HeartLines

TRENDS IN HEART AND VASCULAR DISEASE

A publication from Cardiovascular Consultants of South Florida | www.heartpartners.com | Volume 2 • Issue 4

Supplements and Heart Health

The long-term effects of popular pills are still unknown

CARDIOVASCULAR CONSULTANTS OF SOUTH FLORIDA

Cardiac Resynchronization Therapy Congestive heart failure doesn't have to limit quality of life


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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

As a child I would talk to my parents about their lives. How different their experiences were from the era that I grew up in. What was it like to live without television? How did they fight common diseases without the medicines that we have now? As an adult, I now reflect on the few decades of my own experience. There were no computers as I was growing up. When patients had massive heart attacks, they generally were crippled or died. Now, only a few short years later, we not only have medicines and diagnostic tests that can help fight heart disease, but we also have tests that can predict whether someone will get it. Who would have ever thought that one day a doctor could take a little piece of metal and thread it through an opening in a person's leg and open a clogged artery in the heart — without the need for surgery — and then the patient could go home on the same day. That day is today.

Like airplanes that fly in the air and somehow don't fall down or computers that can compute millions and billions of formulas at one time, medical science has advanced to a stage that is beyond our wildest dreams. And this is just the tip of the iceberg. Medical science is growing at a blinding pace. It seems a daunting task these days to try to stay current with the literature, the changes in pharmaceutical drugs, and technological advances. Yet it is necessary to provide the best care possible. The physicians at Cardiovascular Consultants of South Florida understand this dynamic, and *Heartlines*, our magazine, is the vehicle that displays our passion and excitement for this scientific growth.

Enjoy,

Judah Friedman, MEd, MBA
Chief Executive Officer

Volume 2 • Issue 4

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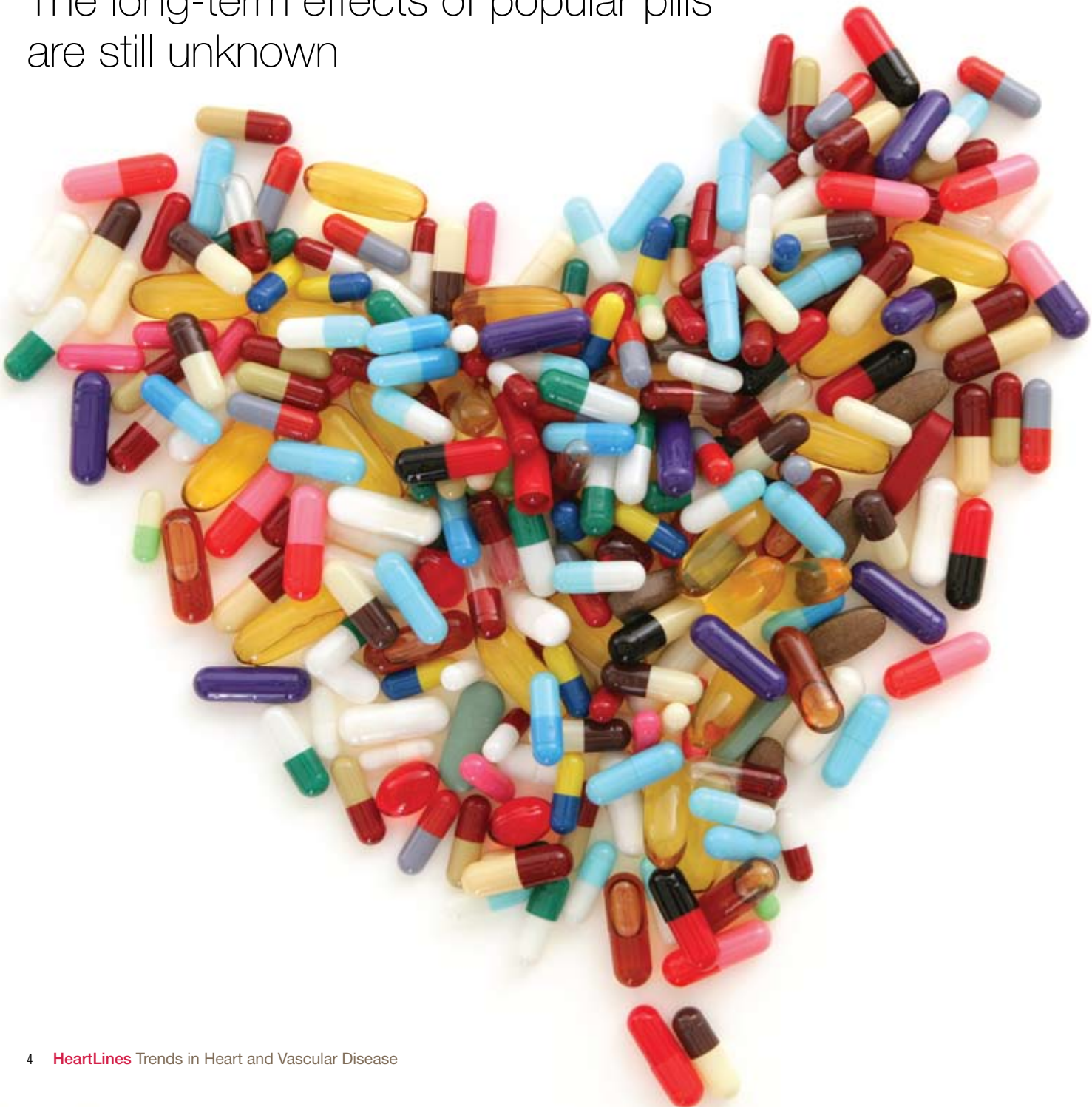
HOWARD F. BERLIN, MD, FACC

