# Oklahoma Heart Institute

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by Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA

## Heart Disease in Women

by Tobie L. Bresloff, MD

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Oklahoma Heart Institute

The *Oklahoma Heart Institute* magazine is direct mailed to referring physicians and other referring health care professionals in the Tulsa area and is also available in our patient waiting areas.

# In this issue



Cover photo: Fall at the Tulsa Garden Center. Photo by Rick Stiller

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Edition 8

# To Our Readers

**TREATMENT STRATEGIES FOR** the management of patients with cardiovascular disease are rapidly changing and continue to expand. This makes it challenging for health care providers to keep up with the latest advances. In addition, it is also difficult to keep patients informed of new advances in medications and treatment strategies. The current issue of Oklahoma Heart Institute magazine focuses on newer therapeutic agents in the field of cardiovascular disease and the growing indications for treatment.

Over the past year three new classes of medications have been approved for the treatment of cardiovascular disease. Ranolazine is an agent for treating chronic angina. Ranolazine provides the first anti-anginal medication that does not significantly alter heart rate and blood pressure. It can be added to current therapies. Varenicline became a new class of medications approved for smoking cessation. It is an alpha 4 beta 2 nicotine acetylcholine receptor partial agonist, shown to be more effective than current anti-smoking cessation agents.

Omacor is the first FDA approved prescription omega 3 fatty acid for the treatment of hypertriglyceridemia. Because of the high concentration of omega 3 fatty acids in Omacor it is much more effective than over-the-counter agents. In order to achieve adequate therapeutic levels using over-the-counter omega 3 fatty acids, large numbers of capsules had to be ingested, placing the patient at risk of gaining weight because of the large number of calories being consumed.

Dr. Sandler, from our Division of Electrophysiology, highlights the treatment strategies that should be considered for patients with palpitations, and he does it in a format that patients will be able to understand. This represents a new section of the Oklahoma Heart Institute magazine, where articles will be provided for physicians to copy as an informational and educational tool for their patients with specific cardiovascular problems. Dr. Bresloff, from our Division of Endocrinology, discusses the issues of cardiovascular disease in women.

As always the research corner provides information on the newest therapies being investigated at Oklahoma Heart Institute. In this issue, we address the problem of anemia and heart disease. The RED-HF trial evaluates the benefit of treating anemia in heart failure patients using the erythropoiese-stimulating protein darbepoetin alpha.

We hope that you enjoy these articles and welcome any comments or suggestions in regards to the magazine content.

*Sincerely,*
Wayne N. Leimbach, Jr., MD

by David A. Sandler, MD, FACC

Oklahoma Heart Institute

# Palpitation: What Is It and What Should I Do About It? A Patient's Guide

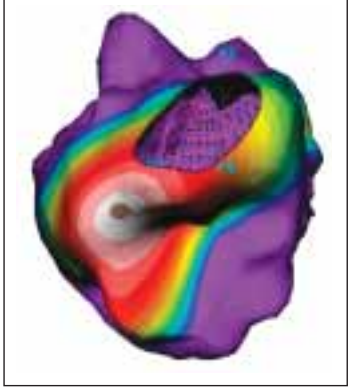
The word *palpitation* simply means the perception of one's heartbeat, but patients use this term to describe a vast array of symptoms. Some of these sensations are normal, while others may require treatment. For many patients who suffer from palpitation, the symptoms can be completely eliminated. In this short article, I will describe four common presentations of palpitation.

There are many circumstances in which feeling one's heartbeat can be normal. It is common for us to feel our heartbeats when we are struck with fear or after vigorous exertion. It is also very common to hear one's own heart beat while lying in bed. These heartbeats should feel regular, steady and not particularly rapid.

A very common complaint is the sensation of "skipped heartbeats". While this symptom may be alarming, it is often quite benign. In truth, the sensation of "skipped heartbeats" is usually caused by an early imperceptible beat, leading to a brief pause in heartbeat. This early "extra" beat may arise from any of the heart's four chambers. Although we all have some extra beats, the degree to which we notice them is highly variable. If these symptoms are frequent and bothersome, one should seek medical care for treatment. Usually, a medication such as a B-Blocker will be prescribed to help reduce the amount of "extra" beats.

Figure 1

Using a Three Dimensional Mapping System to Localize the Focus of an Arrhythmia



Rapid heartbeats for no apparent reason are another form of palpitation. These rhythm disorders are collectively called ***supraventricular tachycardia*** or ***SVT***. Symptoms usually begin abruptly, either provoked by stress/exertion or at rest. The heart will race at a fast rate with a very regular cadence. The symptoms can often be terminated with deep breathing or breath holding. On some occasions, these require emergency room visits for termination of the fast rhythm. The rhythm is usually caused by an extra electrical pathway in the heart allowing for an endless circuit. Patients with SVT should certainly seek consultation with a rhythm specialist since these disorders can be eliminated easily with a procedure called ***ablation***. The success rate of ablation for SVT is over 95%, with complication rates less than 1%.

Some "extra" beats and SVTs can be very difficult to localize and treat with ablation alone. For these tough arrhythmias, one may use a three-dimensional mapping system to help guide ablation. Figure 1 demonstrates the site of initiation of an arrhythmia, which was successfully ablated.

The last arrhythmia I will describe is a rapid, irregular rhythm. In patients with ***atrial fibrillation***, the heartbeat will have no regularity whatsoever. One patient recently described their heart as "dancing to the beat of a drunken drummer". This rhythm may come-and-go (paroxysmal) or may completely replace the normal rhythm (permanent). An important fact about atrial fibrillation is that it can lead to a stroke in certain patients if untreated. Atrial fibrillation is extremely common and is more prevalent in the elderly, hypertensive and/or obese population. Treatment is highly variable, focusing on both symptom control and prevention of stroke.

Patients with atrial fibrillation should keep in close contact with their physician since therapies are evolving continuously. For example, Oklahoma Heart Institute is currently involved in research trials of novel anti-arrhythmics and anticoagulants, which may replace current medications on the market. In addition, some patients who do not respond to medical therapy may be candidates for ablation to possibly cure their atrial fibrillation.

As you can see, palpitation is a symptom that can be used to describe many different heart rhythm abnormalities. If you have symptoms that might be consistent with any of these disorders, you should talk to your health care provider.

*(Dr. Sandler is a cardiologist with subspecialty expertise in electrophysiology.)*

by Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA


# Ranolazine: *A New Pharmacologic Therapy For the Treatment of Chronic Angina*

Angina pectoris was described by Heberden in 1772. Chronic angina affects about 6 million Americans. Current therapies for the treatment of angina include beta blockers, nitrates and calcium antagonists. In addition, external counter pulsation and coronary revascularization are also options for patients refractory to medical therapy. In January 2006, the Food and Drug Administration approved ranolazine (Ranexa) for use in patients with chronic angina who are symptomatic, despite being on either beta blocker or calcium antagonists or nitrates.

