MAYO CLINIC

CARDIOVASCULAR UPDATE

CLINICAL CARDIOLOGY AND CARDIOVASCULAR SURGERY NEWS

Volume 8, Number 1, 2010

Perspectives on the Continuing Evolution of Therapy for Atrial Fibrillation

Inside This Issue

Douglas L. Packer, MD

Heart Rhythm Services
Douglas L. Packer, MD, *Director*
Robert F. Rea, MD, *Implantable Device Director*
Michael J. Ackerman, MD, PhD*
Samuel J. Asirvatham, MD
David J. Bradley, MD, PhD
Peter A. Brady, MD
Yong-Mei Cha, MD
Freddy Del Carpio Munoz, MD**
Raul Emilio Espinosa, MD
Paul A. Friedman, MD
Bernard J. Gersh, MD, PhD
Stephen C. Hammill, MD
David L. Hayes, MD
Hon-Chi Lee, MD, PhD
Grace Lin, MD
Margaret A. Lloyd, MD
Michael D. McGoon, MD
Thomas M. Munger, MD
Michael J. Osborn, MD
Douglas L. Packer, MD
Co-burn J. Porter, MD*
Brian D. Powell, MD
Win-Kuang Shen, MD
Andre Terzic, MD, PhD
Donna M. Kania-LaChance, NP
Charissa L. Koski, NP
Jill J. Nagel, PA
**Pediatric Cardiology*
***Mayo Health System*

Atrial Fibrillation: The Problem

Atrial fibrillation (AF) remains the leading arrhythmia in North America, both in numbers of patients affected and the frequency of accompanying sequelae. The prevalence continues to increase, despite progress in the treatment of contributing factors. Although 1% of individuals in their 60s may have AF, the prevalence increases to 10% to 12% in individuals older than 80 years. Currently 2.5 million Americans have AF, but with the aging population and improved cardiovascular survival, this number may increase to 5 million to 6 million by the year 2050. Atrial fibrillation is an increasing burden on the global health care system because of the numbers of patients affected, the impact of stroke, and the cost of both inpatient and outpatient therapy.

In most patients, AF is initially paroxysmal; other patients, particularly those with underlying heart disease, may have more persistent or even chronic AF. Nevertheless, the previously held belief that most paroxysmal AF ultimately progresses to a chronic form has been questioned. Recent studies have suggested that progression occurs in only 20% to 40% of patients over the course of 3 to 5 years, although longer-term data are lacking.

Drug Therapy for AF

Because of stroke risk, most patients require some form of antithrombotic therapy in the form of aspirin or warfarin. Those patients with no risk factors may completely forgo antithrombotic therapy, while the recent ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation have suggested that therapy with aspirin alone is adequate in those at low risk with a CHADS score less than 1. Patients with several risk factors (age >75 years, hypertension, diabetes, prior stroke or transient ischemic attack, left ventricular dysfunction) are at higher risk, necessitating anticoagulation therapy with warfarin. This recommendation is based on an extensive series of large mortality studies consistently demonstrating the benefit of antithrombotic therapy. Despite clear guidelines and extensive experience with thromboembolic events, many patients who would benefit from antithrombotic therapy do not receive it.

Many patients have a rapid ventricular response rate during AF, which is responsible for symptoms. In some cases, rapid rates may also result in tachycardia-induced cardiomyopathy. While this occurs relatively uncommonly in the absence of other heart disease, the possibility of an AF contribution to ventricular dysfunction should be considered in patients who have a rapid ventricular response rate and reduced ejection fraction. Establishing appropriate rate control, however, requires some assessment of rate during rest and exertion. Most guidelines and recent clinical trials recommend that resting rates during AF be less than 90 to 100 bpm, with exercise heart rates maintained at less than 110 to 120 bpm.

Restoration of normal sinus rhythm may be the most effective means of rate control. A number of studies over the past 30 years have shown the usefulness of membrane-active, antiarrhythmic drug therapy for maintaining sinus rhythm. Approximately 30% to 40% of patients treated with antiarrhythmic therapy achieve control over the course of 1 year of follow-up. These data have been validated by larger comparative clinical trials such as the AFFIRM trial. Similar results have been reported in RACE, STAF, and other studies designed to compare rate and rhythm control therapy. Although an increase in mortality may accompany AF, comparative studies examining the utility of rate vs rhythm control therapy have had disappointing results. The AFFIRM trial, for example, showed no difference in overall mortal-

ity over the course of long-term follow-up with either treatment strategy. Similarly, the RACE, PIAF, and STAF studies yielded similar findings.

