Oklahoma Heart Institute

volume 2 • number 3 • summer 2006

Take a Bite out of Diabetes

by Tobie L. Bresloff, MD

Dual Platelet Therapy: Not for Everyone

by Frank J. Gaffney, MD

Acute Decompensated Heart Failure and Nesiritide

by Alan M. Kaneshige, MD

Closing PFOs to Prevent Refractory Migraine Headaches

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

When It Comes To Heart Disease, Don't Act Like A Lady.

Cardiovascular disease is the number one killer of women. More women die from heart disease than the next seven causes of death combined. In Oklahoma alone, more than 5,000 women die of heart disease each year.*

But you don't have to become a statistic. Stand up and fight heart disease. Punish it with a low-fat, low-sodium diet. Starve it by not smoking. Make it sweat with regular exercise. And bring heart disease to its knees with the help of Hillcrest Medical Center.

Hillcrest Medical Center offers comprehensive cardiovascular services, including research involving new drugs and devices, diagnostics, interventional and non-invasive procedures, surgery, education and rehabilitation programs. We also have Tulsa's only outpatient heart failure care center, a comprehensive clinic that helps patients stay healthier and out of the hospital, while improving their quality of life.

Call (918) 579-NEWS to learn more about preventing and managing heart disease.

Rebecca L. Smith, MD
Noninvasive Cardiologist
Hillcrest Medical Center

Hillcrest℠
Earned Leadership

1120 South Utica Avenue
(918) 579-NEWS
www.hillcrest.com

**Oklahoma Health Department*

OKLAHOMA HEART INSTITUTE AT UTICA
1265 S. Utica Avenue
Suite 300
Tulsa, OK 74104
Phone: 918.592.0999
Fax: 918.592.1021

OKLAHOMA HEART INSTITUTE AT SOUTHPOINTE
9228 S. Mingo
Suite 200
Tulsa, OK 74133
Phone: 918.592.0999
Fax: 918.878.2499

Oklahoma Heart Institute

In this issue

Cover photo: Butterflies in a Tulsa summer garden. Photo by Rick Stiller

Created by Publishing Concepts, Inc.
Virginia Robertson, President • vrobertson@pcipublishing.com
14109 Taylor Loop Road • Little Rock, AR 72223 / 501.221.9986 / 800.561.4686
For advertising information contact: Suzanne Ramsel at 501.221.9986 or 800.561.4686
sramsel@pcipublishing.com visit our website www.pcipublishing.com
Edition 7

To Our Readers

CARDIOVASCULAR DISEASE IS is the number one cause of death in the United States and the world. Over the past decade, some of the greatest advances in cardiology have been in the area of prevention. Risk factor modification has turned out to be more effective than anticipated. Large clinical trials continue to substantiate the tremendous benefit of aggressive risk factor modification. The current issue of Oklahoma Heart Magazine summarizes the latest findings regarding risk factor medication from large clinical trials. These trials address issues ranging from how aggressive we should be in lowering blood pressure and cholesterol, to whether there is any benefit from lowering homocysteine levels.

In addition, Dr. Bresloff, from the Division of Endocrinology, discusses the newest medications for treating diabetes mellitus, one of the major risk factors for cardiovascular disease. With the newer medications, glycemic control can now be achieved without significant increases in weight.

The number one discharge diagnosis for acute care hospitals in the United States continues to be heart failure. Dr. Kaneshige discusses the use of nesiritide for acute decompensated heart failure and the recent controversy about when it should be used.

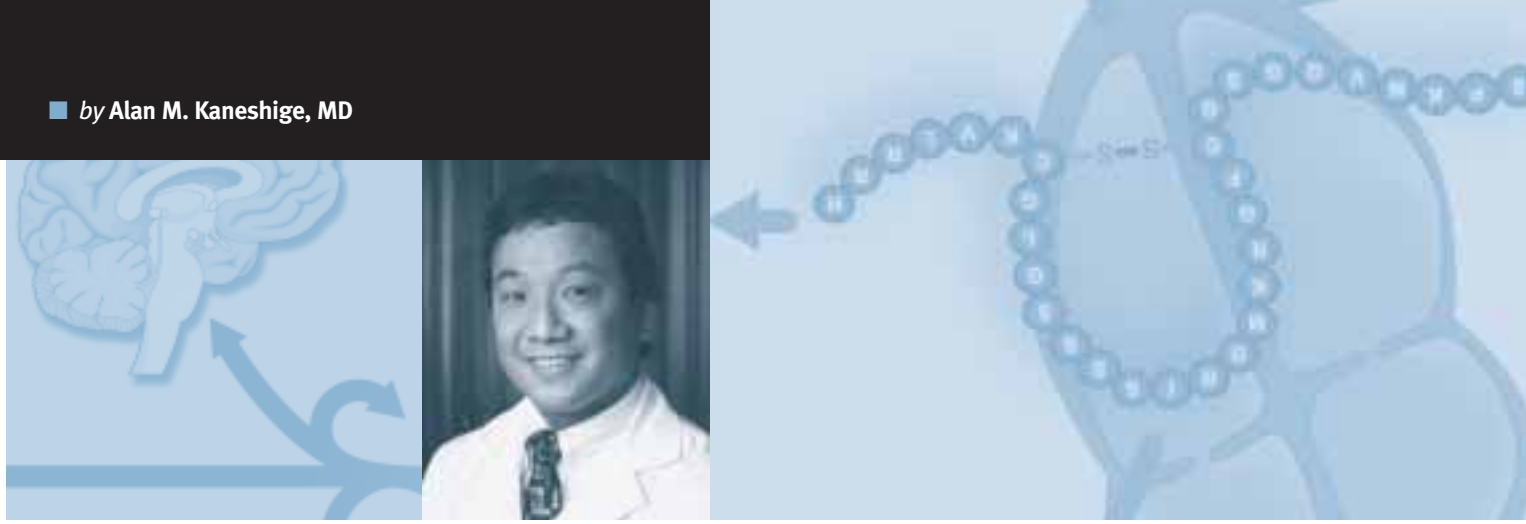
Dr. Gaffney highlights recent results from the CHARISMA Trial, which looked at dual platelet therapy with aspirin and clopidogrel, in both secondary and primary prevention treatment strategies. Dual platelet therapy may not be for everyone.

This issue of Oklahoma Heart Institute magazine also includes the report of the MIST trial, which looked at the value of closing PFOs (patent foramen ovale) with percutaneous closure devices in order to prevent refractory migraine headaches.

As always, the Research Corner provides information on the newest therapies being investigated at Oklahoma Heart Institute. We hope you enjoy these articles and welcome any comments or suggestions in regard to magazine content.