Chronic angina is the initial sign of ischemic heart disease in about half of patients with ischemic heart disease. The symptoms of chronic angina can be debilitating for many patients and significantly affect quality of life. Even with the use of bypass graft surgery and stenting, many patients continue to need anti-anginal medications. Despite current therapies, as many as 60-80% of patients still require anti-anginal medications.

Since angina is caused by myocardial ischemia, which is felt to be due to an imbalance between the oxygen supply and oxygen demand, current therapies are usually directed at altering oxygen supply or demand. Ranolazine, however, has anti-anginal and anti-ischemic effects that do not depend on reductions in heart rate or blood pressure. Ranolazine does not increase the rate pressure product at maximal exercise. There are usually minimal changes in mean heart rate (less than 2 beats per minute) and systolic blood pressure (less than 3mmHg) observed with patients on ranolazine.

Ranolazine is felt to work by blocking the late sodium current channels in the myocardial cells.

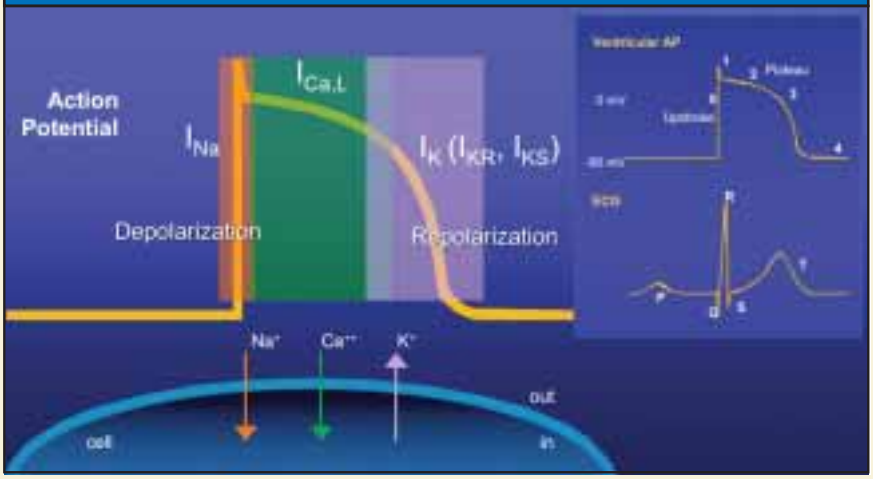
Myocardial ischemia is associated with increased movement of sodium into the cardiac cells. The intracellular sodium is then removed by activation of the sodium calcium exchange pump (Na+/Ca++). The removal of the extra amount of sodium from the cell causes the influx of an increased amount of calcium into the cell and calcium overload. The calcium overload then causes mechanical dysfunction of the cell, as well as possible electrical dysfunction.

Delayed closure or incomplete closure of the late sodium channels is an important contributor to the sodium overload and subsequent calcium overload in the ischemic cells. Ranolazine is felt to work by blocking or reducing the late sodium channel currents into the cell and thereby prevents the calcium overload.

The cardiac cell action potential consists initially of depolarization from an inward movement of sodium into the cell (see Figure 1). Then there is the plateau phase of the action potential associated with the inward movement of calcium, as

**Figure 1**

**Ionic Basis of the Ventricular Transmembrane Action Potential**



the sodium is moved out of the cell. The rest of the action potential normally is driven by the outflow of potassium from the cell. During the plateau portion of the action potential, there are voltage gated sodium channels that fail to inactivate completely and remain open in ischemic myocardium. These late sodium channels normally constitute only about 1% of the peak inward flux of sodium. However, in ischemic or toxic conditions, regulation of the intracellular sodium homeostasis ion channels is abnormal, and significant amounts of sodium continue to move into the cell during the action potential plateau. The increase in intracellular sodium triggers an increase in the influx of calcium via the Na+/Ca++ exchange pump. This results in intracellular calcium overload, causing increased left ventricular diastolic tension and the potential for compression of the vascular space and further reduction of nutrient coronary blood flow to the ischemic territory. Selectively inhibiting the late sodium channels, without affecting the fast current sodium channels accounting for the upstroke of the action potential, prevents the calcium overload, and therefore ameliorates the abnormalities of ventricular repolarization and relaxation.

It should be noted that the effect of ranolazine on late sodium channels is more pronounced in ischemic or failing myocytes in which the current is already abnormally amplified. Reductions in diastolic left ventricular wall tension due to the blocking of the late sodium channels decreases myocardial oxygen requirements in marginally ischemic myocytes and reduces vascular compression, allowing for more coronary blood flow to the affected area. By blocking the late sodium channels, ranolazine prevents sodium overload, which prevents the calcium overload, which prevents ischemia and its complications.

One of the concerns about ranolazine has been the fact that it does prolong the QT interval. It is known that prolonging the QT interval can be associated with the serious dysrhythmia of torsade de pointes. Conventional wisdom has been that pharmacological agents which cause QT prolongation have the potential to induce torsade de pointes and, possibly, sudden death. This has been seen with quinidine and other anti-arrhythmic agents. However it is also known that the amount of QT prolongation alone does not predict the incidence of torsade de pointes. Where sotalol prolongs the QT interval on average of about 55 milliseconds, it has a lower association with torsade de pointes than does dofetilide, which increases the QT interval to the same degree as d-sotalol, yet has a significant incidence of torsade de pointes. Amiodarone increases the QT interval to a greater degree than dofetilide, yet is not associated with a significant increased risk of torsade de pointes. The reason for this disparity may be due to the fact that multiple events are actually required in order to have a drug-induced torsade de pointes.

In order for torsade de pointe to develop, it appears that three events need to occur. The action potential needs to be prolonged (long QTc). However, there must also be increased dispersion across the myocardium. That is, the amount of QTc prolongation must be different between the epicardium, endocardium and mid-myocardial tissue. In addition, there must be the development of early after depolarizations, which act as a trigger. Therefore, it is not just the increased action potential duration associated with the prolonged QT that causes the risk of torsade de pointes. The appropriate substrate associated with increased dispersion of the repolarization and the trigger of early after repolarizations are also necessary (Figure 2).