Supplements and Heart Health

The long-term effects of popular pills are still unknown



Patients frequently ask what supplemental vitamins they should take. This topic has become part of the medical landscape, and as a physician, I am concerned about what advice to give patients safely. Patients are bombarded by advertising, testimonial support, and peer pressure to take supplemental vitamins. The makers and sellers of these products also suggest that patients consult with their physician before taking vitamins or dietary supplements. This puts physicians in a very uncomfortable position.

This article provides a basic understanding of vitamins and further reinforces the recommendations from the National Institutes of Health (NIH) and the American Heart Association (AHA) about vitamins and dietary supplements for healthy adults. Vitamins are organic compounds required in tiny amounts for essential metabolic reactions in a living organism. These do not include minerals, fatty acids, or amino acids, nor do they encompass the large number of other nutrients that promote health but are not essential for life.

Vitamins

Vitamins act both as catalysts and substrates in chemical reactions. When acting as a catalyst, vitamins are bound to enzymes called cofactors. For example, vitamin K is part of the proteases involved in blood clotting. Vitamins also act as coenzymes to carry chemical groups between enzymes. For example, folic acid carries various forms of the carbon group in the cell — methyl, formyl, and methylene.

Until the 1900s, we obtained vitamins solely through food. Changes in diet could occur during a particular growing season that could alter the types and amounts of vitamins ingested. Vitamins have been produced as commodity chemicals and made widely available as inexpensive pills for several decades to allow supplementation of dietary intake.

The U.S. Food and Drug Administration (FDA) is largely responsible for our current predicament, in part because of the way it regulates vitamins. The Office of Dietary Supplements of the NIH has stated:

"Research studies in people to prove that a dietary supplement is safe are not required before the supplement is marketed, unlike for drugs. It is the responsibility of dietary supplement manufacturers/distributors to ensure that their products are safe and that their label claims are accurate and truthful. If the FDA finds a supplement to be unsafe once it is on the market, only then can it take action against the manufacturer and/or distributor, such as by issuing a warning or requiring the product to be removed from the marketplace."

So, manufacturers do not have to prove that a supplement is effective but can claim that the product addresses a nutrient deficiency, supports health, or reduces the risk of developing a health problem — if true. When manufacturers make such claims, this message must follow the claim: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

> "Manufacturers do not have to prove that a supplement is effective but can claim that the product addresses a nutrient deficiency, supports health, or reduces the risk of developing a health problem. … In essence, the multibillion-dollar supplements industry has the legal right to market vitamins without proof of efficacy as long as it is not unsafe for consumers."

In essence, the multibillion-dollar supplements industry has the legal right to market vitamins without proof of efficacy. Only if the product is found to be unsafe after it is on the market can action be taken.

Dietary supplements

Dietary supplements are not intended to treat, diagnose, mitigate, prevent, or cure disease. Sometimes dietary supplements may have unwanted effects, especially if taken before surgery or with other dietary supplements or medicines or by people with certain health conditions. Whatever your choice, supplements should not replace prescribed medications or the variety of foods important to a healthful diet.