Sincerely,
Wayne N. Leimbach, Jr., MD

by Alan M. Kaneshige, MD

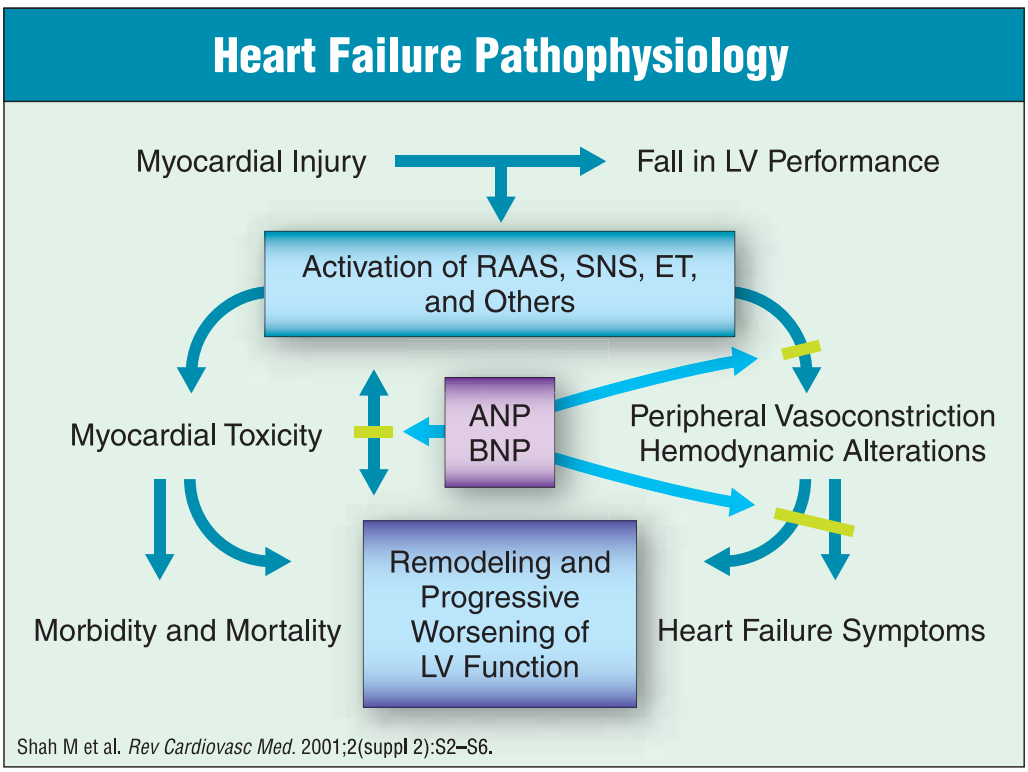


Acute Decompensated Heart Failure and Nesiritide

There have been many major advances in understanding the pathophysiology and management of chronic heart failure. Clinical and laboratory research has led to the usage of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone inhibitors. These agents have significantly reduced the risk of morbidity and mortality in chronic heart failure. Despite these advances, approximately 1 million patients will be hospitalized this year with acute decompensated heart failure (ADHF). The major expenditure for heart failure is hospitalization, with approximately $25 billion spent annually on inpatient management of ADHF. Any therapy that could improve diagnosis and treatment and shift care to the outpatient would have a favorable impact on the massive economic costs associated with this disease.

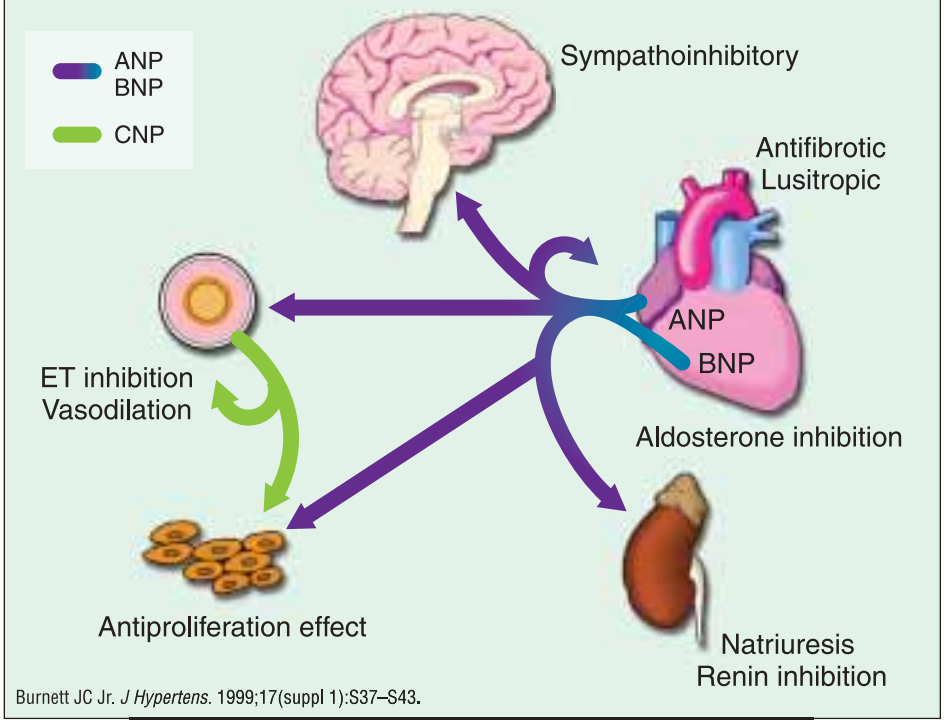
In the past, tools to diagnose ADHF beyond the history and physical examination were limited. The B-type natriuretic peptide (BNP) blood test marks a significant advance in the evaluation of patients presenting with symptoms that may represent acute heart failure. The BNP level also has prognostic value. Elevated BNP levels are associated with increased mortality and worsening clinical outcomes.

The understanding of hemodynamic mechanisms of heart failure (HF) has led to the development of new agents to treat ADHF. The B-type natriuretic peptide, in addition to being a reliable biomarker for acute and chronic heart failure, has also become a reliable treatment for ADHF. The protein is mainly synthesized in, and released from, the ventricular myocardium. Other members of the human natriuretic peptide



Shah M et al. *Rev Cardiovasc Med.* 2001;2(suppl 2):S2–S6.

Natriuretic Peptide System



Burnett JC Jr. *J Hypertens.* 1999;17(suppl 1):S37–S43.

family include atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP).

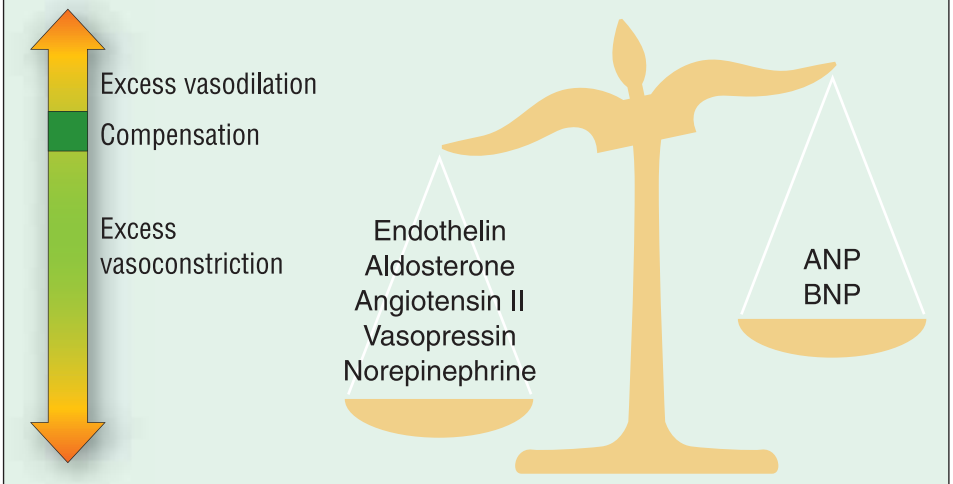
The B-type natriuretic peptide (BNP) is a counter regulatory neurohormone released when there are changes in left ventricular wall stretch and volume overload. It is a "distress hormone," more specific to ventricular disorders than the other natriuretic peptides. BNP is a potent natriuretic, diuretic, and vasorelaxant peptide. It promotes vascular relaxation and lowers blood pressure, especially in a state of volume overload. It also inhibits sympathetic tone, the renin-angiotensin axis, and the synthesis of vasoconstrictors, such as the catecholamines, angiotensin II, aldosterone, and endothelin. In doing so, BNP improves central hemodynamics, suppresses cardiac growth, and prevents compensatory cardiac hypertrophy. Its renal effects include increasing glomerular filtration rate and enhancing sodium excretion.

In both chronic and acute HF, significant neurohormonal changes happen, including upregulation of vasoconstrictors, such as norepinephrine, angiotensin II, and endothelin. There are increased levels of aldosterone and argenine vasopressin that promote salt and free water retention. Oral treatment with ACE inhibitors, ARBs, and beta-blockers as well as aldosterone inhibitors and diuretics are the current standard therapies for these alterations.

Intravenous therapy for ADHF includes positive inotrope activity. These produce symptomatic short-term benefits. Agents such as milrinone, however, have raised serious questions concerning routine usage. Hypotension and dysrhythmias are common. In addition, small studies have shown improved symptomatic outcomes with dobutamine in ADHF, but long-term beneficial results have not been supported in larger studies. Routine use of dobutamine has been associated with an increase in dysrhythmic events and death. Chronic IV inotropic therapy makes the patients feel better, but can shorten life expectancy. Therefore, it is not use chronically anymore.