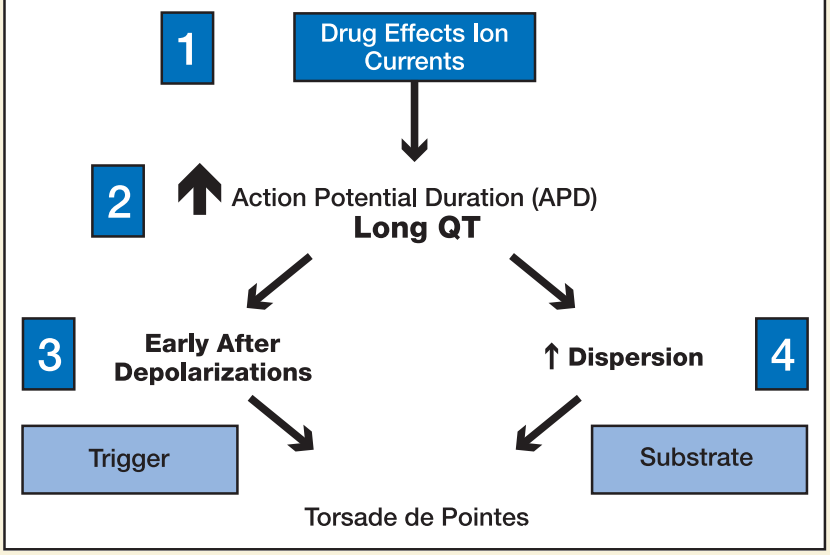
It now appears that early after depolarizations may be due to increased sodium/calcium currents during the plateau phase of the action potential. This leads to ectopic beats. Ranolazine may actually prevent the development of early after depolarizations by its blocking of the late sodium currents. In addition, it appears that the dispersion of ventricular repolarization that occurs with many drugs, such as dofetilide may not occur with ranolazine. In fact, there may be less dispersion from the epicardium to endocardium with ranolazine.

The actual risk of dysrhythmia with ranolazine will need to be further clarified with additional studies and with clinical experience. For this reason, ranolazine is felt to be reserved for patients who have not achieved adequate response with other anti-arrhythmic agents. It should be used in combination with beta blockers or amlodipine or nitrates. When ranolazine is started, it is recommended that a baseline and follow up EKG should be obtained within a week to check the QTc intervals. It should not be used with other drugs that prolong the QTc interval.

Clinical trials showed that ranolazine does significantly reduce angina and prolongs exercise time on the treadmill. The CARISA trial (Combination Assessment of Ranolazine In Stable Angina) was a randomized double-blind placebo controlled trial. 823 patients with angina were treated with placebo or ranolazine extended release 750mg or

**Figure 2**

**Drug-Induced Torsade de Pointes – Relationship to EADs and Dispersion**



1000mg bid. Patients also received either 50mg of atenolol or 5mg of amlodipine or 180mg of diltiazem. The primary end point was the change from baseline in exercise duration at trough and peak levels for ranolazine versus placebo. The treatment period was 12 weeks.

Ranolazine did increase exercise treadmill test performance at 12 weeks. (Figure 3) At trough levels exercise duration, anginal onset, and time to 1mm ST segment depressions all significantly increased with the patients on ranolazine compared to placebo. At peak levels exercise duration also increased from 65 to 91 seconds. Time to onset of angina significantly increased from 88.9 to 126.8 seconds. Time to 1mm ST segment depression also significantly increased from 59.2 to 93.8 seconds. Overall, there was a 36% reduction in angina frequency. Nitroglycerin use was also decreased by 43% in the ranolazine 1000mg bid group.

Similar findings were also reported in the ERICA Trial (Efficacy of Ranolazine in Chronic Angina). 565 patients with angina and a history of greater than 3 anginal attacks per week were randomized to receive 1000mg bid of ranolazine extended release tablets or placebo. At the end of the study there was a 23% reduction in angina frequency and 25% reduction in nitroglycerin use.

Over 2000 patients with chronic angina have been treated with ranolazine in controlled clinical trials. A total of over 1000 patients were treated with ranolazine extended release in three double-blind placebo controlled trials. The most common adverse event that led to discontinuation was dizziness, which occurred in .1% of placebo patients and 1.3% of ranolazine patients. Other side effects leading to discontinuation included nausea in 1%, asthenia in .5%, constipation in .5%, and headaches in .5% of ranolazine patients.

Common reported side effects included constipation in 8% of ranolazine patients and 2% of placebo, nausea in 4% of ranolazine and 1% of placebo, dizziness in 5% of ranolazine and 2% of placebo, and headache 3% for ranolazine and 2% for placebo.

No overall differences in efficacy were observed between older and younger patients. There was a higher incidence of placebo subtracted adverse events in patients over 75 years of age. The most commonly reported adverse event in these patients was constipation. Because ranolazine prolongs the QTc interval in a dose-related manner, the QTc interval should be watched. However, studies are now suggesting that this QTc prolongation may not be of the same clinical significance as with other antiarrhythmic drugs.

Ranolazine should be avoided in patients with long QT syndrome, uncorrected hypokalemia and a history of ventricular tachycardia. In addition, it should be avoided in patients who are on QTc-prolonging drugs such as dofetilide, sotalol and anti-psychotics, such as thorazine.

Because ranolazine is metabolized in the liver using the CYP3A enzymes, it should not be used along with verapamil, ketoconazole, azol anti-fungals, macrolid antibiotics, HIV protease inhibitors, and in patients drinking significant amounts of grapefruit juice. In addition, patients with significant hepatic impairment should not be started on ranolazine.

Ranolazine pharmokinetics are such that the half-life is about 7 hours, time to maximum blood levels is 2-5 hours, and steady state is achieved within 3 days. Its metabolism is mainly by the CYP3A hepatic enzymes and also, to a lesser extent, by the CYP2D6 enzymes. Ranolazine levels appear to increase by about 50% in patients with varying degrees of renal insufficiency. Plasma concentration of ranolazine were increased in subjects with liver impairment. There have been no significant effects on ranolazine pharmakinetics with the elderly, patients with heart failure, or with diabetes mellitus.

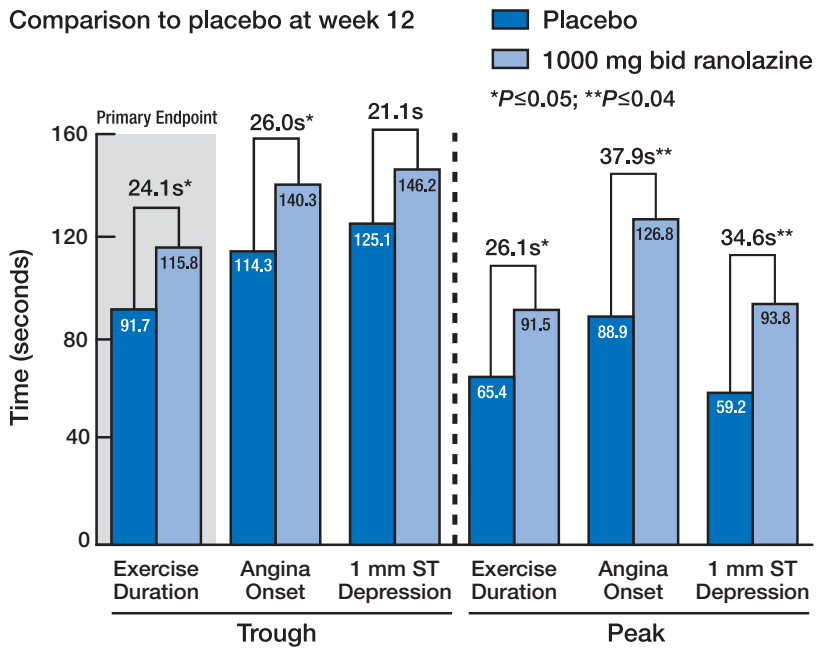
Ranolazine is initiated at 500mg bid. It is increased to 1000mg bid as needed. It should not be used in doses greater than 1000mg bid. It should be noted that the medicine only comes at this time in a 500mg tablet, so the dose would initially be 1 tablet bid and, if needed, would be increased to 2 tablets bid.