There are many examples of scientific findings that contradict certain claims or assumptions about the value of vitamin supplementation. For example, the Agency for Healthcare Research and Quality has issued a consensus document, "Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease — October 2003." This document concludes:

"The available scientific studies offer little evidence that supplementation with vitamin C, vitamin E, or coenzyme Q10 has any benefit on cardiovascular disease prevention or treatment. Indeed, for vitamin E and vitamin C there is good evidence that supplementation at the doses tested provides no benefit, in that large placebo controlled, randomized studies have reported no benefit in terms of all cause mortality, cardiovascular mortality, myocardial infarction, or blood lipids (e.g., the MRC/BHF trial, GISSI, HOPE, PPP, and ATBC). Isolated examples of possible benefit for vitamin E or vitamin C supplementation reported for specific outcomes in certain trials failed to be supported by other outcomes in the same trials (for example, the statistically significant beneficial effect of vitamin E supplementation on incidence of nonfatal myocardial infarction observed in the CHAOS trial must be balanced against the nonsignificant increase in fatal myocardial infarction with vitamin E in the same trial) or be confirmed in other trials. This lack of consistency in the evidence casts doubt on any of the reported associations being causal.

"There is good evidence that vitamin E supplementation has no clinically important effect on lipid levels. Regarding coenzyme Q10, the available evidence is much less, >>

in terms of large randomized trials, than for vitamins C or E. Therefore, our conclusions are less definitive. The reported results have been mixed, with a meta-analysis and some individual studies reporting improvements in measures of cardiac function, but other studies reporting no such benefit. The more recent randomized trials report smaller benefits, if any, than older trials. The most that can be concluded at this point is that there is no conclusive evidence either supporting or refuting an effect of coenzyme Q10 on cardiovascular disease."

Here is another example of findings that question or challenge some popular thinking about vitamin supplementation. The AHA has issued an evidence-based, scientific position paper that states:

"We recommend that healthy people get adequate nutrients by eating a variety of foods in moderation, rather than by taking supplements. An exception for omega-3 fatty acid supplements is explained below.

"The Dietary Recommended Intakes (DRIs) published by the Institute of Medicine are the best available estimates of safe and adequate dietary intakes. Almost any nutrient can be potentially toxic if consumed in large quantities over a long time. Interactions between dietary supplements and prescription drugs and among several dietary supplements taken at the same time may occur. Too much iron can increase the risk of chronic disease, and too much vitamin A can cause birth defects.

"There aren't sufficient data to suggest that healthy people benefit by taking certain vitamin or mineral supplements in excess of the DRI. While some observational studies have suggested that lower rates of cardiovascular disease and/or lower risk factor levels result in populations who use vitamin or mineral supplements, it isn't clear if this is due to the supplements. For example, supplement users may be less overweight and more physically active."

In 2004, AHA's Council on Nutrition, Physical Activity, and Metabolism summarized findings about vitamin supplementation and its affect on cardiovascular disease (CVD). It said, "No consistent data suggest that consuming micronutrients at levels exceeding those provided by a dietary pattern consistent with AHA dietary guidelines will confer additional benefit with regard to CVD risk reduction."

Antioxidant vitamin supplements

The AHA also has examined the role of antioxidant vitamins, which some studies indicated might contribute to cardiovascular health. The association noted that studies of healthy adults taking large doses of Vitamins A, C, and E did not establish a cause-and-effect relationship between vitamin intake and any observed changes in cardiovascular health. The AHA added,

Patients are bombarded by advertising, testimonial support, and peer pressure to take supplemental vitamins.

"Scientific evidence does not suggest that consuming antioxidant vitamins can eliminate the need to reduce blood pressure, lower blood cholesterol, or stop smoking."

So, while there is no conclusive proof that increased antioxidant vitamin intake may have an overall cardiovascular benefit, antioxidant food sources — especially plant-derived foods such as fruits, vegetables, whole-grain foods, and vegetable oils — are recommended.

Omega-3 fatty acid supplements

Fish consumption has been linked to lower risk of heart disease. AHA recommends that patients without documented heart disease eat a variety of fish, preferably containing omega-3 oil, at least twice a week. Preferred species include salmon, herring, and trout.