Additionally, the AF-CHF trial, which involved 1,376 patients with AF, also failed to demonstrate any difference in the end points of total mortality, worsening heart failure, or the composite of cardiovascular mortality, stroke, or worsening heart failure. Furthermore, bradycardia and rehospitalization were more common in those treated with antiarrhythmic drugs intended to maintain sinus rhythm. These findings may have been attributable to the following scenarios:

1. Other factors, including underlying disease, were responsible for the morbidity and mortality in AF patients, such that AF was a risk marker for mortality, rather than a risk factor.

2. A benefit from treatment with antiarrhythmic drug therapy may have been masked by the occurrence of organotoxicity or proarrhythmic events.

3. Silent AF in patients treated with rhythm control or undetected sinus rhythm in those treated with rate control drugs may have decreased the ability of the AF-CHF trial protocol to detect real differences in overall outcomes.

Despite the pessimism generated by these studies, the results of the recent ATHENA trial have encouraged reconsideration of drug therapy for AF. In comparing the class III antiarrhythmic agent dronedarone with placebo in more than 4,500 patients, this study showed a 24% reduction in cardiovascular hospitalization or mortality, a 29% decrease in cardiovascular mortality, and a 26% decrease in cardiovascular hospitalization with active therapy at 22±5 months of follow-up. There were significantly lower rates of acute ischemic syndrome and stroke with dronedarone therapy when rates of proarrhythmia and heart failure were also low. These data support the potential for cancellation of benefit from drug therapy by untoward toxicities of drug interventions, although the control rate with this drug is less than that of amiodarone.

Nonpharmacologic Therapy for AF

Atrial fibrillation ablation has been shown in a number of observational studies to be of benefit in eliminating AF, reducing its frequency, and improving patients' quality of life (Figure). In most studies, 75% to 85% of patients with paroxysmal AF have been rendered free of this arrhythmia over the course of 1 year of observation. In patients with persistent or chronic AF and those with underlying disease, AF is decreased in 10% to 20% of patients. After longer-term follow-up, the ablation of patients with more advanced underlying disease, and a more critical view of treatment benefit without additional antiarrhythmic drugs or repeat ablative intervention, these overall success rates are lower than the more optimistic values touted in the first part of this decade.

Douglas L. Packer, MD, director of the Section of Electrophysiology at Mayo Clinic in Rochester, Minnesota, and the 2010-2011 president of the Heart Rhythm Society, reviewed outcomes of ablation at Mayo Clinic. He found that over 2 years of long-term follow-up the response to ablation was excellent in more than 75% of patients with paroxysmal AF. Patients with persistent and chronic AF likewise have shown enhanced benefit, although a more aggressive ablative approach has been required. In those with paroxysmal AF, ablation for the isolation of pulmonary veins may be sufficient, while wider-area circumferential ablation with additional linear ablation or energy delivery directed at the underlying substrate has been required. Additional review demonstrated notable benefit in patients with underlying dilated cardiomyopathies. In many patients, not only was AF eliminated, but a substantial improvement in ejection fraction was observed, particularly in those with nonischemic left ventricular dysfunction.

CLINICAL TRIALS

Clarification of Optimal Anticoagulation Through Genetics (COAG) Trial

A randomized, multicenter, double-blind clinical trial to evaluate the efficacy of clinical plus genetic information to guide the initiation of warfarin therapy and to improve anticoagulation control for patients. The protocol includes

- Warfarin therapy for at least 3 months
- Target INR 2-3
- Study enrollment before receiving the first dose
- Follow-up visits at the Gonda 4 Thrombophilia Clinic

For more information, contact Nancy Lexvold, RN: 507-255-7013
Robert D. McBane, MD: 507-266-3964

Anatomy vs Physiology-Guided Ablation for Atrial Fibrillation

A study to establish the differential success rate for complete elimination of atrial fibrillation (AF) with combined wide-area circumferential ablation and linear ablation vs combined wide-area circumferential ablation and complex fractionated atrial electrogram (CFAE) ablation. Inclusion criteria are

- History of symptomatic persistent/permanent AF
- Patient recommended for catheter-based, wide-area pulmonary vein isolation
- Available for 13 months of follow-up after ablation.

For more information, contact Nancy Lexvold, RN: 507-255-2501
Yong-Mei Cha, MD: 507-255-2501

Several recent studies have gone beyond observational reports to compare the efficacy of ablative vs drug therapy in patients with paroxysmal AF. The CACAF, RAAFT, APAF, and A4 trials demonstrated a 76% recurrence rate in patients treated with drug therapy vs 24% recurrence in those treated with ablative intervention. These studies were limited, however, because of shorter-term follow-up and the exclusion of patients with underlying disease or advancing age. The impact of ablative therapy on the overall cost of health care is less certain.