If a dose is missed, the next dose should be taken at the regularly sched-

*continued on page 26*

**Figure 3**

**CARISA: Ranolazine Increases Exercise Treadmill Test Performance**




The improvement in exercise treadmill tests in females was about 33% of that in males receiving 1000 mg bid ranolazine

CVT data on file RAN00253-2. Chaitman BR, et al. *JAMA*. 2004. Ranexa® (ranolazine extended-release tablets) PI. February 2006.

*by* **Alan M. Kaneshige, MD, FACC, ASE**

# THE RED-HF TRIAL
## *Anemia and Chronic Heart Failure*

Heart failure remains one of the most significant and prevalent health care problems in the United States today. Acute heart failure syndromes cause approximately 1 million hospitalizations and contribute to an additional 2.4 million hospitalizations a year. Many patients go on to manifest chronic heart failure. Chronic heart failure affects at least 5 million patients in the United States. It is a disease of the elderly, with a majority of patients being over 65 years of age.

Anemia is common in patients with chronic heart failure. Approximately 20-30% of heart failure patients are anemic. The prevalence and severity of anemia increase with the severity of heart failure. Anemia is associated with worse symptoms and outcomes in heart failure. Preliminary studies have suggested that treatment of anemia in patients with heart failure may be beneficial. Specifically, treatment with erythropoieses-stimulating proteins (ESPs) may have benefit. Treatment of anemia with these proteins may improve cardiac function, exercise capacity, and quality of life. Treatment may also reduce hospitalizations and the use of diuretics.

The etiology of anemia in heart failure is multifactorial. The burden of chronic inflammation, chronic disease, pharmacotherapy, renal dysfunction, malnutrition, and decreased cardiac output may all play roles in anemia. The results are bone marrow suppression, abnormal iron usage, intravascular fluid management problems, and EPS deficiency or resistance. In the past, critical care specialists noted that packed red blood cell transfusion therapy to correct anemia in critically ill patients had a higher mortality rate than patients just supported. On the other hand, small studies have suggested that treatment of anemia in chronically ill patients with ESPs may have benefit.

The RED-HF Trial will evaluate hard endpoints for the treatment of anemia in patients with heart failure. Primary endpoints for this trial will be to evaluate mortality and hospitalizations for worsening heart failure. Secondary endpoints will evaluate symptoms and quality of life, as well as CV events. The study medication is darbepoetin alpha, a long acting ESP. Patients will have to have hemoglobin between 9 and 12 gm/dl, a left ventricular ejection fraction of 35 % or less, and be at a New York Heart Association functional class III to IV. The study will enroll 3,400 to 3,500 patients. There will be a 1:1 randomization between a darbepoetin alpha group and a placebo group. Enrollment will be 16 months, with follow-up after 18 months. The trial will be stopped after 1,450 events have occurred (all cause mortality or hospitalization for worsening heart failure).

In spite of advances in drug therapy and mechanical device therapy, heart failure continues to be a growing problem. Within the heart failure population, anemia is common and is predictive of worse outcomes. The RED-HF trial offers an opportunity to treat the heart failure treatment paradigm. With the design and power of this trial, we can hopefully determine whether treating anemia with ESPs can improve outcomes.

If you have a heart failure patient with anemia that you would like considered for this trial, contact Jolene Durham, the Research Coordinator, at 579-4939 or the Heart Failure Clinic at 579-2600.

*(Dr. Kaneshige is a noninvasive cardiologist with expertise in adult echocardiography, stress echocardiography and transesophageal echocardiography. He is Director of the Adolescent and Adult Congenital Heart Clinic at Oklahoma Heart Institute and Director of the Congestive Heart Failure C.A.R.E. Center at Hillcrest Medical Center.)*

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# THE DOCTORS OF OKLAHOMA HEART INSTITUTE

### Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA

Dr. Leimbach is a subspecialist in interventional cardiology, including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy, laser, intravascular ultrasound imaging and direct PTCA for acute myocardial infarction. He is Chief of Cardiology at Hillcrest Medical Center, where he is also Director of the Cardiac and Interventional Laboratories at Hillcrest Medical Center. Dr. Leimbach is Co-Director of the Lipid and Wellness Clinic at Oklahoma Heart Institute. He is Director of the James D. Harvey Center for Cardiovascular Research at Hillcrest Medical Center, as well as Director of the Oklahoma Heart Research and Education Foundation. He also serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. Dr. Leimbach completed a Clinical Cardiology Fellowship and a Research Fellowship at the University of Iowa Hospitals and Clinics. He also completed his Internal Medicine Internship and Residency programs at Iowa, where he was selected Chief Resident in Medicine. He received his medical degree from Northwestern University in Chicago and his Bachelor of Science degree from the University of Michigan.

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### Robert C. Sonnenschein, MD, FACC, ASE, RVT

Dr. Sonnenschein specializes in echocardiography and noninvasive peripheral vascular imaging. He is Director of Peripheral Vascular Ultrasound Imaging at Hillcrest Medical Center and Oklahoma Heart Institute and serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He completed his Cardiology Fellowship at the State University of New York Upstate Medical Center in Syracuse, where he also completed his Internal Medicine Internship and Residency programs. Dr. Sonnenschein received his medical degree from Rush Medical College in Chicago and his Bachelor of Arts degree from the University of Pennsylvania.

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### Robert E. Lynch, MD, FACC

Dr. Lynch is a specialist trained in noninvasive and invasive cardiology. He is former Chief of Cardiology at Hillcrest Medical Center, where he also has served as Chief of Medicine and President of the medical staff. Dr. Lynch is Co-Director of the Lipid and Wellness Clinic at Oklahoma Heart Institute and Director of the Executive Health Program. He is also a Clinical Assistant Professor at the University of Oklahoma College of Medicine – Tulsa. He completed his Cardiology Fellowship, as well as his Internal Medicine Internship and Residency, at the University of Oklahoma Health Sciences Center. Dr. Lynch received his medical degree from the University of Oklahoma School of Medicine and his Bachelor of Science degree from the University of Tulsa. Before establishing his practice in Tulsa, he served as Chief of Medicine at the U.S. Army Hospital, Bangkok, Thailand.