AHA also recommends that patients with documented heart disease consume about 1 gram of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are types of omega-3 fatty acids. The preferred source for these acids is by eating fish, although physicians may consider recommending EPA and DHA supplements. Finally, AHA recommends people with high triglycerides consume 2 to 4 grams of EPA and DHA per day in the form of capsules as directed by physicians.

For more information on omega-3, see volume 110 of Circulation, *pages 637 to 641.*

Vitamin E and beta carotene

The Cleveland Clinic Foundation published results of its analysis of seven randomized trials of vitamin E supplementation, alone or in combination with other antioxidants, and eight trials of beta carotene supplements. The research involved 81,788 patients taking vitamin E and 138,113 taking beta carotene. Vitamin E did not lower mortality and did not significantly decrease the risk of cardiovascular death or stroke. Beta carotene produced a small but significant increase in death from all causes and a slight increase in cardiovascular death. The study, reported in *The Lancet* in 2007, discouraged use of beta carotene supplements because of the risk of death.

At this time, the totality of information indicates that there is no substitute for good eating habits and that a Mediterranean diet, aerobic exercise, weight loss, and smoking cessation are favorable steps to reduce the risk of cardiovascular disease. Research is ongoing and may yet reveal significant benefits from vitamin supplementation. But physicians must practice evidence-based medicine. We need to try to curb our patients' current enthusiasm for vitamins until we are sure of the benefits and possible risks. ■

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

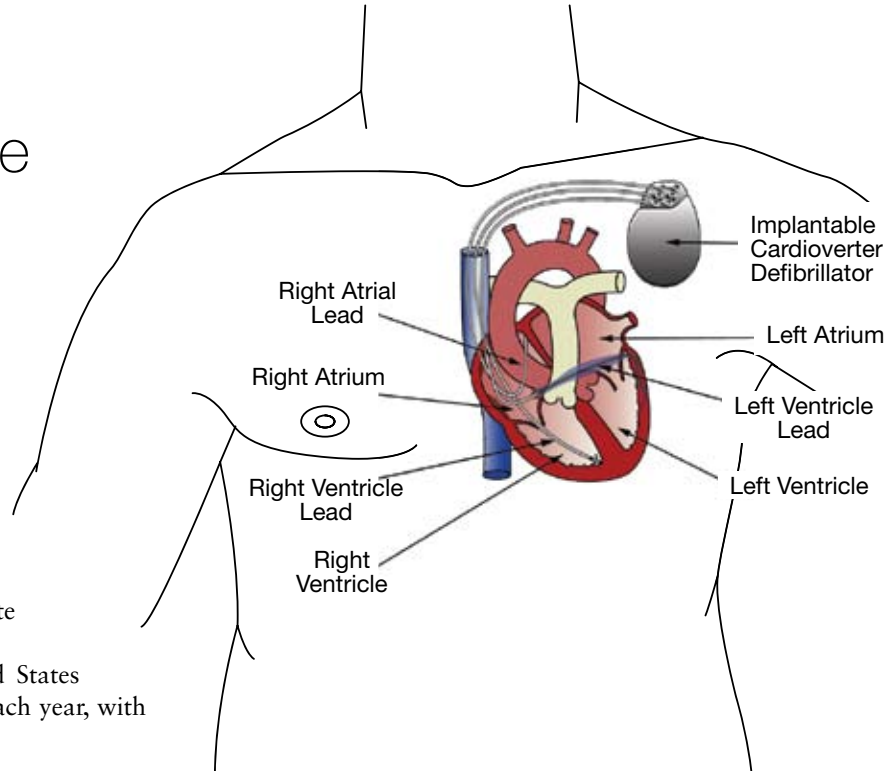
BY JOHN COGAN, MD

Cardiac Resynchronization Therapy

Congestive heart failure doesn't have to limit quality of life

Congestive heart failure (CHF) is a complex syndrome where the ventricle's ability to fill or eject blood is impaired. It is a final common pathway in a number of conditions that alter the structure or function of the heart. Progression of CHF occurs as a consequence of complex cellular, metabolic, and neurohormonal mechanisms that attempt to compensate for injury.

An estimated five million patients in the United States have CHF, and 550,000 new cases are diagnosed each year, with an annual mortality of 290,000.



The illustration shows two typical locations for implanting cardiac resynchronization therapy defibrillators.