Intravenous vasoactive therapy began with nitroglycerin. Although used for many years, there was little data to guide usage. Hemodynamic effects including lowering systemic vascular resistance, increase in stroke volume, and improvement in clinical status. More recently, nesiritide infusion has been very effective. Infusion of nesiritide (recombinant BNP) at a specified dose will increase circulating BNP up to 5 times higher than measured in typical heart failure patients. This subsequent overwhelming effect on the

The NPS Is Overwhelmed in Acutely Decompensated Heart Failure

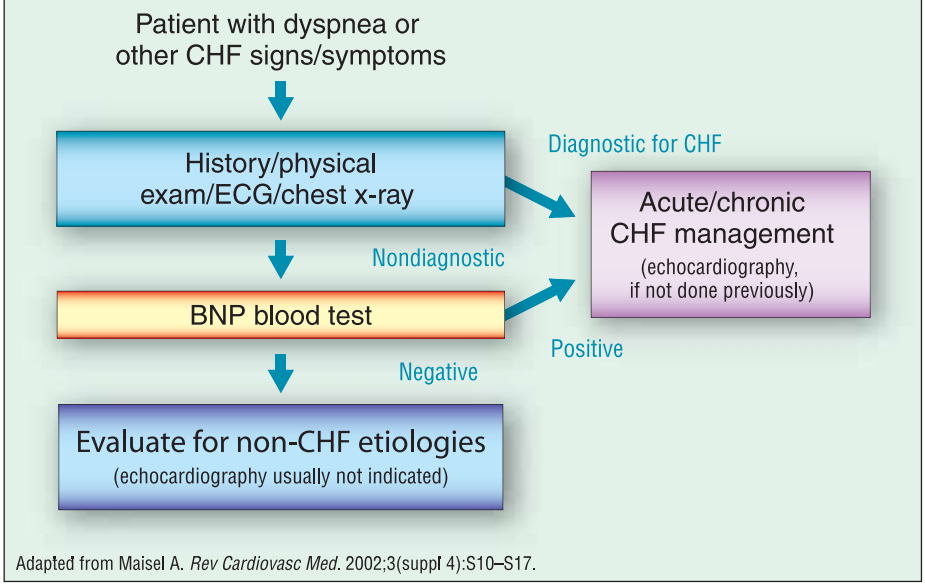


Adapted from Shah M et al. *Rev Cardiovasc Med.* 2001;2(suppl 2):S2–S6.

system results in beneficial changes for HF patients. Changes that occur include peripheral vasodilatation, diuresis, improvement in pulmonary capillary wedge pressure (left ventricular filling pressure), and reduction in angiotensin and norepinephrine levels. Compared to intravenous nitroglycerin, nesiritide has a more rapid onset of action, greater lowering of pulmonary capillary wedge pressure, and earlier improvement in patients' symptoms of dyspnea and global well-being. Symptomatic hypotension can occur in approximately 4%, similar to nitroglycerin. A small proportion (<1%) will develop bradycardia. There is no reflex tachycardia with nesiritide.

Nesiritide is well established in the management of the hospitalized patient with ADHF. Clinical trials have shown favorable outcomes when nesiritide is compared to agents such as nitroglycerin and dobutamine. In the Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial, nesiritide was significantly more effective than nitroglycerin and placebo in lowering pulmonary capillary wedge pressure and improving other hemodynamics in patients with ADHF. Nesiritide significantly improved dyspnea and overall clinical status at 24 hours compared to nitroglycerin.

Heart Failure Diagnostic Algorithm

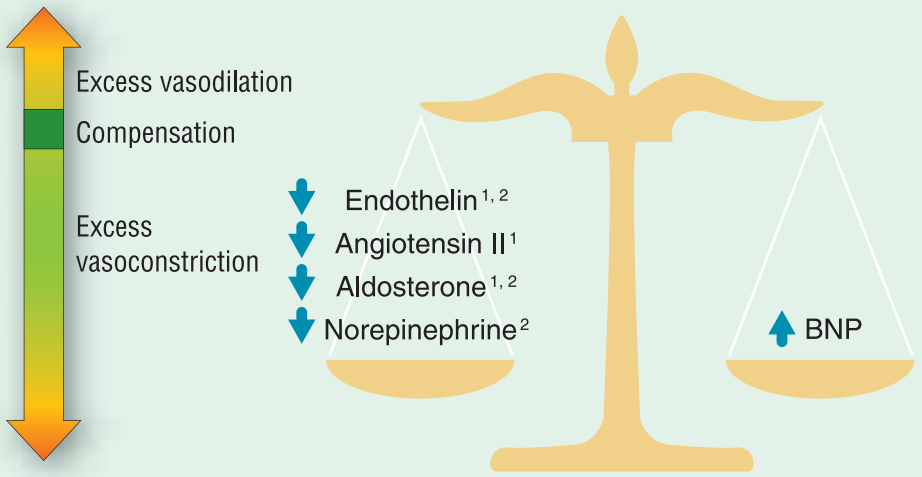


Adapted from Maisel A. *Rev Cardiovasc Med.* 2002;3(suppl 4):S10–S17.

Outcomes at 30 days and 6 months did not significantly differ. The Prospective Randomized Evaluation of Cardiac Ectop (PRECEDENT) trial showed that nesiritide and dobutamine were similarly effective in improving signs and symptoms of patients with ADHF. Nesiritide did not increase ventricular ectopy.

Prior data supported the safety and feasibility of nesiritide for the treatment of chronic decompensated HF (NYHA class III and IV) in an outpatient setting. The Follow-Up Serial Infusion Of Nesiritide (FUSION I) study was a multicentered, randomized, open-label, 12-week evaluation of 210 patients with decompensated HF (class III and IV) for at least 60 days and had received 2 or more intravenous treatments for ADHF in the preceding 12 months. All patients were receiving standard care oral medications. Patients were randomized to continue standard care or standard care with intermittent nesiritide infusions on an outpatient basis. Nesitide was infused as a bolus dose of 1 to 2 micrograms/kg followed by a continuous infusion of 0.005 to 0.01 micrograms/kg/min for 4 to 6 hours. Patients receiving standard care were allowed to receive inotropic agents if the investigators deemed this necessary to alleviate symptoms. Adverse effects (mostly hypotension) and clinical outcomes did not differ greatly between the nesiritide and the standard treatment group. In a prospectively defined higher risk subgroup (patients who had at least 4 of 7 prognostic risk factors for hospitalization and death), nesiritide significantly reduced the incidence of all-cause death and hospitalization. Reductions in aldosterone and endothelin levels were noted in the nesiritide group.

Nesiritide Reverses Acute CHF



1. Maisel A. Rev Cardiovasc Med. 2002;3(suppl 4):S10–S17.
2. Fonarow GC. Rev Cardiovasc Med. 2002;3(suppl 4):S18–S27.

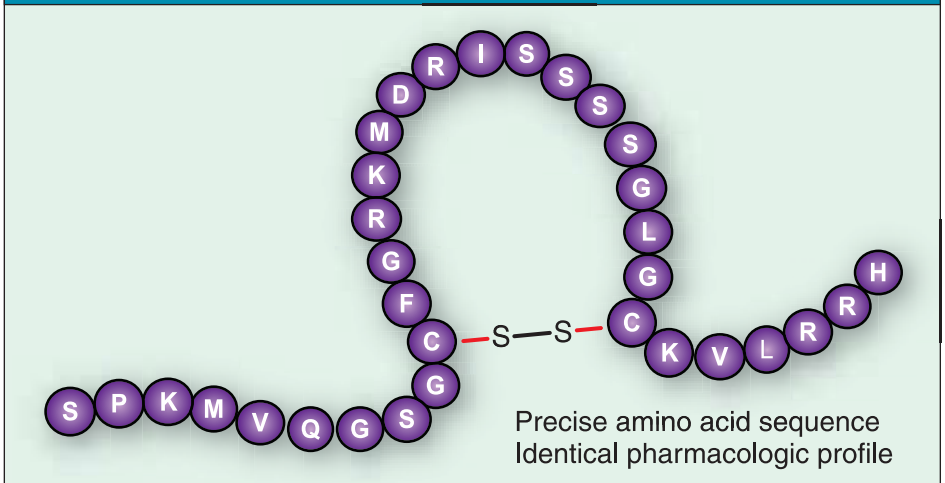
Several smaller, single-center studies have also shown that nesiritide can be administered safely and effectively in the outpatient setting for those with chronic decompensated HF. Data from these studies and from FUSION I have prompted the development of a larger outpatient trial called FUSION II. FUSION II is a randomized double-blind study involving 900 patients with chronic HF at high risk for rehospitalization. Patients will be randomized to 1 of 4 treatment arms and will receive serial infusions of placebo or nesiritide (dosed at 0.01 micrograms/kg/min after a standard bolus of 2 micrograms/kg) once or twice a week for 12 weeks followed by 12 weeks of follow-ups. FUSION II will also control for increased counseling and education that is typical for disease management clinics.