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Dr. Pickering is a cardiology specialist trained in noninvasive and invasive cardiology with subspecialty expertise in cardiac catheterization and angioplasty. He is Chief of Cardiology at SouthCrest Hospital and past Chief of Cardiology at Tulsa Regional Medical Center. He completed a Cardiovascular Disease Fellowship at Baylor College of Medicine in Houston, TX. Dr. Pickering's Internal Medicine Residency was completed at Oklahoma Osteopathic Hospital in Tulsa. He received his medical degree from Philadelphia College of Osteopathic Medicine and his Bachelor of Science degree from Shelton College, Ringwood, NJ.

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*Board certified in Internal Medicine and Cardiovascular Disease*

by Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA

# Omacor: *For the Treatment of Hypertriglyceridemia*

Omacor is an Omega-3 fatty acid prescription pharmaceutical product. It is the first in its class to treat very high triglyceride levels. Omacor contains 90% Omega-3 fatty acid esters, compared to less than 30% Omega-3 fatty acids in standard over-the-counter fish oil capsules. Omacor is FDA approved to reduce triglyceride levels greater than 500mg/dl in adult patients. It is a safe and tolerable medication. No significant liver or kidney toxicities have been observed. This makes it particularly useful in patients who are having problems with liver toxicity while taking other lipid lowering medications.

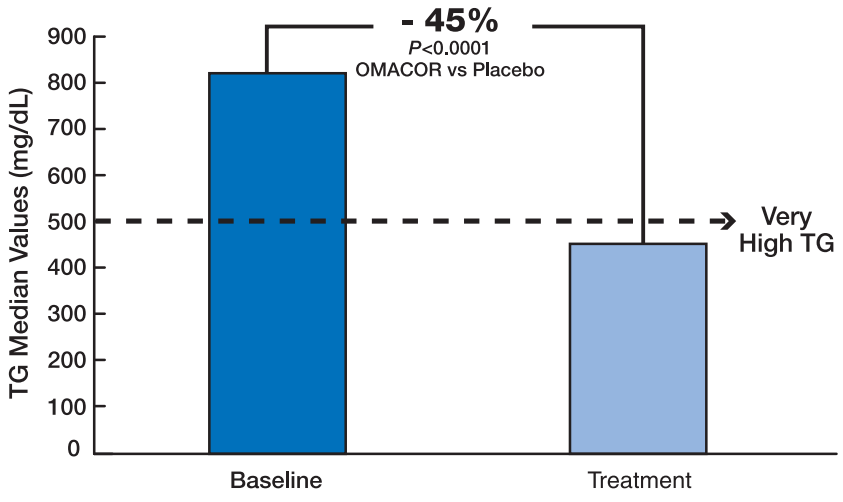
Omega-3 fatty acids have been shown to not only decrease triglycerides, but they also appear to have anti-inflammatory properties. This may be due to the fact that the Omega-3 fatty acids are transformed by the cyclooxygenase and lypooxygenase pathways into prostanoids and leukotrienes which have anti-inflammatory and anti-thrombotic properties. This is in contrast to the Omega-6 and linoleic acids, which are converted by the cyclooxygenase and lypooxygenase pathways into prostanoids and leukotrienes with pro-inflammatory and pro-thrombotic properties. The potential mechanisms by which Omacor reduces plasma triglycerides may be related to a decrease in the synthesis of triglycerides, as well as to stimulation of free fatty acid oxidation. In addition, there may be increased LPL mediated clearance of triglycerides. Omacor has been shown to reduce triglycerides by 45% in patients with greater than 500 mg/dl (Figure 1). In addition, HDL levels seem to be unchanged or increased slightly by up to 9%.

Omacor's safety profile is very favorable. In the randomized trials between Omacor and placebo, one or more adverse event occurred in 35% of the Omacor patients and in 27% of the placebo patients. The most common events included dyspepsia in 3.1% of the Omacor patients versus 2.6% of the placebo patients. Eructation occurred in 4.9% of the Omacor patients as compared to 2.2% of the placebo patients, and taste perversion in 2.7% of the Omacor patients versus 0% of the placebo patients. Significant drug interactions due to Omacor are not expected in humans. Some Omega-3 studies do demonstrate prolongation of the bleeding time and increased bruising.

For reduction of triglyceride levels of greater than 500mg/dl, 4 grams per day is the standard dose. This can be taken as either four 1 gram capsules

**Figure 1**

**Lipid Benefits of OMACOR® in Patients with TG ≥500 mg/dL**




Pownall JH et al. *Atherosclerosis*. 1999;143:285-297.
Harris WS et al. *J Cardio Risk*. 1997;4:385-391.

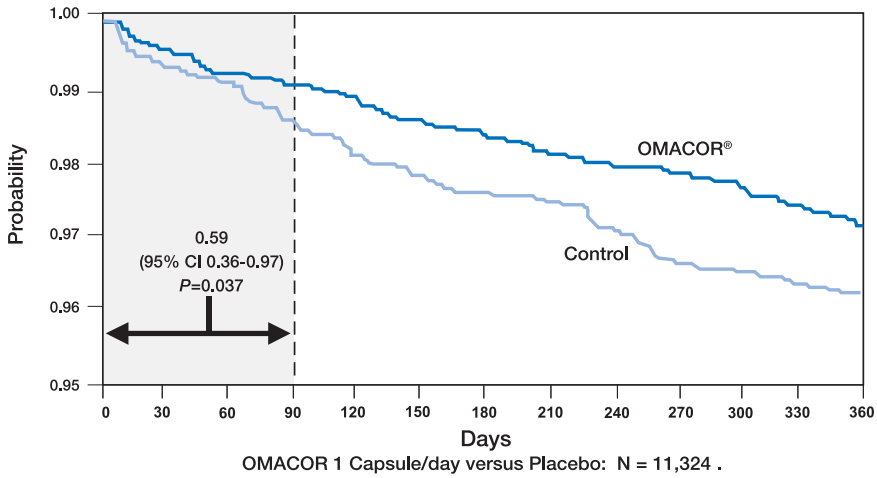
once a day or two 1 gram capsules twice a day.