Pathology of CHF

The pathophysiology of CHF involves different neurohormonal mechanisms including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). A cascade of effects includes increased afterload and preload, vasoconstriction, sodium and water retention, and cardiovascular remodeling.

The focus of medical therapy is to block neurohormonal compensatory mechanisms that lead to ventricular remodeling and progression of heart failure. Different medications, including ACE inhibitors, angiotensin receptor blockers, spironolactone, beta blockers, digoxin, and diuretics, are used to counteract the neurohormonal compensatory mechanisms.

Ventricular remodeling is defined as a change in the structure and function of the ventricle in response to injury. It includes ventricular dilation, myocyte hypertrophy, interstitial fibrosis, apoptosis, and beta receptor down-regulation.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) may benefit patients with CHF caused by depressed ejection fraction and who continue to have severe symptoms despite drug therapy.

Between 35 percent and 50 percent of patients with severe CHF have delayed ventricular conduction (wide QRS), which is a marker for ventricular dyssynchrony. These patients have disorganized ventricular activation due to altered electrical conduction, often resulting in inefficient timing of contraction between the septal and lateral walls of the left ventricle (LV). Features of ventricular dyssynchrony include abnormal interventricular septal wall motion, reduction in stroke volume, diminished diastolic filling times, worsening of mitral regurgitation, and compromised pumping effectiveness resulting in decreased cardiac output, reduced ejection fraction (EF), and increased symptoms. Ventricular dyssynchrony can even be seen among patients with systolic CHF and normal QRS duration.

Biventricular devices were designed to treat dyssynchrony. These involve placing three pacing leads, one in the right atrium to synchronize the ventricular conduction with the atria, one in the right ventricle, and a third lead inserted via the coronary sinus to a postero-lateral branch of the left ventricle (LV). With this,

atrial contraction is synchronized to ventricular contraction as with a regular pacemaker. Additionally, by adjusting the timing of the right and left ventricular activation and contraction, the left ventricular systolic function may be resynchronized. This results in increased LV systolic function, which thereby can reduce symptoms of CHF and improve patient outcomes.

Several randomized trials have shown evidence that CRT improves patient symptoms, hemodynamics, functional status, quality of life, and ventricular remodeling and reduces hospitalizations. The recent Cardiac Resynchronization in Heart Failure (CARE-HF) trial demonstrated that CRT not only improves symptoms, but also decreases mortality.

When implanting a CRT-defibrillator, not only do patients benefit from the effects of alleviating dyssynchrony, but also from having a backup implantable defibrillator. This includes the ability to overdrive pace or shock dangerous ventricular arrhythmias and has proven in many randomized trials to help reduce mortality.

CRT is indicated in patients with medically refractory CHF with persistent NYHA class III or IV symptoms with a QRS wider than 120 msec (evidence of dyssynchrony) and an ejection fraction equal or below 35 percent. ■

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

The role of echo

Cardiac ultrasound can improve cardiac function

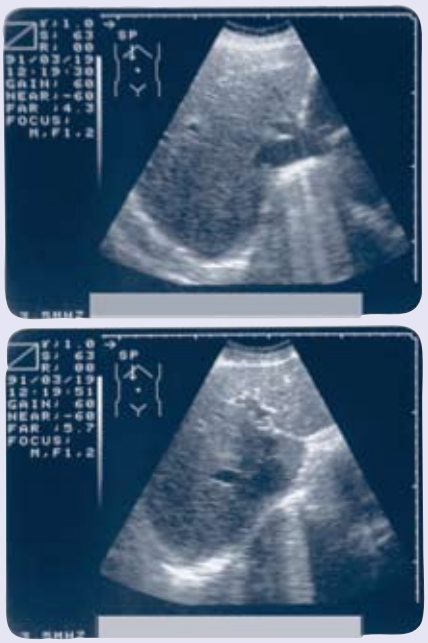
BY RAUL D. MITRANI, MD, FACC, FHRS

Cardiovascular Consultants of South Florida (CCSF) recently began using echocardiographic guidance in patient selection for CRT devices as well as in guiding optimal programming. The practice has purchased the state-of-the art GE Vivid 7 echocardiogram (echo) machine in order to better serve patients before and after CRT device implant. An echo, also known as a cardiac ultrasound, is a sonography of the heart.