Inpatient usage of nesiritide continues to be supported and effective for treating ADHF

Clinical outcomes are improved by early and more accurate diagnosis of ADHF. Heart failure shares many signs and symptoms of other chronic illnesses common to the elderly population. Endogenous BNP levels are elevated in patients with ADHF, and the extent of the elevation correlates with HF severity. Patients with chronic decompensated HF may require intravenous administration of vasoactive agents if their disease is refractory to standard therapy. Though intermittent infusions of inotropic agents may improve short-term hemodynamics, these agents are no longer recommended for long term usage because of the increase in adverse events. Intermittent nesiritide infusions may be a safe and effective adjunct to oral pharmacotherapy. Nesiritide is generally well tolerated, though symptomatic hypotension may occur occasionally. Evidence from the FUSION I trial was favorable for outpatient heart failure treatment. FUSION II will explore the efficacy and safety of outpatient nesiritide infusions in comparison to placebo in high-risk patients. Although a recent meta-analysis of 3 trials reported that nesiritide may be associated with increased mortality risk, inpatient usage of nesiritide continues to be supported and effective for treating ADHF. FUSION II has been allowed to go to completion and will give insight for further assessment of outpatient intermittent nesiritide infusion for high-risk HF patients through a specialized disease management clinic. Until then, nesiritide infusion will need to be monitored closely and held off from chronic intermittent outpatient infusion.

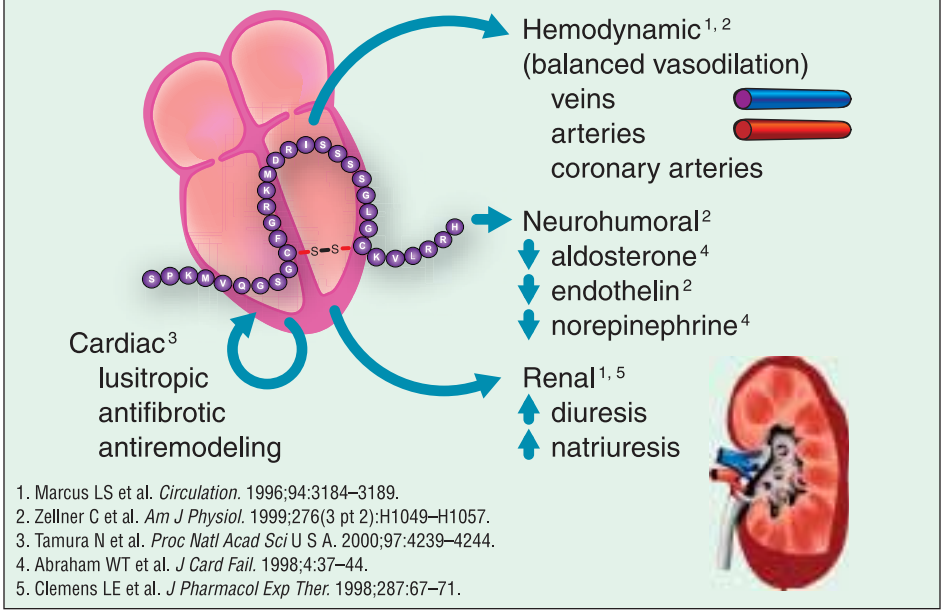
(Alan M. Kaneshige, MD is a noninvasive cardiologist with subspecialty expertise in adult echocardiography, stress echocardiography and transesophageal echocardiography.)

Nesiritide (hBNP) Is Identical to the Endogenous Hormone



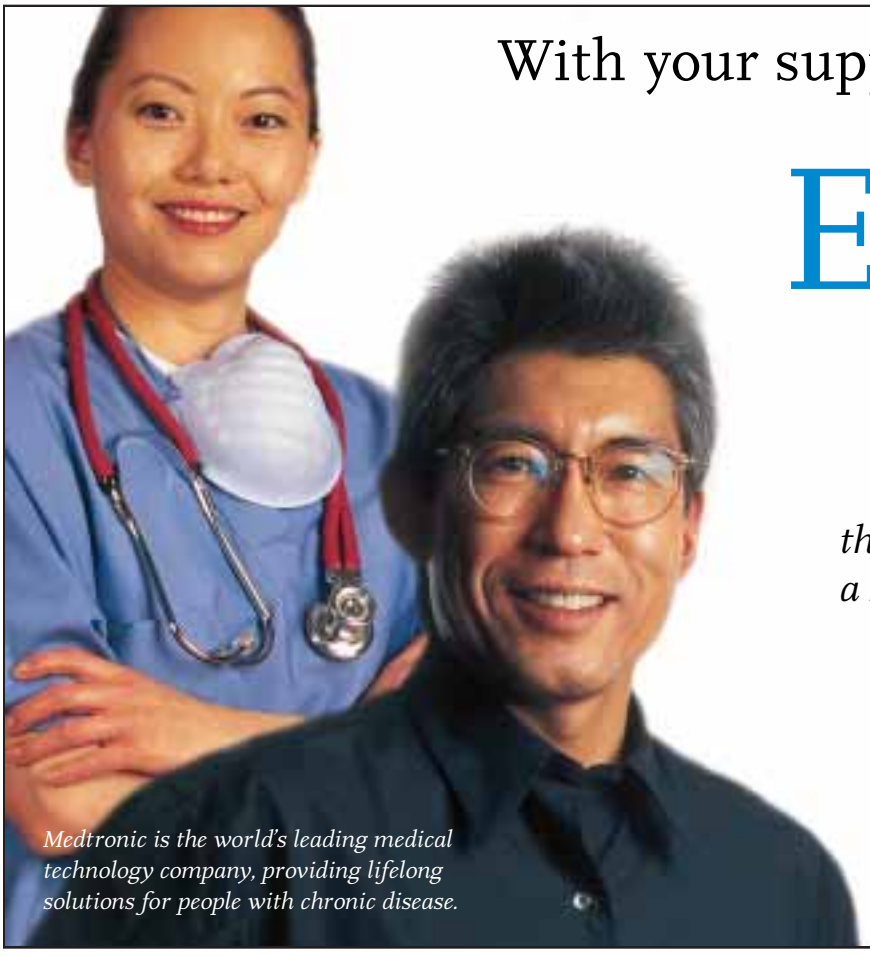
Clemens LE et al. *J Pharmacol Exp Ther.* 1998;287:67–71.

Pharmacologic Actions of hBNP



1. Marcus LS et al. *Circulation.* 1996;94:3184–3189.
2. Zellner C et al. *Am J Physiol.* 1999;276(3 pt 2):H1049–H1057.
3. Tamura N et al. *Proc Natl Acad Sci* U S A. 2000;97:4239–4244.
4. Abraham WT et al. *J Card Fail.* 1998;4:37–44.
5. Clemens LE et al. *J Pharmacol Exp Ther.* 1998;287:67–71.

Boone Smith AD
1\2H
To Come



With your support,

Every 7 seconds

the life of someone is improved by a Medtronic product or therapy.

Medtronic is the world's leading medical technology company, providing lifelong solutions for people with chronic disease.

enquiryap@medtronic.com
www.medtronic.com

Medtronic
When Life Depends on Medical Technology

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

New Treatments for Atrial Fibtillation

Atrial fibrillation is a major cardiovascular problem. Because of the risk of embolic events, especially strokes, chronic anticoagulation is necessary in patients with atrial fibrillation.