Unlike over-the-counter Omega-3 fatty acids, Omacor contains 90% of the Omega-3 fatty acids, as compared to, at best, 30% in over-the-counter products. In addition, since Omacor has been FDA approved as a prescription drug, its manufacturing is required to provide batch-to-batch consistency, which is often not seen in over-the-counter products. In the past, the use of Omega-3 fatty acid fish oils for the treatment of hypertriglyceridemia was limited, due to the fact that greater than 12 capsules a day were required to achieve therapeutic goals. With more than 12 grams of fat being added to the diet, the development of obesity becomes a problem. Because Omacor has concentrated Omega-3 fatty acid fish oils in each capsule, only four capsules per day are required for full therapeutic effect.

There are ongoing studies looking at the value of Omacor for the treatment of hypertriglyceridemia between 200 and 400mg/dl. Studies have shown additive effects for the use of Omacor with statins. In addition, the role of Omacor for primary prevention of cardiovascular disease is being evaluated. Figure 2 shows the results of the GISSI PREVENZIONE Trial, which does suggest a primary prevention role for Omacor. Additional prevention trials are underway looking at the value of Omega-3 fatty acids for the prevention of atherosclerotic vascular disease.

Figure 2

GISSI-Prevenzione Trial – Early Effect on All-Cause Mortality




OMACOR 1 Capsule/day versus Placebo: N = 11,324 .

Marchioli R et al. *Circulation*. 2002;105:1897-1903.

In summary, Omacor represents a safe therapeutic option for the treatment of significant hypertriglyceridemia. Because of its excellent safety profile and lack of liver toxicity, Omacor represents a good therapeutic option for patients with mixed dyslipidemias who experience liver enzyme elevations with other lipid lowering agents.

*(Dr. Leimbach is a subspecialist in interventional cardiology, including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy, laser, intravascular ultrasound imaging and direct PTCA for acute myocardial infarction.)*

■ *by* **Wayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHA**

# Varenicline: *A New Class of Medications for Smoking Cessation*

The FDA has recently approved varenicline (Chantix) to be used as an aid for smoking cessation.

Cigarette smoking remains the leading preventable cause of illness and premature death in the United States. Although nearly 41% of smokers try to quit smoking each year, only about 7% to 10% successfully achieve and maintain abstinence. Most smokers relapse within a few days of quitting, and the average smoker has tried to quit six to nine times.

According to the World Health Organization, a person dies every 8 seconds from smoking-related disease. It has been estimated that 150 billion dollars a year is spent on treating smoking-related diseases in the United States alone.

Until recently, only two classes of smoking cessation aids were available. These included nicotine replacement agents with multiple delivery methods including patches, gum, inhalers, and lozenges, and the antidepressant bupropion, which is thought to work by inhibiting the reuptake of dopamine and norepinephrine. Varenicline is an alpha 4 beta 2 subtype nicotinic acetylcholine receptor partial agonist. When smokers inhale a lit cigarette, nicotine is inhaled and reaches the brain within seconds. It binds to a nicotinic receptor, which activates the reward path within the brain circuitry. This creates a powerful sense of satisfaction. The initial effects recede quickly, and a cycle of craving and withdrawal ensues. As a partial agonist, varenicline (Chantix) offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving through its agonist action, while blocking the reinforcing effects of continued nicotine use though its antagonist action. Varenicline has been shown to be efficacious, safe, and well tolerated as a smoking cessation agent.

Three clinical randomized trials have recently been published in the July 5, 2006 Journal of the American Medical Association. Two of these trials compared varenicline to not only placebo, but also to bupropion SR, a known efficacious first line smoking cessation agent. In both trials, patients were treated for 12 weeks. The medications were then stopped and the patients were followed for 52 weeks. In the first trial by Gonzales at al, the abstinence rates for weeks 9-12 were 44% for varenicline, versus 29.5% for bupropion SR versus 17.7% for placebo. The difference between varenicline and bupropion and for varenicline versus placebo were statistically significant. The continuous abstinence rates at 52 weeks were 21.9% for varenicline versus 16.1% for bupropion SR versus 8.4% for

placebo. These differences were also statistically significant. Varenicline reduced craving and withdrawal, and for those who smoked while receiving study drugs it decreased smoking satisfaction.

A second trial by Jorenby at al, found similar results. The smoking cessation at 12 weeks was 43.9% for varenicline versus 29.8% for bupropion SR versus 17.6% for the placebo group.

In a third trial, published in the July 5, 2006 issue of the Journal of American Medical Association, the effect of maintenance therapy with

varenicline on smoking cessation was reported. In this trial, 1,928 patients were assigned to receive open label varenicline. Those patients who were able to achieve smoking cessation by 12 weeks were then randomized to either continue varenicline for another 12 weeks or to receive placebo. Continuous abstinence rates for weeks 13-24 were higher in the varenicline group than in the placebo group. The continuous abstinence rates for weeks 13-52 were also higher in the varenicline group with an odds ratio of 1.34.

In all of the studies, the drug was relatively well tolerated. Nausea was reported in approximately 30% of patients treated with varenicline 1 mg b.i.d., but only 3% discontinued the drug due to adverse side effects. The nausea was generally described as mild or moderate and often transient. The most common side effects for varenicline were nausea, headache, insomnia, and abnormal dreams.

Varenicline is supplied with a starting month pack, containing four boxes. The first box contains the starting titration. On days 1 through 3, the patient takes 0.5 mg q day, on days 4 through 7 the patient takes 0.5 mg tablets b.i.d., and for days 8 through 28 the patient takes 1 mg b.i.d. The patient continues with a continuation month pack, which contains packets of 1 mg tablets b.i.d. Patients continue for a total of 12 weeks. For those who have quit smoking at 12 weeks, an additional 12 weeks is recommended to further increase the likelihood of long-term abstinence. It is recommended that the patient set a target date to quit smoking completely. It should usually occur somewhere around day 4 to 7 of the initial starting pack.

Because varenicline is excreted primarily through the urine, dosing adjustments have to be made in patients with greater than moderate degrees of renal impairment. Weight gain was noticed with patients randomized to varenicline. Weight gains were 2.37 kg to 3.62 kg, on average.

In conclusion, extended use of varenicline helped patients to quit smoking and to maintain smoking abstinence. This drug represents the first smoking cessation aid to demonstrate long-term benefit in relapse prevention. At the end of the trial, with one year of follow-up, more than 50% of participants in each group did return to smoking. Despite this, varenicline can be an additional tool for the physician to use for patients who are trying to quit smoking.

*(Dr. Wayne N. Leimbach Jr. is a subspecialist in interventional cardiology including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy, laser, intravascular ultrasound imaging and direct PTCA for acute myocardial infarction and PFO and ASD closures.)*

## Ranolazine

*ontinued from page 8*

uled time and the next dose should not be doubled. The tablets should be swallowed whole and not crushed or chewed, since they are extended release tablets.