Whereas patients with wide QRS (>130 msec), LV systolic dysfunction, and CHF Class 3 would be indicated for CRT devices, it is unclear whether similar patients with borderline QRS durations (110-130 msec) also may derive benefit. Several studies have shown echocardiographic evidence of dyssynchrony using tissue Doppler imaging as well as tissue tracking techniques to be better predictors of patient response to CRT compared with electrocardiogram (ECG) criteria of QRS complex width. Therefore, if patients have borderline QRS width but otherwise meet criteria for CRT, physicians at CCSF look at these echo-derived indices of dyssynchrony.

If there is clear dyssynchrony, physicians recommend resynchronization as part of the strategy of treatment for these patients. Based on the practice's previous experience, and consistent with reports from other literature, patients with borderline or normal QRS width, but with echo-proven dyssynchrony, have excellent response to CRT.

Additionally, after implant, CCSF physicians use echo to guide them in precisely programming pacing parameters to optimize resynchronization as well as hemodynamic function. Specifically, the physicians use echo to guide the optimal A-V interval as well as the optimal RV to LV pace interval.



Before using echo to guide programming, the nonresponse rate to CRT has been reported to be as high as 35 percent. Physicians at CCSF have seen nonresponders to CRT improve after echo-guided A-V and V-V optimization. Therefore, CCSF seeks to provide its patients with every opportunity to improve their CHF status after CRT device implant by using echo when necessary to improve patients' overall cardiac function.

***Raul Mitrani, MD**, earned his medical degree from Columbia University College of Physicians and Surgeons. He completed an internship and a residency at Case Western Reserve University and a fellowship in cardiovascular diseases and cardiac electrophysiology at Indiana University. Dr. Mitrani is a diplomat and is board certified in cardiovascular disease and clinical cardiac electrophysiology. He has served as a consultant for local hospitals, as an associate professor of medicine at the University of Miami School of Medicine, and as director of the Arrhythmia and Pacemaker Center at Jackson Memorial Hospital. He works as director of electrophysiology for Memorial Regional Hospital and director of CCSF's cardiac electrophysiology practice. Dr. Mitrani's offices are located in Hollywood and Aventura.*

BY KASHMIRA P. BHADHA, MD, FACC

Women and Heart Disease, Part II

Risk-reduction techniques for a silent killer

Coronary heart disease (CHD) is the leading cause of death in women, and more women die from it each year than men. The Centers for Disease Control and Prevention attributes 38 percent of deaths in women to CHD, compared with 22 percent to cancer.

Back in issue two of *Heartlines*, the differences in coronary heart disease (CHD) symptoms between men and women as well as conditions that increase the risk of CHD in women were discussed in the "An Equal Opportunity Killer" article. As a follow up, this article discusses diagnostic testing, treatment options, and risk-reduction techniques for CHD.

Diagnostic tests: Diagnostic testing should include a stress echocardiogram or nuclear stress test with myocardial perfusion scans, coronary computed tomography (CT) angiogram, or cardiac catheterization. These tests are popularly referred to as stress tests, CT scans, and cardiac caths. But a simple stress test alone is often not sufficient for women. A regular stress test (using electrocardiograms at rest and during exercise) carries a low sensitivity and specificity, which is why it is not the preferred form of stress testing in women.

Treatment: In general, CHD treatment is the same for men and women. However the benefits of aspirin in primary and secondary prevention of CHD have not been proven in women. Medications such as beta blockers (Lopressor, Tenormin, etc.), angiotensin-converting enzyme (ACE) inhibitors (Altace, Lisinopril), and lipid lowering agents, also known as statins (Lipitor, Zocor), are equally beneficial for men and women.

Percutaneous transluminal coronary angioplasty (PTCA): Women undergoing catheter-based revascularization (angioplasty) are typically older with more risk factors than the men who receive this procedure. They also consequently suffer more complications and have poorer results. Initial angiographic success rates are similar for men and women, but women are more likely to experience vascular complications (such as abrupt closure of the artery or groin complications), emergency bypass surgery, and death. But for the long term, restenosis rates (reclosure of the stent) are fairly similar in men and women.

Coronary artery bypass grafting (CABG): Women face increased long-term and short-term risk of complications and a higher death rate than men after the procedure. This is because women who undergo bypass surgery are typically older and sicker than men. Women also have a greater likelihood of procedural complications, such as heart failure, perioperative infarction, and hemorrhage, as well as death. Death rates in women one month after surgery are more than double that in men — the 30-day mortality is 7 percent in women vs. 2.8 percent in men. A series involving more than 2,100 patients noted higher mortality in women even up to two years after the procedure. High short-term mortality in women was attributed to patient-related factors such as age, coronary risk factors, small body size, and smaller coronary artery size.

