced operators and centers. Many operators are now providing credible outcome data to support such an approach. In intracenter analysis, if prospective, independent neurologic audit shows, for example, that in a group of surgically eligible symptomatic or asymptomatic patients, the 30-day death rate is less than 1% and total 30-day stroke events are less than 3%, then stenting should be an attractive therapeutic option.

There are notable exceptions to these therapeutic principles. Subsets of patients are emerging as better candidates for stenting, and other patients are better candidates for CEA. It is, therefore, now becoming important for the medical community to understand the relative indications and contraindications. Patients who have comorbid medical conditions that increase their risk from an open surgical approach or the use of general anesthesia are one important group that should be primary candidates for stenting. Based on the results of the recently published Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHiRE) and ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR) trial, those conditions include advanced age (>80 years), New York Heart Association class III/IV for congestive heart failure, chronic obstructive pulmonary disease, contralateral occlusion, prior CEA, prior myocardial infarction within 30 days, unstable angina, two or more coronary vessels with more than 70% stenosis, a need for coronary artery bypass graft or valve surgery within 30 days, dialysis dependant-renal patient, or unfavorable anatomy (i.e., s/p radical neck surgery, prior neck radiation, surgically inaccessible lesions, spinal immobility, tracheostomy stoma, contralateral laryngeal nerve paralysis)[23].

However, until recently the carotid stent trails have focused on indications for high-risk patient populations that are unlikely to answer the overall question of whether carotid artery stenting with state-of-the-art technology (embolic protection devices) is equivalent to the standard of care (i.e., CEA) for most patients with carotid stenosis who are at risk for stroke.

> "The mission to develop safer, percutaneous solutions to carotid arterial stenosis was pioneered in 1977 by Mathias and colleagues, who performed the first balloon angioplasty to the carotid artery bifurcation."

The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) trial was designed on the basis of the broad category of standard risk by using symptomatology as a defining criterion for stratification in the study.

The choice of treatment by CAS or CEA was based solely on physician and patient preference. This design more accurately reflects the true clinical environment. The 30-day composite morbidity and mortality results of 4.4% for CEA and 2.1% for CAS compare well with both NASCET and ACAS. The cumulative one-year major adverse event rates in SAPPHiRE were 20.1% for CEA and 12.2% for CAS; those in CaRESS were 14.3% vs. 10.9%, respectively.

The CaRESS phase 1 study suggests that the risk of death or stroke one year after CAS by using distal protection is equivalent to that after CEA in a broad-category population with carotid stenosis. The CaRESS phase 1 study was able to closely resemble clinical practice by enrolling patients on the basis of the degree of carotid stenosis and symptomatology rather than surgical risk[24].

Conclusion

Stroke is a major threat to our aging patient population for whom surgical options are not always well-tolerated or accepted.

Certainly, it will take a few more years to know if minimally invasive therapies like carotid stenting indeed will replace carotid surgery as the choice of treatment, as it has done with other vascular territories.

So far, it can be clearly stated that carotid stenting with distal protection, by experienced operators, is the procedure of choice for high-surgical-risk patients with extracranial carotid disease for stroke prevention and that carotid artery stenting is likely the treatment of choice for low-risk surgery patients in the near future. ■