Ranolazine seems to help patients most who are having active myocardial ischemia. This may be due to the fact that the late sodium channels are more apt to be dysfunctional in ischemic cells. Patients whose symptoms are not related to ischemia of the myocardial cells may be less likely to benefit from ranolazine.

In summary, ranolazine is a novel approach to the treatment of chronic angina and represents the first pharmacological new agent for the treatment of angina in the United States in the last couple decades. Unlike other anginal medications, ranolazine has minimal effect on heart rate and blood pressure. The one exception to this is that ranolazine can increase blood pressure significantly in patients with severe renal impairment. But, note that ranolazine is not indicated in patients with severe renal impairment.

Ranolazine is indicated for the treatment of chronic angina in combination with either amlodipine or beta blockers or nitrates. Because of its metabolism by the CYP3A enzymes in the liver, ranolazine should not be used with potent inhibitors of the CYP3A pathways, including verapamil, ketoconazole, macrolid antibiotics, HIV protease inhibitors, higher doses of diltiazem and people drinking large amounts of grapefruit juice.

Ranolazine has demonstrated significant efficacy in reducing anginal episodes for patients who are still symptomatic on standard therapies. It has been shown to increase treadmill exercise duration in patients with chronic stable angina. The ongoing MERLIN-TIMI 36 Trial will address whether ranolazine can reduce the composite end point of cardiovascular death, myocardial infarction or recurrent ischemia in high-risk patients with acute coronary syndrome. This study is expected to be completed in 2006. The study will also further test the safety profile of this promising new agent.

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**Concerto™ Model C154DWK and Virtuoso™**
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**Indications for Concerto:** Concerto is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration. **Indications for Virtuoso:** Virtuoso DR/VR devices are indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients with NYHA Functional Class II/III heart failure. The Virtuoso DR device is also indicated for use in the above patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. Atrial rhythm management features, available on the Virtuoso DR, such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in ICD-indicated patients with atrial septal lead placement and an ICD indication. Due to the addition of the OptiVol® diagnostic feature, the Virtuoso indication is limited to NYHA Functional Class II/III heart failure patients who are indicated for an ICD. The clinical value of the OptiVol fluid monitoring diagnostic feature has not been assessed in those patients who do not have fluid retention related symptoms due to heart failure. **Contraindications for Concerto:** Concerto is contraindicated in patients whose ventricular tachyarrhythmias may have transient or reversible causes; patients with incessant VT or VF; and patients who have a unipolar pacemaker. **Contraindications for Virtuoso:** Virtuoso DR/VR devices are contraindicated for patients experiencing any of the following conditions: tachyarrhythmias with transient or reversible causes, incessant ventricular tachycardia or ventricular fibrillation, present implant of a unipolar implantable pulse generator, and primary disorder or bradyarrhythmia. Virtuoso DR is also contraindicated for patients who have a primary disorder of chronic atrial tachyarrhythmia with no concomitant VT or VF. Additionally, Virtuoso VR is contraindicated for patients who have a primary disorder of atrial arrhythmia. **Warnings and Precautions:** Changes in a patient's disease and/or medications may alter the efficacy of the device's programmed parameters. Patients should avoid sources of magnetic and electromagnetic radiation to avoid possible underdetection, inappropriate sensing and/or therapy delivery, tissue damage, induction of an arrhythmia, device electrical reset, or device damage. Do not place transthoracic defibrillation paddles directly over the device. Certain programming and device operations may not provide cardiac resynchronization. **Potential Complications:** Potential complications include, but are not limited to, rejection phenomena, erosion through the skin, muscle or nerve stimulation, oversensing, failure to detect and/or terminate tachyarrhythmia episodes, acceleration of ventricular tachycardia, and surgical complications such as hematoma, infection, inflammation, and thrombosis.

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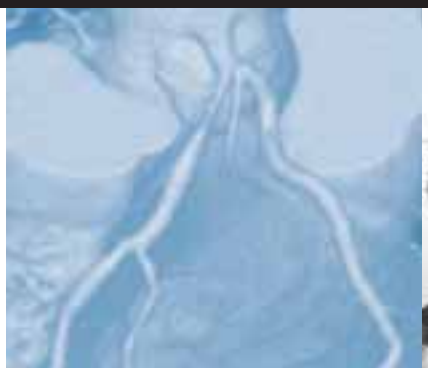
*by* **Tobie L. Bresloff, MD**



# Heart Disease in Women

Most people do not realize that heart disease is the leading cause of death in women. Every minute one woman dies from heart disease. Eight million American women have heart disease.

Heart attacks kill 6 times more women each year than breast cancer. Heart disease and stroke together kill more females than the next 7 causes of death combined. Yet women still fear cancer more than heart disease.

Even with these sobering statistics, women are less likely to be screened – or seek screening – for cardiac problems. They are also less likely to seek medical care when symptoms start, and, once heart disease is diagnosed, they are less likely to receive medications or interventions that we know can prolong life or decrease recurrent problems.

To change this, women should be educated about what tests to ask for and what symptoms to look for. The first step is evaluating who is at risk. Some risk factors cannot be changed. These are gender, age and family history. Those risks that can be modified include:

- High blood pressure
- Smoking
- High total or bad (LDL) cholesterol, low good cholesterol (HDL) or high triglycerides
- Physical inactivity
- Excess weight, especially in the abdominal area

- Abnormal blood sugars

Women with known coronary artery disease, diabetes, chronic kidney disease or other known vascular diseases are at the highest risk. These women need aggressive risk factor modification, often with medications, and need to be evaluated for treatable abnormalities of the coronary arteries. In order to decrease risk, the American Heart Association recommends:

- Smoking cessation
- Physical activity/cardiac rehabilitation
- Healthy diet to decrease weight, if needed, and optimize the lipids
- Aggressive BP and lipid control with medications if needed
- Aspirin, ß-blocker, ACE inhibitor or ARB to be considered
- Tight glycemic control in diabetes

Those in the intermediate risk group have several risk factors (hypertension, lipid abnormalities, abnormal blood sugars, abdominal obesity) or a first degree relative with early onset coronary or vascular disease. This

group may be screened for CAD, and should be on treatment to improve lipid, sugar or blood pressure abnormalities. Lower risk is present in those with mild abnormalities or only one risk factor.

Women often present with symptoms that are not thought of as the typical presentation of angina. These symptoms may be:

- Pain in upper back, jaw, abdomen or neck
- Shortness of breath
- Flu-like symptoms: nausea or vomiting, cold sweats
- Fatigue or weakness
- Feelings of anxiety, loss of appetite, discomfort

The difference in symptoms may be that the coronary arteries in women are more likely to have diffuse narrowing than the discreet blockages that males usually have. Because of this, some of the standard tests for disease may not be as helpful in women. Most of the current recommendations for testing are based on studies done in men. Still, standard exercise treadmill remains the recommended initial test.