Often, patients may not exhibit classic symptoms of CHD. To rule out CHD in this group, newer tests have been developed and may be indicated.

Coronary artery calcium screening

Measurement of coronary calcium using cardiac CT and expressed as an Agatston or volumetric score is an effective way to gauge cardiovascular disease risk and provide information that can complement the Framingham risk score (FRS). FRS defines the risk of developing CHD during a span of 10 years.

Calcium scores can aid decision making regarding drug treatment and whether more aggressive lifestyle changes are needed. A coronary calcium score of 400 or more indicates a severe atherosclerotic plaque burden. A score of 100 to 309 denotes a moderate coronary plaque burden. >>

Coronary Heart Disease: Reducing the Risk

The American Heart Association (AHA) and the American College of Cardiology (ACC) have guidelines for women to reduce their risk for CHD. These guidelines include:

Cigarette smoking: Women should completely stop smoking and avoid passive smoking (secondhand smoke).

Physical activity: Women should get 30 minutes or more of moderate-intensity physical activity on most days of the week. For those with recent cardiovascular events or procedures, participation in cardiac rehab, a physician-guided home exercise program, or a comprehensive secondary prevention program is recommended.

Nutrition:

- In general, women should consume less than 30 percent of their calories from fat and 8 to 10 percent from saturated fat, and they should consume no more than 300 mg of cholesterol a day.
- Women with CHD or significantly elevated cholesterol should get 7 percent or less of their calories from saturated fat and consume no more than 200 mg of cholesterol a day.
- Women should take in 25 to 30 grams of fiber a day from food.
- Salt (sodium chloride) intake should be limited to 6 gm a day. Women with high blood pressure may require even further restrictions in salt intake.

Weight management:

- A target body mass index (BMI) is 18.5 to 24.9 kg/m^2.
- The desirable waist circumference is less than 88 cm, or 35 inches, in women with a BMI of 25 to 34.9 kg/m^2.

  Note: A BMI of 25 kg/m^2 equals 110 percent of a desirable body weight.

Blood pressure:

- A blood pressure of 140/90 mm Hg or less is desirable.
- Optimal blood pressure is 120/80 mm Hg.

Treatment of diabetes:

- Maintain blood sugar of approximately 100 to 110 mg/dl.

Lipid control:

- In women, elevated triglycerides and reduced high-density lipoprotein (HDL) are significant risk factors.
- In younger women with a family history of CHD, elevated Lp(a) levels may predict a high risk for accelerated atherosclerosis, even in the presence of normal total cholesterol levels.

  Note: Lp(a) is a type of lipoprotein.

This screening procedure is particularly useful for women between the ages of 50 and 70 who have an FRS of 5 to 10 percent — especially those with a family history of coronary disease — because in these patients with borderline risk, it is unclear whether they should be treated with lifelong aspirin and statin therapy.

Very few women 65 years of age and younger have enough risk factors to produce an FRS greater than 10 percent. Some of these women, however, especially those with a family history of premature coronary heart disease and components of metabolic syndrome, have relatively high levels of coronary calcium and could benefit from knowing their score in order to start more aggressive lifestyle changes and consider a regimen of aspirin and a statin.

Measuring C-reactive protein levels

C-reactive protein (CRP) is a marker of inflammation; inflammation in blood vessel walls may lead to CHD. The Reynolds Risk Score adds the CRP to the FRS equation to estimate the 10-year risk of cardiac death or myocardial infarction with improved predictability in women compared to the FRS alone. However, in middle-aged people, calcium scores seem to be more reliable for predicting future coronary disease events than do serum levels of hs-CRP.

Measuring carotid artery thickness

Atherosclerotic deposits in the carotid artery can be determined by an ultrasound examination of carotid intimal-medial thickness (thicknesses of the inner and middle layer of the carotid artery wall).

Note: Calcium scores are easier to measure in a reproducible way than carotid intimal-medial thickness, which depends more on the skill of the person taking the measurement.