Indications for Ablative Intervention

Even in the absence of cost data, there is sufficient information from observational studies, meta-analyses, and comparative studies to support more widespread application of AF ablation in patients failing a single antiarrhythmic drug because of AF recurrence or intolerability. The Guidelines for the Management of Patients With Atrial Fibrillation, endorsed by the American Heart Association and the American College of Cardiology, recommend this nonpharmacologic approach as second-line therapy. Similarly, the Expert Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-up, developed by the Heart Rhythm Society and endorsed by the AHA and ACC, comes to a similar conclusion. A number of centers are moving toward a primary therapy role for ablation, as success rates increase and complication rates decline.

In clinical practice, it is crucial to be clear on the indication for any intervention in AF patients. Of primary importance is the need to prevent stoke or other peripheral thromboembolic events. Warfarin therapy has been best demonstrated to reduce this risk. Additional studies will be required to establish a benefit in this area with membrane-active drug therapy or ablation. The role of therapy to establish and maintain sinus rhythm in patients with left ventricular dysfunction is acceptably clear-cut in recent ablation studies. Of greatest importance is the need to reduce or eliminate AF in symptomatic patients. This remains the primary indication for ablative intervention. Patients who have failed to respond to 1 drug may be good candidates for intervention, although the anticipated success rate depends on the type of AF and the presence of underlying left ventricular or left atrial dysfunction. Age appears to be a less important issue than previously thought. Patients with underlying valvular heart disease and hypertrophic cardiomyopathy have excellent short-term outcomes although much more aggressive procedures are required.

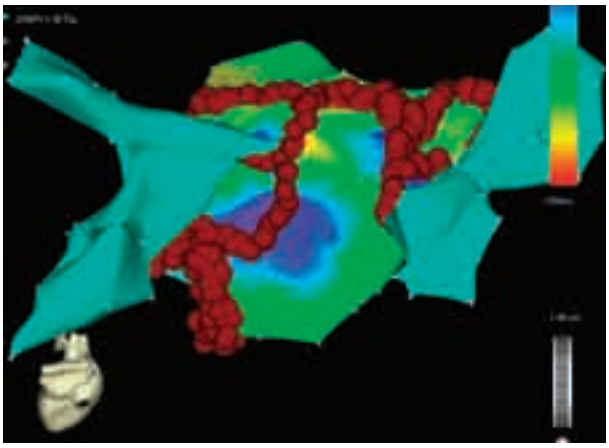

Figure. Computer-generated map of left atrial activation. Red dots indicate ablation sites.

Experience With Pulmonary Vein Isolation at Mayo Clinic

Since 1997, more than 2,500 pulmonary vein isolation procedures for the treatment of AF have been performed at Mayo Clinic in Rochester. In the most recent review, 73% of patients with paroxysmal AF and 66% of patients with persistent AF maintained sinus rhythm for 1 year after the procedure without antiarrhythmic drug therapy. Another 10% of patients with paroxysmal AF and 11% with persistent AF were able to maintain sinus rhythm with previously ineffective antiarrhythmic drug therapy. The procedure was repeated in 13% of patients. Complication rates have been low, with severe pulmonary vein stenosis occurring in 0.8% and cardiac tamponade occurring in 2.1%. There have been 2 atrioesophageal fistulas. The majority of patients (71%) were younger than 65 years.

Ongoing Large Multicenter Trials

While observational studies and limited randomized comparisons demonstrate symptomatic improvement in patients undergoing ablation and early data suggest a cost benefit, larger long-term studies are required to establish a mortality benefit and a reduction in stroke risk. As a result, the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy in Atrial Fibrillation) trial was designed. This study, originating from Mayo Clinic, will examine the benefit of ablation vs drug therapy in 3,000 patients with AF enrolled in 140 centers around the world. Mayo Clinic recently received $48 million in grants from the National Institutes of Health and from industry to lead this collaborative effort. The study will also establish long-term complications of AF treatment and their prevention by appropriate ablative or drug therapy, and determine the actual impact of the arrhythmia and its treatment on a patient's quality of life and health care costs.

Until these studies are completed, the application of ablative intervention will continue to be guided by a decade of observational studies and smaller randomized clinical trials, as well as information coming from national and international ablation registries.

New Insights Into the Mechanisms of Degenerative Aortic Valve Stenosis

Jordan D. Miller, PhD

Risk factors for aortic valve stenosis (AVS) are similar to those for atherosclerosis and include increasing age, male sex, hypercholesterolemia, and hypertension. More than 25% of patients over the age of 65 years have extensive aortic valve sclerosis, while as many as 10% of individuals in this age range have AVS.