Newer technologies hold great promise for identifying stenoses and measuring blood flow. Cardiovascular magnetic resonance imaging can show function of the heart muscle, and also uses no radiation.

Increased thickness of the walls of the carotid arteries, as measured by ultrasound, seems to be a marker for increased risk of coronary disease in women. Computed tomography measures the calcium in the coronary arteries. Low calcium scores correlate with low risk, but it is not clear if higher scores help determine who is at risk more than other testing might. The best strategy is to let the doctor, who can evaluate the entire picture, recommend where to start. The utility of multislice CT scanning is being evaluated.

*(Dr. Bresloff is a specialist in Endocrinology, Metabolism and Hypertension, with expertise in diabetes, lipids, hypertension and thyroid diseases.)*

## The American Heart Association recommends that women

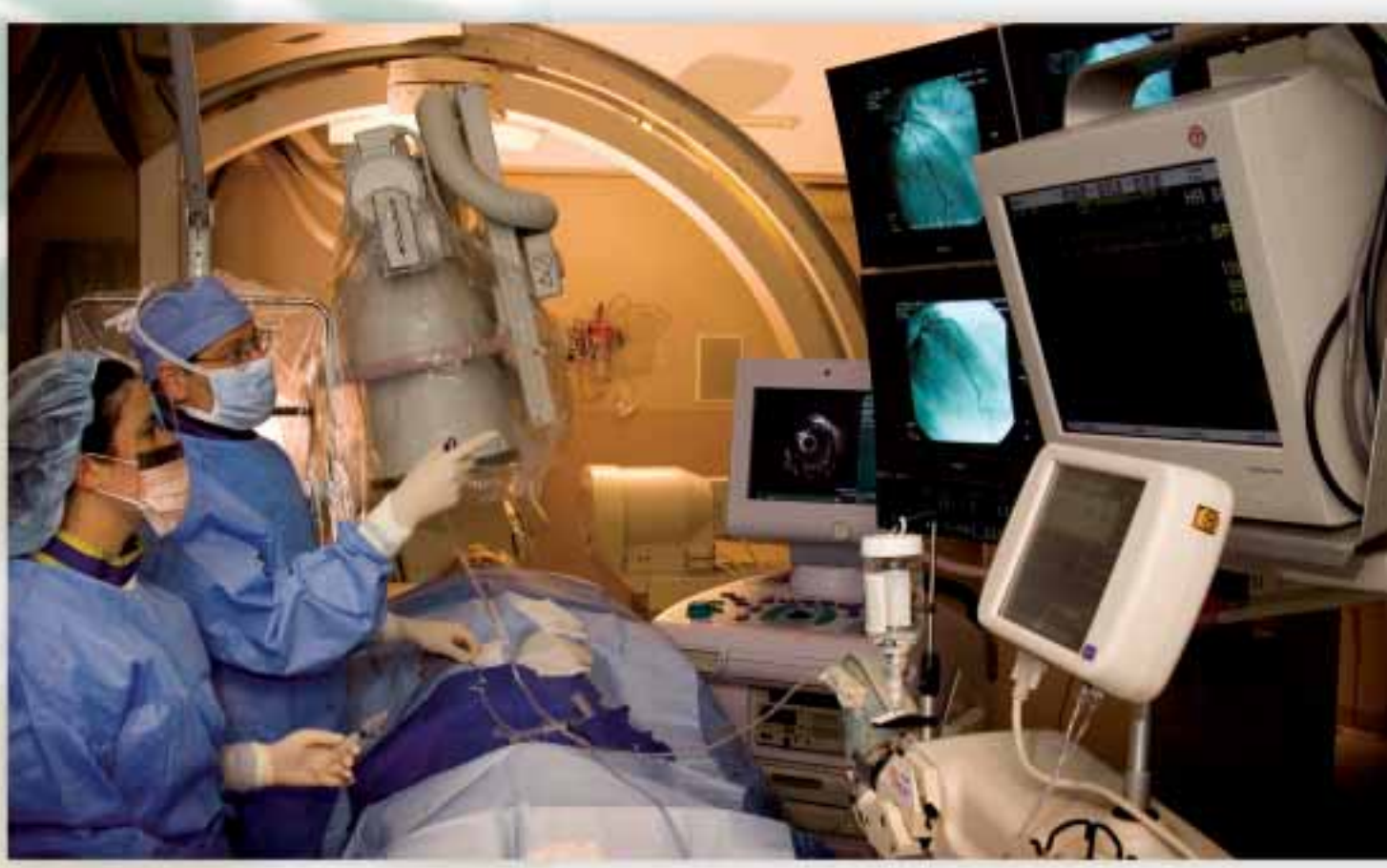
- Have a yearly check up and discuss cardiac risk factors and determine which can be modified
- Increase activity by at least 30 minutes most days of the week
- Quit smoking
- Drop weight (deceasing calorie intake by just 100 calories per day will decrease weight by 10 pounds in a year if everything else is the same)
- Decrease salt to no more than 2300 milligrams of sodium per day
- Drink more water
- Eat more vegetables

For more recommendations, see *www.goredforwomen.org*. This site has a risk calculator that tells you your risk of heart attack, as well as what you need to do. It has many tips for exercise, diet, and suggestions on kicking the smoking habit.

# No One In Tulsa Has Better Success Rates.

**When your heart is on the line, isn't that what you want?**

For over 16 years, the cardiologists and endocrinologists at Oklahoma Heart Institute have successfully treated all kinds of heart problems. Our patients are living proof.



**We provide complete cardiology care for our patients.**

- Interruption of heart attacks
- Balloon angioplasty & stent procedures
- Rhythm ablation procedures
- Pacemakers and implantable defibrillators
- Heart failure management
- Cardiovascular MRI
- Adult ASD/PFO closures
- Prevention of heart disease
- Prevention and treatment of diabetes, hypertension and other metabolic disorders

Oklahoma Heart Institute

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OKLAHOMA HEART INSTITUTE
1265 S. Utica Avenue
Suite 300
Tulsa, OK 74104




# Heart disease doesn't fight fair. We can help you fight back.

The next time you think a heart attack is something that happens to other people, here are a couple of facts to consider.

Heart disease is still the #1 killer of American adults. And more women die each year from heart disease than from all three leading cancers combined.

The good news is, we have more resources than ever to help you fight back. With a unique blend of industry-leading technology and old-fashioned TLC, we can help you with both the prevention and treatment of this deadly disease.

To find out more about cardiac care at SouthCrest, call us or log on to our Web site today.

SouthCrest
Tulsa's Heart Hospital℠

**When seconds count, SouthCrest-Tulsa's Heart Hospital is ready and standing by at 91st and Highway 169.**
**Call 294-DOCS or visit our Web site at www.southcresthospital.com**