Currently, warfarin is the only effective chronic anticoagulation therapy available for patients with atrial fibrillation but necessitates the inconvenience of frequent monitoring of prothrombin times and INRs. In addition, the onset of warfarin is slow, requiring days to achieve a therapeutic state. Reversal of the anticoagulated state is also a slow process following cessation of warfarin. Because of these limitations, newer anticoagulants are being investigated. One of these is dabigatran. Dabigatran is a direct thrombin inhibitor that can be taken orally. Dabigatran has favorable pharmacokinetics compared with warfarin. There is more rapid and predictable onset and offset of action. Dabigatran produces an anticoagulated state within hours of taking the first dose. In addition, the anticoagulated state is reversed within 12 to 24 hours of stopping the dabigatran. This allows continued treatment up to 24 hours prior to any invasive procedures.

In order to better evaluate the efficacy and safety of dabigatran, Oklahoma Heart Institute is involved in the RELY trial. The RELY trial (Randomized Evaluation of Long-term Anticoagulant Therapy), compares efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolization in patients with non-valvular atrial fibrillation. It is a perspective, multi-center, parallel group, non-inferiority trial.

Patients with non-valvular atrial fibrillation of moderate to high risk for stroke or systemic embolization will be randozimed to receive either warfarin, using standard dosing to maintain the INR in the therapeutic range of 2 to 3, versus one of two doses of dabigatran; patients will either receive 110 mg bid or 150 mg bid. There will be 5,000 patients in each of the randomization arms.

Patients with renal insufficiency (creatinine clearance less than 30 mls per minute) will be excluded. Aspirin and Plavix will be allowed, if indicated for other reasons.

Patients will be followed for three years on the randomized drug strategy. Both efficacy and safety will be evaluated during the study.

The efficacy of direct thrombin inhibitors, such as dabigatran, has already been demonstrated in trials involving a similar direct thrombin inhibitor, ximelagatran. The efficacy of ximelagatran was clearly established. However, there was increased risk of liver toxicity with ximelagatran. Dabigatran appears to have a much lower risk of liver toxicity than ximelagatran. Therefore, this drug appears to be a very promising agent which may replace warfarin in the treatment of patients with atrial fibrillation.

The main advantage of participating in the trial is that patients are closely monitored by the research nurses. In addition, they have a two out of three chance of getting the newer agent. This will minimize the inconvenience of blood draws associated with warfarin therapy. In addition, the drug may be safer than warfarin and easier to manage.

If physicians have patients they would like to refer for consideration for the RELY trial, they can contact Dr. Leimbach or ask for one of the Research Nurses at Oklahoma Heart Institute by calling 918-592-0999.

OKLAHOMA HEART INSTITUTE AT UTICA

1265 S. Utica Avenue
Suite 300
Tulsa, OK 74104
Phone: 918.592.0999
Fax: 918.592.1021

OKLAHOMA HEART INSTITUTE AT SOUTHPOINTE

9228 S. Mingo
Suite 200
Tulsa, OK 74133
Phone: 918.592.0999
Fax: 918.878.2499

SERVICES OF OKLAHOMA HEART INSTITUTE

Noninvasive Cardiology

- Nuclear Cardiology
- Echocardiography & Doppler Studies
- Nuclear and Echocardiographic Exercise & Pharmacological Stress Testing
- Transesophageal Echocardiography
- Arterial Venous Peripheral Vascular Imaging & Doppler Studies
- Peripheral Arterial Doppler and Duplex Imaging
- Cardiovascular Magnetic Resonance Imaging
- External Counterpulsation (ECP) Therapy

Invasive Cardiology

- Cardiac Catheterization
- Coronary Angioplasty
- Atherectomy
- Rotablator Atherectomy
- Thrombolytic Therapy
- Coronary Stents
- Intravascular Ultrasound
- Myocardial Biopsy
- Pericardiocentesis
- Intravascular Radiation Therapy
- Peripheral Angioplasty
- Peripheral Stents
- Percutaneous PFO Closures
- Percutaneous ASD Closures
- Intracardiac Echocardiography

Electrophysiology

- Electrophysiology Studies
- Ablation Therapy
- Pacemaker Implantation
- Pacemaker and Lead Extraction
- Pacemaker Programming
- Pacemaker Monitoring & Clinic
- Implantable Cardioverter Defibrillator (ICD) Replacement
- ICD and Hardware Removal
- ICD Programming
- ICD Monitoring and Clinic
- Holter Monitoring and Interpretation
- 30 Day Cardiac Event Monitors
- Implantation and Interpretation of Long-Term Heart Monitors
- Signal Averaged EKG's and Interpretation
- Head Up Tilt Testing and Interpretation
- Direct Current Cardioversion
- Antiarrhythmic Drug Loading and Monitoring

Metabolic Disorders

- Diabetes
- Thyroid
- Hypertension
- Hyperlipidemia
- Other Endocrine Problems

Specialty Clinics

- Executive Health Clinic
- Adolescent & Adult Congenital Heart Clinic
- Lipid & Wellness Clinic
- Heart Failure Clinic
- Dysrhythmia & Pacer Clinic
- Metabolic Syndrome Clinic

Oklahoma Heart Institute®

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 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.

Board certified in Internal Medicine, Cardiovascular Disease and Interventional Cardiology

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.

Board certified in Internal Medicine, Cardiovascular Disease, and Adult Echocardiography
Registered Vascular Technologist

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.

Board certified in Internal Medicine and Cardiovascular Disease

James J. Nemec, MD, FACC

Dr. Nemec is a subspecialist in echocardiography, stress echocardiography and nuclear cardiology. He serves as Director of Nuclear Cardiology for Oklahoma Heart Institute. Dr. Nemec has served as Assistant Professor of Internal Medicine, Division of Cardiology, at Creighton University and as Assistant Professor, Department of Radiology, also at Creighton University. He completed his Clinical Cardiology Fellowship at the Cleveland Clinic Foundation and his Internal Medicine Internship and Residency at Creighton University. Dr. Nemec also completed a year of training in pathology at the University of Missouri, Columbia, MO. He received his medical degree from Creighton University, where he also received his Bachelor of Arts degree.

Board certified in Internal Medicine and Cardiovascular Disease

John G. Ivanoff, MD, FACC, FSCAI

Dr. Ivanoff specializes in interventional cardiology, including cardiac catheterization, coronary angioplasty and related interventional procedures such as stents, atherectomy and direct PTCA for acute myocardial infarction. He is Director of the Catheterization Laboratories at SouthCrest Hospital. Dr. Ivanoff serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He has also served as Assistant Professor of Medicine at the Medical College of Pennsylvania, as well as Associate Director of the Coronary Care Unit and Assistant Professor of Medicine at Hahnemann University Hospital, where he also completed his Cardiology Fellowship. He completed his Internal Medicine Internship and Residency at the Medical College of Pennsylvania, where he served as Chief Resident. Dr. Ivanoff also received his medical degree from the Medical College of Pennsylvania. He completed his Masters degree in biochemistry at Columbia University and received his Bachelor of Arts degree from the University of Pennsylvania.

Board certified in Internal Medicine, Cardiovascular Disease and Interventional Cardiology

Gregory D. Johnsen, MD, FACC

Dr. Johnsen is an interventional cardiologist with expertise in cardiac catheterization, angioplasty and related interventional procedures, such as stents and atherectomy. He is Director of Cardiac Rehabilitation at Hillcrest Medical Center and Director of the Hillcrest Exercise and Lifestyle Programs. He completed his Clinical Cardiology Fellowship at the University of Oklahoma – Oklahoma City, where he then finished an extra year of dedicated training in interventional cardiology. He completed his Internal Medicine Internship and Residency training at the University of Oklahoma – Oklahoma City, where he also received his medical degree. Dr. Johnsen received his Bachelor of Science degree from Oklahoma StateUniversity.

Board certified in Internal Medicine, Cardiovascular Disease and Interventional Cardiology

Alan M. Kaneshige, MD, FACC

Dr. Kaneshige is a noninvasive cardiologist with expertise in adult echocardiography, stress echocardiography and transesophageal echocardiography. He is Chief of Cardiology at Hillcrest Medical Center. Dr. Kaneshige is also the 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. Dr. Kaneshige completed his Internal Medicine Internship and Residency at Creighton University School of Medicine, where he also received his medical degree. He received a Bachelor of Science in chemistry at Creighton University. Dr. Kaneshige completed his Clinical Cardiology Fellowship at Creighton, where he also served as Chief

Cardiology Fellow for two years. He completed an additional Cardiac Ultrasound Fellowship at the Mayo Clinic in Rochester, MN. Dr. Kaneshige served as Assistant Professor of Medicine at Creighton University School of Medicine, where he was Director of the Noninvasive Cardiovascular Imaging and Hemodynamic Laboratory.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Adult and Transesophogeal Echocardiography

Ernest Pickering, DO, FACOI

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.