In the past, AVS was considered a passive, degenerative process, and this perspective has changed and it is now viewed as an active, dynamically regulated process. Within the past 15 years, 3 major discoveries have contributed to this shift. First, detailed histopathologic studies have identified the presence of osteoblast-like cells, osteoclast-like cells, and actual bone matrix in tissue explanted during valve replacement surgery. Second, studies in animals have demonstrated that pro-osteogenic pathways are activated early in valve disease and that calcification can be prevented by administering lipid-lowering therapy in the early stages of valve disease. Finally, investigations by Jordan D. Miller, PhD, a researcher in the Division of Cardiovascular Surgery at Mayo Clinic in Rochester, Minnesota, have revealed that the initiation of lipid-lowering therapy in mild valve disease markedly reduces pro-osteogenic signaling in the aortic valve and halts progression to severe AVS. Collectively, these data provide strong evidence that the progression of aortic valve disease—when caught early enough—is in fact a malleable process.

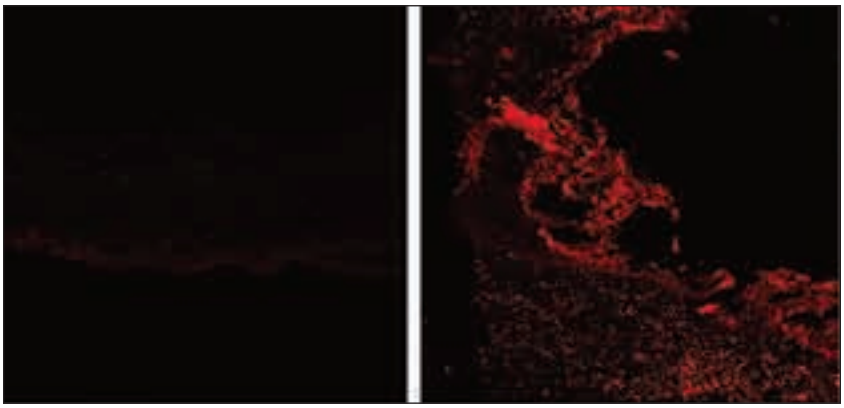

Figure 1. Levels of oxidative stress in a normal human aortic valve (left) and in the calcified region of a stenotic aortic valve excised at the time of valve replacement surgery (right). Increased oxidative stress is indicated by the intense red fluorescence, located almost exclusively in the calcified and pericalcific regions of the stenotic aortic valves.

A particularly interesting observation has been that calcium deposition and pro-osteogenic signaling in stenotic valves are both associated with increases in oxidative stress (Figure 1). Subsequently, Dr Miller and his colleagues demonstrated that increased oxidative stress in AVS is derived from 2 major sources: 1) a profound suppression antioxidant enzyme expression and activity in the calcified regions of the valve, and 2) dysfunctional nitric oxide synthases, which produce superoxide instead of nitric oxide. Interestingly, this differs fundamentally from what has been described in atherosclerotic plaques, where increases in oxidative stress are attributed to increases in NAD(P)H oxidase activity (and are actually associated with increases in antioxidant enzyme expression). Consequently, a major focus of Dr Miller's laboratory is to determine the role of increased oxidative stress in the initiation and progression of aortic valve disease and atherosclerosis and also to determine whether the alterations in antioxidant enzyme expression are adaptive or maladaptive.

Furthermore, recent studies have shown that the subcellular compartmentalization of reactive oxygen species plays a critical role in the biological effects of altering antioxidant mechanisms. For example, reducing the cytosolic isoform of superoxide dismutase slows the progression of atherosclerosis in mice, whereas reducing the mitochondrial isoform of superoxide dismutase accelerates the progression of atherosclerosis in mice.

To determine whether increases in mitochondrial oxidative stress are an independent contributor to the progression of AVS, Dr Miller crossed mice that are deficient in a mitochondrial antioxidant enzyme with hypercholesterolemic mice that develop AVS. As shown in Figure 2, at 18 months of age, wild-type mice have only modest AVS (peak velocity of about 2.7 m/s). However, mice with increases in mitochondrial oxidative stress have far greater impairments in aortic valve function (peak velocity of about 4.5m/s). These preliminary studies suggest that mitochondrial oxidative stress may play a critical role in determining the rate of progression of AVS, and Dr Miller is currently conducting studies to determine whether mitochondria-targeted antioxidant therapies slow the progression of AVS.

As AVS is most common in older patients, it is critical that interventions aimed at slowing the progression of valvular calcification do not alter skeletal ossification. Thus, Dr Miller has also examined changes in skeletal ossification that occur with altera-