Testing of endothelial function

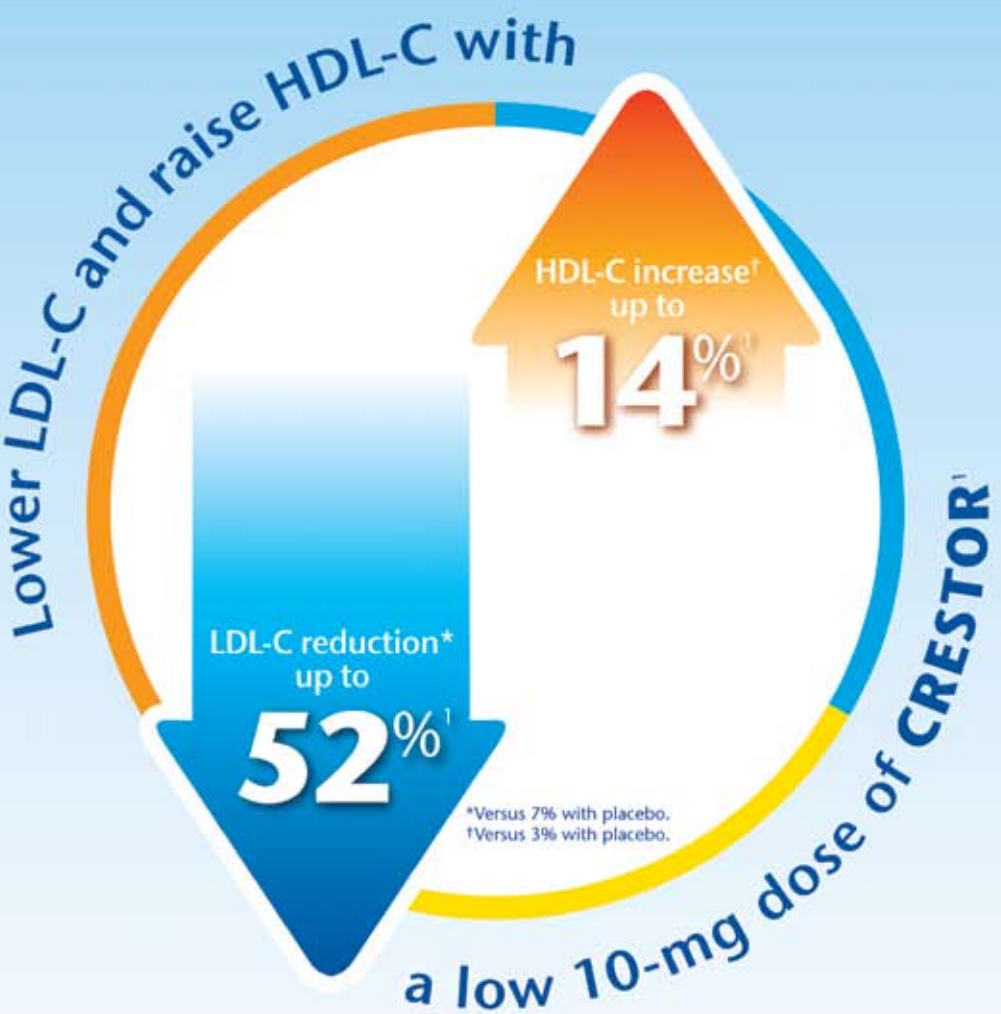
Testing can be done either invasively (by injecting acetylcholine into the coronary or brachial arteries) or noninvasively (by brachial artery reactivity testing).

The good news is that since 2003, female heart disease awareness has increased. The American Heart Association's Go Red for Women Awareness campaign, WomenHeart's Red Bag of Courage plastic tote bags, red silicone bracelet, talk shows, and major media coverage have all helped inform the public of women's risk of heart disease. ■

***Kashmira P. Bhadha, MD, FACC**, received her medical degree from the University of Bombay, India, in 1985. She then completed an internship and a residency in internal medicine at Sinai Hospital in Baltimore, Maryland. Her cardiology fellowship was earned at Presbyterian Medical Center (affiliated with the University of Pennsylvania), in Philadelphia in 1994. Dr. Bhadha is board certified in internal medicine and cardiovascular disease, and she is licensed in nuclear medicine. She works out of the Hollywood and Pembroke Pines offices. Her special interests include heart disease in women and heart disease in Asian-Indians.*

As an adjunct to diet

The statin you choose makes a difference



- 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
- 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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rosuvastatin calcium

AstraZeneca

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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