Board certified in Internal Medicine and Cardiovascular Disease

James A. Coman, MD, FACC

Dr. Coman is a subspecialist in cardiac electrophysiology, ablation therapy and pacemakers. He is Director of Electrophysiology at Hillcrest Medical Center. Dr. Coman also serves as Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. He completed an Electrophysiology Fellowship at the Cleveland Clinic Foundation, where he was Chief Fellow. His Cardiology Fellowship was also performed at the Cleveland Clinic Foundation. Dr. Coman's Internal Medicine Internship and Residency training were completed at the University of Alabama, Birmingham, AL. He received his medical degree from the University of Alabama School of Medicine and his Bachelor of Science degree in biomedical engineering from Vanderbilt University, Nashville, TN.

Board certified in Internal Medicine, Cardiovascular Disease and Electrophysiology

Edward T. Martin, MS, MD, FACC, FACP, FAHA

Dr. Martin is a noninvasive cardiologist with subspecialty expertise in non-invasive imaging. He is Director of Cardiovascular Magnetic Resonance Imaging at Oklahoma Heart Institute, SouthCrest Hospital and Hillcrest Medical Center. Dr. Martin is also Director of Nuclear Cardiology at SouthCrest Hospital. In addition, he is a Clinical Associate Professor of Medicine at the University of Oklahoma College of Medicine – Tulsa. Dr. Martin has specialty training in Nuclear Medicine, as well as additional training dedicated to Cardiovascular Magnetic Resonance Imaging. He completed his Cardiology Fellowship at the University of Alabama. Dr. Martin's Internal Medicine Internship and Residency training were performed at Temple University Hospital in Philadelphia. He received his medical degree from the Medical College of Ohio. Dr. Martin completed his Master of Science degree in mechanical engineering at the University of Cincinnati and his Bachelor of Science degree in physics at Xavier University. Dr. Martin is a founding member of the Society of Cardiovascular Magnetic Resonance and is an editorial board member of the Journal of Cardiovascular Magnetic Resonance.

Board certified in Internal Medicine and Cardiovascular Disease

Roger D. Des Prez, MD, FACC

Dr. Des Prez is a noninvasive cardiologist with subspecialty expertise in echocardiography, nuclear cardiology and transesophageal echocardiography. He is Director of Echocardiography and Peripheral Vascular Ultrasound Imaging at SouthCrest Hospital. Dr. Des Prez received his medical degree and Bachelor of Arts degree from Vanderbilt University. He completed his Residency in Internal Medicine and Pediatrics at University Hospital of Cleveland. Dr. Des Prez practiced for six years as an internist with the Indian Health Services in Gallup, NM. He returned to Vanderbilt University as a member of the Internal Medicine Faculty, at which time he also completed his cardiology training. In addition to noninvasive cardiology, Dr. Des Prez is interested in outcomes research and computers in medicine.

Board certified in Internal Medicine, Pediatrics, Critical Care and Cardiovascular Disease

Board certified in Adult and Transesophageal Echocardiography

Christian S. Hanson, DO, FACE

Dr. Hanson is a specialist in Endocrinology, Metabolism and Hypertension at Oklahoma Heart Institute with expertise in diabetes, lipids and hypertension. He also serves as Clinical Associate Professor of Medicine in the College of Osteopathic Medicine – Oklahoma State University. He completed a Fellowship in Endocrinology, Metabolism and Hypertension at the University of Oklahoma in Oklahoma City. Dr. Hanson's Internal Medicine Residency and Rotating Internship were completed at Tulsa Regional Medical Center. He received his medical degree from Oklahoma State University and his Bachelor of Science degree from Northeastern Oklahoma State University in Tahlequah.

Board certified in Internal Medicine
Board certified in Endocrinology and Metabolic Diseases

Rebecca L. Smith, MD

Dr. Smith is a noninvasive cardiologist with subspecialty expertise in transesophageal echocardiography, intra-operative echocardiography, stress and pharmacological echocardiography and contrast echo-cardiography. She completed an Advanced Cardiac Imaging Fellowship at the Cleveland Clinic Foundation and her Cardiology Fellowship at the University of New Mexico Health Sciences Center, Albuquerque, NM. Dr. Smith's Internal Medicine Internship and Residency training were performed at the University of Arizona Health Sciences Center in Tucson. She received her medical degree from the Medical College of Ohio. Dr. Smith completed her Bachelor of Science degree at Cleveland State University.

Board certified in Internal Medicine

Board eligible in Cardiovascular Disease

Tobie L. Bresloff, MD

Dr. Bresloff is a specialist in Endocrinology, Metabolism and Hypertension, with expertise in diabetes, lipids, hypertension and thyroid diseases. She also serves as Assistant Professor in Clinical Medicine at the University of Oklahoma College of Medicine - Tulsa. She completed an NIH Fellowship in Endocrinology and Metabolism at Vanderbilt University in Nashville, TN. Dr. Bresloff's Internal Medicine Internship and Residency were completed at Sinai Hospital of Detroit, Detroit, MI. She received her medical degree from Wayne State University School of Medicine in Detroit and her Master of Science and Bachelor of Science degrees at the University of Michigan, Ann Arbor, MI.

David A. Sandler, MD

Dr. Sandler is a cardiologist with subspecialty expertise in electrophysiology. He completed his Cardiac Electrophysiology Fellowship and his Cardiovascular Medicine Fellowship at New York University Medical Center, New York, NY. Dr. Sandler's Internal Medicine Internship and Residency were performed at Mount Sinai Medical Center, New York, NY. He earned his medical degree from Georgetown University School of Medicine in Washington, DC. Dr. Sandler received his Bachelor of Arts degree at the University of Pennsylvania in Philadelphia.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Cardiac Electrophysiology

Raj H. Chandwaney, MD, FSCAI

Dr. Chandwaney is an interventional cardiologist with expertise in cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures. He completed his Clinical Cardiology Fellowship at Northwestern University Medical School in Chicago, IL., where he also completed an Interventional Cardiology Fellowship. Dr. Chandwaney's Internal Medicine Internship and Residency were performed at Baylor College of Medicine in Houston, TX. He received his medical degree from the University of Illinois at Chicago. Dr. Chandwaney completed his Master of Science degree at the University of Illinois at Urbana Champaign, where he also received his Bachelor of Science degree.

Board certified in Internal Medicine and Cardiovascular Disease
Board certified in Interventional Cardiology

D. Erik Aspenson, MD, FACE, FACP

Dr. Aspenson is a subspecialist in Endocrinology, Metabolism and Hypertension at Oklahoma Heart Institute, with expertise in diabetes, lipids, hypertension and thyroid diseases. He completed a Fellowship in Endocrinology at Wilford Hall Medical Center, Lackland AFB, Texas. Dr. Aspenson's Internal Medicine Internship and Residency were completed at David Grant Medical Center, Travis AFB, California where he served as Chief Resident. He received his medical degree from the University of Oklahoma and his Bachelor of Science degree at Oklahoma State University.

Board certified in Internal Medicine
Board certified in Endocrinology and Metabolic Diseases

Frank J. Gaffney, MD

Dr. Gaffney is an invasive and noninvasive cardiologist with subspecialty expertise in transesophageal echocardiography. He completed his Cardiovascular Medicine Fellowship at Scott & White Memorial Hospital in Temple, Texas. Dr. Gaffney completed his Internal Medicine Internship and Residency at Brooke Army Medical Center in San Antonio. He then remained on staff at Scott & White Memorial Hospital for several years, before entering his Fellowship in Cardiovascular Medicine. Dr. Gaffney earned his medical degree from New York Medical College, Valhalla, New York, and he received his Bachelor of Arts degree at Hofstra University in Hempstead, New York.