References

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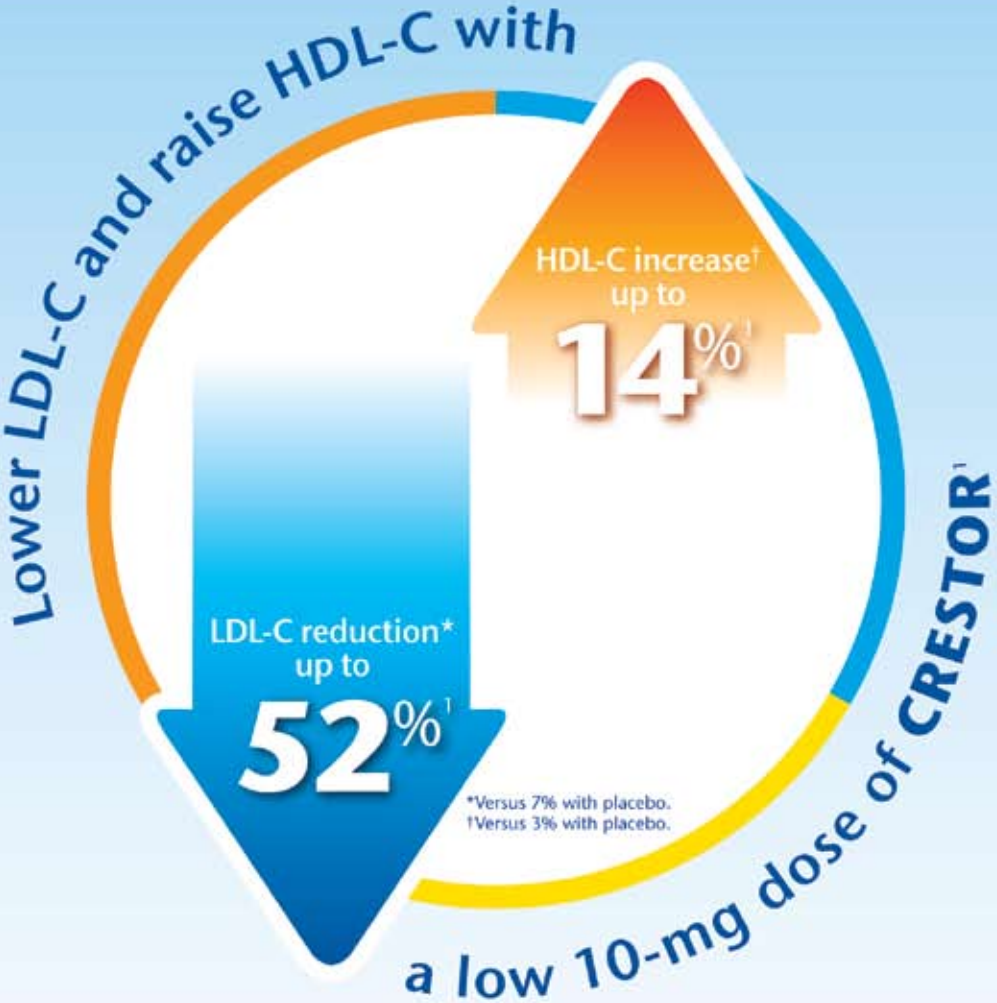

- CRESTOR is indicated as an adjunct to diet to reduce elevated levels of total-C, LDL-C, ApoB, non–HDL-C, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product, 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. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CRESTOR is recommended
- The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined; long-term outcome studies are currently under way

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- 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
- CRESTOR 40 mg is reserved only for those patients not achieving LDL-C goal at 20 mg. Patients initiating statin therapy or switching from another statin should begin treatment with CRESTOR at the appropriate starting dose
- 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%)[1,2]

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

INDICATIONS AND USAGE CRESTOR is indicated: 1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); 2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV); 3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **CONTRAINDICATIONS** CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes). **Pregnancy and Lactation** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus. **WARNINGS Liver Enzymes** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. **It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS). **Myopathy/Rhabdomyolysis Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency. Consequently: 1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism. 2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. 3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION). 4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions). 5. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General). 6. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).** **PRECAUTIONS General** Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE). Administration of rosuvastatin 20 mg to patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION). The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.) **Information for Patients** Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions). **Laboratory Tests** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing. **Drug Interactions Cyclosporine:** When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION). **Warfarin:** Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants. **Gemfibrozil:** Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION). **Lopinavir/Ritonavir:** Coadministration of CRESTOR and a combination product of two protease inhibitors (400 mg lopinavir/100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state $AUC_{(0-24)}$ and C_{max}, respectively. These increases should be considered when initiating and titrating CRESTOR in patients with HIV taking lopinavir/ritonavir. **Endocrine Function** Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in

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

Table 1. Adverse Events in Placebo-Controlled Studies

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

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in ≥2% of these patients. **Body as a Whole:** *Abdominal pain, accidental injury, chest pain, infection, pain,* pelvic pain, and neck pain. **Cardiovascular System:** *Hypertension,* angina pectoris, vasodilatation, and palpitation. **Digestive System:** *Constipation, gastroenteritis,* vomiting, flatulence, periodontal abscess, and gastritis. **Endocrine:** Diabetes mellitus. **Hemic and Lymphatic System:** Anemia and ecchymosis. **Metabolic and Nutritional Disorders:** *Peripheral edema.* **Musculoskeletal System:** *Arthritis, arthralgia,* and pathological fracture. **Nervous System:** *Dizziness, insomnia, hypertonia, paresthesia,* depression, anxiety, vertigo, and neuralgia. **Respiratory System:** *Bronchitis, cough increased,* dyspnea, pneumonia, and asthma. **Skin and Appendages:** *Rash* and pruritus. **Laboratory Abnormalities:** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range [i.e., 80 mg]. However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.) Other abnormal laboratory values reported were elevated creatinine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities. Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis. **Postmarketing Experience** In addition to the events reported above, as with other drugs in this class, the following event has been reported during post-marketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice and memory loss. **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).

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References: 1. Prescribing Information for CRESTOR. AstraZeneca Pharmaceuticals LP, Wilmington, DE. **2.** Data on file, DA-CRS-01.

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