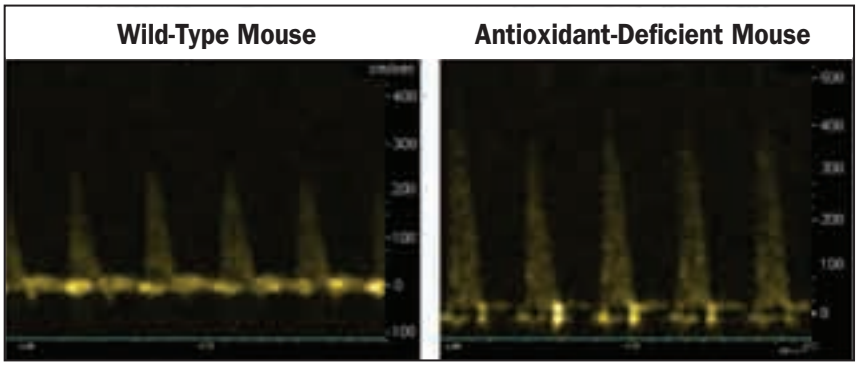

Figure 2. Echocardiographic approaches are used to routinely evaluate aortic valve function in mice with valve disease. The left panel depicts a hypercholesterolemic mouse with normal antioxidant enzyme expression (peak velocity about 2.7 m/s), whereas the right panel depicts a hypercholesterolemic mouse with reduced mitochondrial antioxidant gene expression (peak velocity about 4.5 m/s).

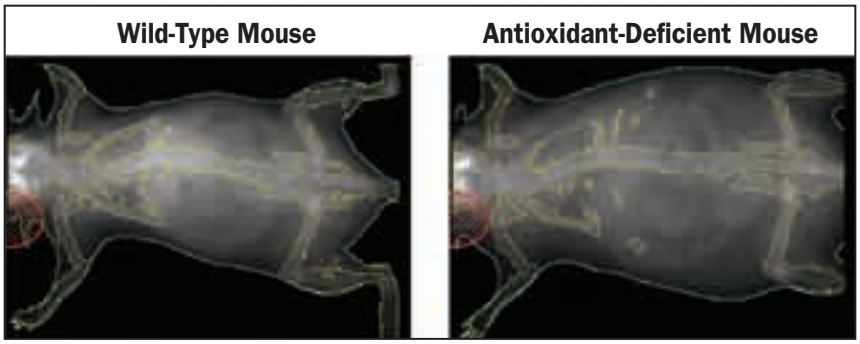

Figure 3. Dual x-ray absorptiometry evaluation of bone mineral density and body composition in same mice with valve disease. The yellow outlined area depicts bone/calcified tissue. Quantitation of bone mineral density in the femur of these mice showed that bone mineral density decreased from 81.2 mcg/cm² in the wild-type mouse to 71.7 mcg/cm² in the mouse deficient in mitochondrial antioxidant enzymes. These preliminary data suggest that antioxidant therapies targeted to the mitochondria may be an effective means to reduce valvular and vascular calcification while reducing age-related bone loss.

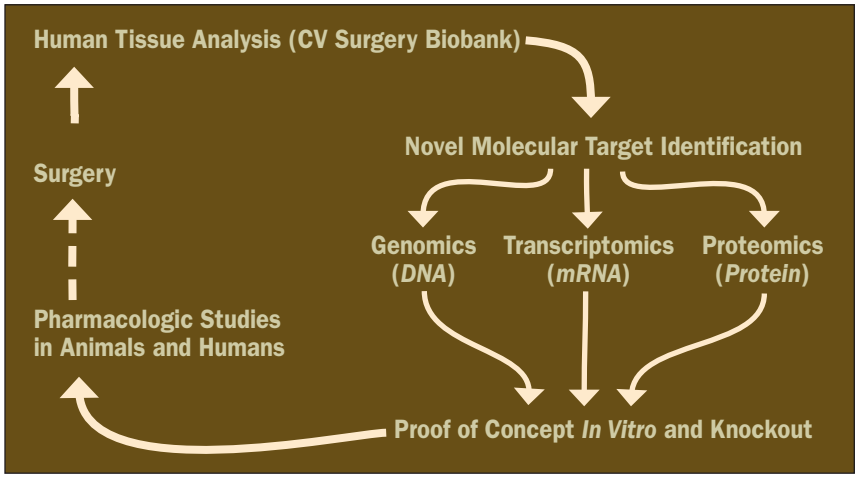

Figure 4. The research model used by the Division of Cardiovascular Surgery at Mayo Clinic in Rochester. A large-scale biobanking effort is being implemented that will allow researchers to conduct molecular screens on human tissue to identify novel molecules contributing to cardiovascular disease. Genetically modified mice and in vitro models are used to identify mechanisms through which these molecules drive disease processes. Studies in humans and animal models can then be conducted to identify pharmacologic interventions that will slow or reverse the progression of disease.

tions in mitochondrial oxidative stress. In contrast to what has been observed in valvular tissue, losses in mitochondrial antioxidant enzyme activity markedly reduce bone mineral density and content in mice (Figure 3). Collectively, the use of mitochondria-targeted antioxidants appears to be a promising avenue to pursue to slow valvular calcification while increasing skeletal ossification.