Board certified in Internal Medicine
Board certified in Cardiovascular Disease

Michael J. Fogli, MD

Dr. Fogli is a subspecialist in magnetic resonance imaging, nuclear cardiology, echocardiography, stress echocardiography and transesophageal echocardiography. He completed a fellowship in Advanced Cardiac Imaging at the University of Texas, Southwestern Medical Center in Dallas, TX. His Cardiology fellowship was also performed there, as were his Internal Medicine Internship and Residency. Dr. Fogli earned his medical degree at the University of California, San Francisco School of Medicine and his Bachelor of Arts degree at the University of California, Berkley.

Board certified in Internal Medicine
Board certified in Cardiovascular Disease

Eric G. Auerbach, MD

Dr. Auerbach is a subspecialist in magnetic resonance imaging, nuclear cardiology, echocardiography, stress echocardiography and transesophageal echocardiography. He completed his Cardiovascular Magnetic Resonance Imaging fellowship at Oklahoma Heart Institute, Tulsa, OK. His Cardiology fellowship was performed at the University of Miami/Jackson Memorial Hospital in Miami, FL. Dr. Auerbach's Internal Medicine Internship and residency were also completed at the University of Miami/Jackson Memorial Hospital in Miami. Prior to that, he performed a Surgery Internship at New York Hospital/Cornell Medical Center, New York, NY. Dr. Auerbach earned his medical degree at the University of Miami School of Medicine, Miami, Florida and his A.B. degree at Princeton University, Princeton, New Jersey.

Board certified in Internal Medicine
Board certified in Cardiovascular Disease

Kelly Flesner-Gurley, MD

Dr. Flesner-Gurley is a subspecialist in Endocrinology, Metabolism and Hypertension at Oklahoma Heart Institute, with expertise in diabetes, lipids, hypertension and thyroid diseases. Prior to joining Oklahoma Heart, she was at St. John Medical Center in Tulsa. She completed her fellowship in Endocrinology at the University of Texas at Galveston. Her Internal Medicine Internship and Residency were completed at the University of Texas in Houston, where she also received her medical degree. She earned her Bachelor of Science degree at Texas A&M University in College Station, TX.

Board certified in Internal Medicine and Endocrinology, Diabetes and Metabolic Diseases

by **Tobie L. Bresloff, MD**

Take a Bite out of Diabetes

What do a Gila monster from the desert and many overweight people in America have in common? How are they different?

- Gila monsters eat huge amounts at once, far more than their bodies need at that time. But they eat only 3 or 4 times per year, total. Unfortunately, many people also eat far more at one time than they need, but they do it several times every day.

- Gila monsters store the extra calories as inert fat in their tails. People store it as intra-abdominal fat, which is metabolically active in many detrimental ways.
- Gila monsters do not develop diabetes. People do.
- These observations prompted one scientist to see why the Gila monster doesn't develop diabetes mellitus.

The super-sizing of America is a fact. More people are more overweight than ever before. A much higher percentage of the population is morbidly obese. This trend is obviously the result of too many calories ingested and too little activity. We now know that obesity is more than just a cosmetic problem. The intra-abdominal fat cells are metabolically active and the substances these fat cells make greatly increase the rates of diabetes and vascular disease. We know that obesity is a risk factor for diabetes, as well as an independent risk factor for cardiac and vascular disease.

The number of diabetics in America is increasing each year. We now diagnose teenagers and pre-teens with type 2 diabetes fairly frequently. We are also diagnosing pre-diabetes, impaired glucose tolerance, insulin resistance and metabolic syndrome at much higher rates.

By preventing obesity, we can help to eliminate the problems which are caused by obesity – diabetes and vascular disease.

Once someone has a diagnosis of diabetes, elevated blood sugars must be treated. Most traditional diabetes treatments increase the serum insulin and are associated with weight gain. Even people on TZDs, which act by decreasing insulin resistance, tend to gain weight.

Metformin has been the one agent so far that does not result in weight gain. However, there are people who cannot tolerate the GI side effects of metformin and some patients cannot use it due to renal insufficiency.

What is needed is a hypoglycemic agent that allows patients to control blood sugar and lose weight at the same time. We finally have it.

Byetta (exenatide) is a recently FDA approved drug that represents a new therapeutic class called "Incretin Mimetics." This protein is found in the saliva of the Gila monster lizard. It mimics the glucagons-like peptide 1 (GLP-1) that is released in the human gut in response to food, and helps maintain glucose homeostasis.

The Story Behind Byetta

In the 1980s, Dr. John Eng, an endocrinologist researcher, was working for the Veterans Administration trying to find new hormones. Using Gila monster venom he purchased from a lab in Utah, he discovered a hormone that he named exendin-4. It was similar in structure and action to human GLP-1 which regulates blood sugar, slows gastric emptying and increases satiety. The major difference is that, while GLP-1 has a half-life of several minutes, exendin-4 is measurable in plasma up to 10 hours after injection. Dr. Eng published his work in 1992. He realized that this hormone might be developed into a diabetes treatment. Dr. Eng patented the compound and ultimately licensed the patent to Amylin.

In 1999, Amylin filed a new drug application with the FDA. In April 2005, Byetta was approved for glycemic control in type 2 diabetics. By the way, Gila monsters are not used in making the drug. It is synthesized in a lab.

What is an Incretin Mimetic?

Incretins (substances that INcrease seCRETion of insulin from the pancreas) are secreted from the GI tract upon the ingestion of food. The incretin mimetic increases the "first phase" insulin response (causes more to be released) to an oral glucose load. An incretin mimetic produces the same effect as naturally occurring GLP-1, but the effect is sustained for a longer period.

What does Byetta do?

1. Increases glucose dependant insulin secretion. This insulin then decreases as glucose approaches normal, even with the same amount of exenatide being present. This means little hypoglycemia, except when used with insulin or insulin secretagogues.
2. Decreases glucagon secretion, causing less hepatic glucose production.
3. Slows gastric emptying. Nutrients get absorbed more slowly. Blood sugar rise is slower. Patients feel full sooner and satiated longer.
4. Has a direct CNS effect to increase satiety and reduce food intake.

All of these add up to decreased post-prandial hyperglycemia, decreased nocturnal glucose production, decreased hunger and decreased food intake. Best of all, the beta cell workload is decreased, which should help preserve beta cell function.

Indication

From the package insert:

Adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control.

Results of Use

Phase 3 randomized, double blind, placebo controlled trials of Byetta added to previous treatment, showed significant reductions in fasting glucose, post-prandial glucose, HbA1C, and more patients achieved target HbA1C goals. In addition, weight loss occurred, and was most impressive, in those whose BMIs started the highest. The average weight loss may not seem huge, 6-7 pounds in 30 weeks, but for these people any loss is an improvement. In addition, weight loss appears to continue and not taper off, as it does with most diets and weight loss medicines.

What patients need to know?

Byetta is a sub-cutaneous injection given twice a day before the morning and evening meals. It is NOT insulin! All patients start with 5mcg BID and, if well tolerated, increase to 10mcg in one month.

The major side effect is nausea, which, if it occurs, is usually at the start of treatment or after increases in dosages. It generally spontaneously subsides. The other major side effect is hypoglycemia. This usually occurs if the patient is on a sulfonylurea. To prevent hypoglycemia, the sulfonylurea dose can be halved or stopped when starting Byetta, and added back if needed.

Precautions

Absorption of other drugs may be delayed due to slowed gastric emptying. If rapid GI absorption for a medication is needed, the medicine may be given at least 1 hour before the Byetta.

Byetta is also not recommended for patients with a creatinine clearance of less than 30 ml/min. The dose does not need to be adjusted for mild to moderate renal impairment.

How To Start a Patient

Many patients fear injections. Demonstrating the pen needle helps them realize that the injections are not to be feared.

Other Diabetes News

Symlin – Pramlintide generic name, also made by Amylin, has some of the same actions as Byetta. It can be used in type 1 or 2 diabetics. It is used along with insulin to reduce post meal hyperglycemia. It must be taken with each meal, by sub-cutaneous injection. It can cause severe hypoglycemia, so insulin doses need to be adjusted carefully. It can also cause nausea and slow gastric emptying. Some patients love it, since it stabilizes their post meal glucose excursions. It also helps with weight loss by improving satiety and reducing insulin dose, as well as food intake. Patients need to be carefully selected for this drug, and it is somewhat tricky to start. Studies are being done to see if it can help with weight loss in non-diabetics.