While much effort is focused on understanding the role of oxidative stress in the development of cardiovascular disease, other work in Dr Miller's laboratory involves screening human tissue to identify novel adaptive and maladaptive changes that occur with the progression of AVS. Along these lines, a cardiovascular tissue biobank is being developed in the Division of Cardiovascular Surgery (Figure 4). Specifically, researchers will be acquiring blood and tissue samples for the isolation of DNA, RNA, and protein from patients undergoing surgery at Mayo Clinic in Rochester. By conducting large-scale genomic, transcriptomic, and proteomic screening of human tissue, Dr Miller hopes to identify novel mediators of valvular calcification and atherosclerosis, thoroughly investigate the mechanisms of action of such mediators in genetically altered mice and in vitro, and deepen the understanding of fundamental differences between AVS and atherosclerosis.

While it has been fascinating to unveil some of the major pro-osteogenic signaling pathways that regulate valvular and intimal plaque calcification, the greatest challenge is in the translation of these discoveries to clinically relevant interventions. Although "knocking down" pro-osteogenic genes with gene therapy was once thought to be a useful tool to slow the progression of valvular calcification, it was quickly realized that the absence of a method to provide local, highly efficacious treatment will likely result in severe bone loss and worsened osteoporosis in affected patients. Thus, efforts have been directed toward identifying reciprocal regulators of ectopic and skeletal ossification. This is particularly feasible in mouse models of AVS, where both soft tissue and skeletal tissue can be examined at various time points during the progression of disease. By using integrative systems approaches to understanding disease, Dr Miller hopes his research will develop clinically relevant therapies that will not only slow the progression of cardiovascular disease, but also slow age-related reductions in bone mass and improve the quality of life for patients.

Questions for *Cardiovascular Update*, send us an e-mail to CVUpdate@mayo.edu.

New Statin Intolerance Clinic

Stephen L. Kopecky, MD

Cardiovascular Health Clinic
Randal J. Thomas, MD, ***Director***
Thomas G. Allison, PhD
Thomas Behrenbeck, MD, PhD
Frank V. Brozovich, MD, PhD
Gerald T. Gau, MD
Bruce D. Johnson, PhD
Birgit Kantor, MD
Stephen L. Kopecky, MD
Iftikhar J. Kullo, MD
Francisco Lopez-Jimenez, MD
Ray W. Squires, PhD
Martha A. Mangan, CNP

The first 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, lovastatin, obtained approval from the US Food and Drug Administration in 1987. Now, after a little more than 2 decades of clinical availability, the "statins," as this group of drugs is more commonly known, have emerged at the forefront of pharmacologic treatment of high cholesterol. Statin therapy is estimated to be indicated in up to 25% of the US adult population, and therapy significantly reduces the incidence of heart attack, stroke, and cardiovascular death. Because hypercholesterolemia is largely asymptomatic, any unpleasant effects of pharmacologic agents used to manage it can undermine patient compliance. In several cohort studies, the reported rate of adherence to statin therapy at 1 year ranged from 26% to 85%, with a rapid decline in adherence rates typically observed within the first few months. In the Lipid Research Clinics Coronary Primary Prevention Trial, the reduction in risk of coronary events was 39.3% among patients fully compliant with lipid-lowering therapy, compared with risk reductions of 10.9% and 26.1% among patients with approximately 25.0% and 50.0% adherence, respectively. Also, in the West of Scotland Coronary Prevention Study of men without a history of coronary artery disease, the risk of all-cause mortality was reduced 33% more among those who took 75% or more of their prescribed medication compared with those taking less than 75%.

The majority of adverse effects reported to be associated with statins are musculoskeletal, hepatic, gastrointestinal, and psychiatric. The most prevalent are musculoskeletal, and the spectrum of statin-associated myotoxicity ranges from the more common but less severe myalgia (5%-10%) to the less common but more severe myopathy (0.1%) and its potentially fatal complication, rhabdomyolysis (0.01%). Among patients who develop myalgias, the most common symptom is muscle aches in slightly more than half and clinically noticeable muscle weakness in one-third, while 10% report cramping as the predominant symptom. Muscle-related symptoms in clinical trials, which involve highly selected patient groups with high treatment adherence and statin tolerance, do not reflect the true prevalence of myalgia in the clinic, as evidenced by findings in observational studies. Although only 3% of patients in randomized research studies developed intolerance, in clinical practice up to 15% of outpatients receiving statins have reported muscle pain. One reason that higher rates of adverse effects are observed in general use is that many clinical studies involving statins had a "run-in" phase and excluded patients if intolerance to the drug developed. Clinical trial protocols also often exclude patients who may be more prone to myopathy (such as the elderly) or who may have abnormal liver test results at baseline.

Among patients taking high-dose statins (atorvastatin, 40-80 mg; extended-release fluvastatin, 80

IN THE NEWS

Mayo Clinic Testing Shockwave Therapy for Refractory Angina

Mayo Clinic in Rochester, Minnesota, is 1 of 3 sites in the United States (the only one in the Midwest) testing shockwave therapy for refractory angina (chronic chest pain). This therapy is being examined as a potential treatment for patients whose daily life is limited by chest pain and who are not candidates for a stent procedure or surgery. Many of these patients have already had stents placed or coronary artery bypass grafting and are receiving optimal medical therapy, but are still having symptoms.

High-energy shockwave therapy has been effective in increasing tissue blood supply in animal models. This study—Extracorporeal Shockwave Therapy for the Treatment of Refractory Angina Pectoris—is a phase 1 clinical trial to test the safety and efficacy of the treatment. Patients are not randomized. Patients have focused lower-energy shockwaves directed at segments of the ventricular muscle lacking adequate blood supply. The idea is to stimulate angiogenesis that improves tissue blood supply and thus reduce chest pain. Treatments are painless, last about an hour, and extend over a 9-week treatment schedule.

For additional information, contact the principal investigator, Guy S. Reeder, MD, at 507-538-1469.

mg; pravastatin, 40 mg; or simvastatin, 40-80 mg), the proportion of patients reporting muscle-related symptoms is even higher—5% in those taking extended-release fluvastatin vs 10% of those taking high-dose pravastatin, 15% for atorvastatin, and 18% for simvastatin. The median time to onset of muscle symptoms is 1 month after either initiation of statin therapy or titration to a higher dosage, although approximately 15% of patients have symptoms that appear more than 6 months after the start of treatment. When discomfort occurs, it is widespread in 60% of patients, with 24% reporting pain "all over." Pain is more common in the lower extremities, including the thighs and calves, than in the upper extremities or trunk.

Although more than 100,000 patients have been studied in randomized trials of statins, research on the mechanism or treatment of statin intolerance has been limited. Adding to the uncertainty, the National Lipid Association, US Food and Drug Administration, and ACC/AHA/NHLBI have all come out with different definitions of statin-associated myalgia, myopathy, and myositis.

In the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, patients with a family history of muscle pain during lipid-lowering therapy had double the risk of muscle-related symptoms compared with patients who did not have this family history. This implies the prospect of identifying particular genes or single-nucleotide polymorphisms that may increase the risk of myopathy or reduce the maximal tolerated dose.

To better care for these patients, Mayo Clinic in Rochester, Minnesota, has established a Statin Intolerance Clinic as part of the Cardiovascular Health Clinic to better diagnose, risk stratify, and treat patients with statin-associated adverse effects. In addition to evaluating muscle symptoms with a validated questionnaire, standard work-up includes levels of creatine kinase and vitamin D, along with renal and thyroid function testing. When appropriate, genetic testing for statin efficacy and potential toxicity, proximal muscle strength evaluation, and percutaneous outpatient muscle biopsy are important assessment tools. "Treatment depends on the individual patient and the patient's history of statin intolerance symptoms and may include either changing the dose or type of statin or switching to a nonstatin agent to treat hyperlipidemia," according to Stephen L. Kopecky MD, director of the new Statin Intolerance Clinic. Other treatment options include supplements to reduce the myotoxicity symptoms attributable to impairment of fatty acid oxidation or mitochondrial dysfunction that result from the statin therapy. Patients who are either on statin therapy or have a family history of severe reactions to these agents but have never actually taken a statin drug can be referred to the Statin Intolerance Clinic by calling 507-538-6857.

RECOGNITION


Rick A. Nishimura, MD


Virend Somers, MD, PhD


Timothy M. Olson, MD


Stephen C. Hammill, MD


Vuyisile T. Nkomo, MD

Mayo Clinic in Rochester announced the recipients of the 2009 Department of Medicine Education and Research Recognition Awards. Honorees from the Division of Cardiovascular Diseases included Rick A. Nishimura, MD, Lifetime Achievement Award for Outstanding Contributions in Medical Education; Virend Somers, MD, PhD, Outstanding Investigator Award; and Timothy M. Olson, MD, Landmark Contribution to the Literature Award.

Stephen C. Hammill, MD, consultant in the Division of Cardiovascular Diseases, received the 2009 Distinguished Mayo Clinician Award.

Vuyisile T. Nkomo, MD, Division of Cardiovascular Diseases, received a Champion of Diversity award January 27, 2010, at the Partner Appreciation Celebration hosted by the College of Medicine Office for Diversity at Mayo Clinic.

Upcoming Courses

Continuing Medical Education, Mayo Clinic

To request additional information or to register, unless noted otherwise, please call 800-323-2688, e-mail cme@mayo.edu, or visit www.mayo.edu/cme.

Controversies in Cardiovascular Disease: Practical Approaches to Complex Problems: Medical and Surgical
May 8-9, 2010, St Paul, MN

Nicotine Dependence Center 17th Annual Conference: A Focus on the Changing Tobacco Landscape
May 24-26, 2010, Rochester, MN

Cardiology Update in Sedona
Aug 6-8, 2010, Sedona, AZ
Phone: 480-301-4580; e-mail: mca.cme@mayo.edu

Success With Failure: New Strategies for the Evaluation and Treatment of Congestive Heart Failure
Aug 8-10, 2010, Whistler, BC

Echocardiographic Symposium at Vail: New Technologies, Live Scanning, and Clinical Decision Making
Aug 15-19, 2010, Vail, CO
Phone: 507-284-0536; e-mail: echocme@mayo.edu

Mayo Echocardiography Review Course for Boards and Recertification
Aug 21-24, 2010, Rochester, MN

Electrophysiology Review for Boards and Recertification
Aug 25-28, 2010, Rochester MN

Pediatric Cardiology 2010 Board Review Course
Aug 29-Sep 3, 2010, Dana Point, CA

Mayo Cardiovascular Review Course for Cardiology Boards and Recertification
Sep 25-30, 2010, Rochester, MN

Mayo Interventional Cardiology Board Review
Oct 1-3, 2010, Rochester, MN

26th Annual Echocardiography in Pediatric and Adult Congenital Heart Disease
Oct 10-13, 2010, Rochester, MN
Phone: 507-284-0536; e-mail: echocme@mayo.edu

Coronary Artery Disease: Prevention, Detection and Treatment
Oct 22-24, 2010, Las Vegas, NV

10th Annual Nutrition and Wellness in Health and Disease
Nov 4-5, 2010, San Francisco, CA

The Heart Beat of Cardiology: From Stethoscope to Echoscope
Dec 9-11, 2010, Chicago, IL
Phone: 507-284-0536; e-mail: echocme@mayo.edu

Continuing Medical Education, Cosponsored With American Society of Echocardiography

Sites and Sounds of Echocardiography in the Heart of the Big Apple
May 27-30, 2010, New York, NY
Phone: 507-261-4270; e-mail: info@medmeetingsetc.org

5th Annual The Beat Goes On
Sep 23-26, 2010, Orlando, FL
Phone: 336-716-4505; e-mail: lnixon@wfubmc.edu

Other Education Opportunities

Heart Rhythm 2010 31st Annual Scientific Sessions
May 12-15, 2010, Denver, CO
http://www.hrsonline.org/

RECOGNITION

C. Noel Bairey Merz, MD, presented the fourth annual Gerald T. Gau lecture on January 27, 2010 (shown here with Dr Gau). She is Women's Guild Endowed Chair in Women's Health and medical director of the Cedars-Sinai Women's Health Program, Women's Heart Center, and the Preventive and Rehabilitative Cardiac Center at Cedars-Sinai Medical Center. She is professor of medicine at UCLA.

NEW AT MAYO CLINIC

New Online Scholarly Opportunities for Physicians

Are you enrolled? Online Services for Referring Physicians is a secure, user-friendly Web site that provides a window into the care of your patients referred to Mayo Clinic through Online Services. It allows health care providers to make appointment requests electronically 24 hours a day, 7 days a week and view/print Mayo Clinic medical documents for patients referred through Online Services. These reports can include consultative and surgical notes, laboratory and radiology reports, and hospital discharge summaries.

To find Online Services or to view a demonstration, go to www.mayoclinic.org/online-services and click on the Physicians Outside Mayo Clinic tab.

Nichole Nicholas at the Referring Physicians Office is available to address concerns by phone at 800-881-9764 or by e-mail at nicholas.nichole@mayo.edu.

Locations and Phone Numbers

Mayo Clinic is located in Scottsdale/Phoenix, Arizona, Jacksonville, Florida, and Rochester, Minnesota.

Arizona

General Information:	480-301-8000
Fax:	480-301-7006
Appointments:	800-446-2279 (toll-free)

Florida

General Information:	904-953-2000
	904-953-2300 (TDD)
Appointments:	904-953-2272
Fax:	904-953-2898
International Services:	904-953-7000
Fax:	904-953-7329

Minnesota

General Information:	507-284-2511
	507-284-0161 (fax)
	507-284-9786 (TDD)
Appointment Office:	507-538-3270
International Medicine:	507-284-2899
	507-284-3891 (fax)

Mayo Clinic Cardiovascular Update

Editor: Margaret A. Lloyd, MD

Editorial Board: David L. Hayes, MD, Hartzell V. Schaff, MD, Frank Cetta, MD, Gurpreet S. Sandhu, MD, PhD, Hugh M. Martin, Marjorie G. Durhman

Managing Editor: Jane C. Wiggs, MLA, ELS

Art Director: Marjorie G. Durhman

Photography: Amanda R. Durhman

Cardiovascular Update is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
www.mayoclinic.org