Rimonabant – A drug being developed to decrease overeating is now being looked at by the FDA. The brand name will be Acomplia if it is approved. This drug works by blocking the endocannabinoid system. These are the receptors that are stimulated by marijuana and cause "the munchies," as well as impulsive behavior and disinhibition. Blocking the system decreases cravings for food and possibly other habits, like smoking. Rimonabant leads to decreases in waist circumference, triglycerides and insulin resistance, while increasing HDL cholesterol.

Exubera is the first inhaled insulin to be FDA approved. Marketing may start in the summer of 2006. I suspect it will be mainly for type 2 diabetics. It will need to be used with each meal, since it is a short acting insulin. It will not substitute for basal insulin doses. There may also be restrictions on who should use it, based on pulmonary functions. Pulmonary toxicity may still be a concern.

In summary, it is exciting times for those of us who take care of diabetics. Byetta shows huge promise, and has already made a major difference to some patients. Our bag of tricks is greatly expanding to allow us to better treat diabetics, and to minimize or reverse some of the weight gain that has been such a major problem.

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

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

Closing PFOs to Prevent Refractory Migraine Headaches

A PFO (Patent Foramen Ovale) is a small defect between the right atrium and left atrium. The defect can be opened by increased pressure in the thoracic cavity (i.e., a cough). Because of this defect, paradoxical emboli can cross the PFO and cause a stroke. It is also possible that vaso-active chemicals and hormones cross the PFO, triggering migraine headaches.

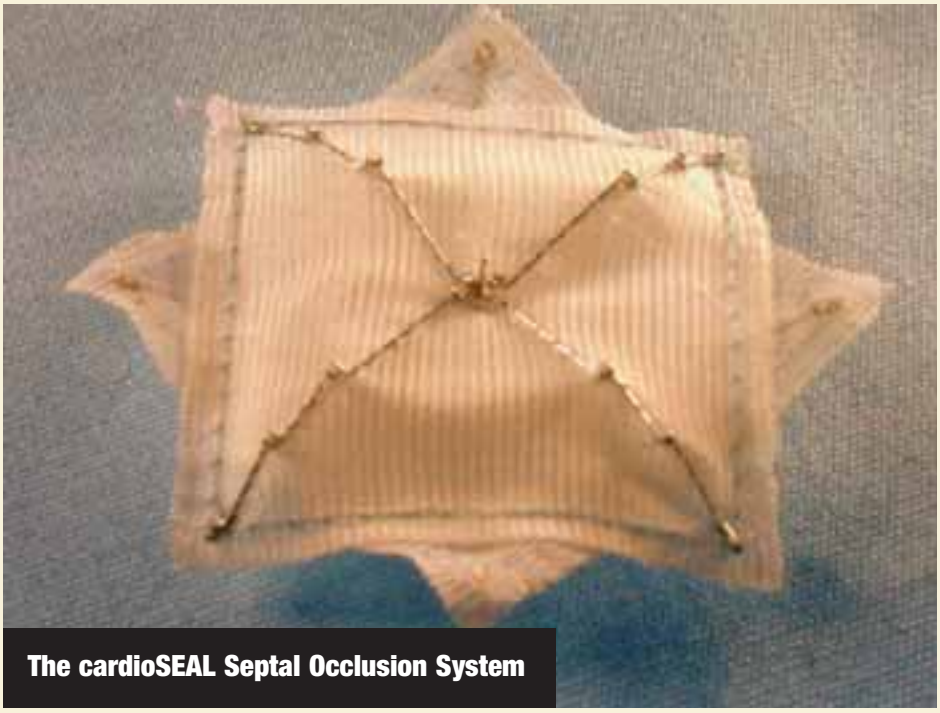
Currently we are closing PFOs percutaneously, using one of two types of devices. One is the Cardioseal closure device and the other is the Amplatzer Septal Occluder device. Both of these devices are placed percutaneously by going through the femoral veins.

Patients who have had paradoxical embolic events while on coumadin anticoagulation are eligible for closure of their PFO. The relationship between PFOs and migraines was recognized because of reports by patients who had their PFOs closed to prevent recurrent strokes. Some of these patients also had significant migraine headaches. With the closure of their PFO, a marked decrease in the frequency of their migraine headaches was reported. Some patients had complete resolution of their migraine headaches following closure of their PFO.

It is known that greater than 50% of migraine patients have intracardiac shunts, such as a PFO. This is in contrast to 10 to 15% of the general population. In addition, PFOs in migraine patients tend to be larger than the PFOs in autopsy studies of the general population. Because of the complete resolution of migraine headaches in some patients after PFO closure, it has been speculated that many patients have migraine headaches because of chemical or hormonal shunting across the PFO. These chemicals or hormones would normally be filtered out in the lung. By crossing over to the systemic circulation through the PFO, they act as triggers for migraines. In order to test this theory, the MIST trial was performed in England. In this trial, patients with refractory migraine headaches were randomized to either a percutaneous closure of their PFO using a closure device or were randomized to a sham procedure. The patients were followed to see whether they had improvement or resolution of their migraine headaches.

The relationship between PFOs and migraines was recognized because of reports by patients who had their PFOs closed to prevent recurrent strokes.

To be approved in the United States for the treatment of migraine headaches, it is usually necessary for a drug to demonstrate a 50% reduction in migraine events. It should also be noted that in normal drug trials, there can be up to a 23% reduction in migraine events with placebo therapy. Therefore, it might be expected that a trial looking at the effectiveness of PFO closure in treating migraine headaches would also have as its endpoint a 50% reduction in migraine events.



The cardioSEAL Septal Occlusion System

In this trial, however, investigators pursued a much more aggressive primary endpoint. The primary end point for the MIST trial was complete cessation of migraine headaches.

Needless to say, the trial failed to achieve its primary endpoint. However, the trial did demonstrate a significant reduction in headache days. In regards to the endpoint of a 50% reduction in migraine events, 42% of the PFO closure patients achieved the endpoint, compared to a 23% reduction in the sham-treated group. Headache burden, which is defined as frequency times duration, resulted in a 37% reduction in the implant patients, as compared to a 16% reduction in the sham treated patients. Thus, it appears that some patients with migraine headaches and PFOs do experience significant decreases in their headache burden with closure of the PFO.

Closing a PFO for the treatment of migraines is still experimental, and there is not FDA approval of the procedure for this indication. Additional trials are ongoing to better clarify the utility of PFO closure for prevention of migraines. From the current MIST trial, it is clear that not all migraine headaches are secondary to shunting across the PFO in those patients who have migraine headaches and PFOs. However, the study does suggest that many patients with refactory migraine headaches could have their headaches abolished, or at least significantly reduced, by a percutaneous procedure with only an overnight stay in the hospital.

AMPLATZER

(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.)

■ *by* **Frank J. Gaffney, MD**

Dual Platelet Therapy: Not for Everyone

In our last issue we discussed the findings of the COMMIT and CLARITY trials regarding the expanded role for clopidogrel (Plavix) in ST Elevation Myocardial Infarction. Both studies showed clopidogrel could be safely added to the current regimen of aspirin, and, when appropriate, heparin, fibrinolytics and PCI (percutaneous coronary intervention) without increased risk of bleeding and with a statistical reduction in the study endpoints.

The benefits of adding clopidogrel to aspirin in patients with acute coronary syndromes, or in those undergoing percutaneous coronary intervention, have already been demonstrated in a number of trials, including the CURE and CREDO trials.

Additionally, the CAPRIE study compared clopidogrel and aspirin in the secondary prevention of cardiac events in patients who had a recent MI, a recent stroke, or peripheral vascular disease. The main result showed was an 8.7% relative risk reduction in the combined end point of MI, stroke or vascular death with clopidogrel. Patients with peripheral arterial disease experienced the largest advantage with clopidogrel; those with a previous stroke benefited less substantially, and post-MI patients showed a trend toward a better effect with aspirin.

In the April 20th issue of The New England Journal of Medicine, the results of the CHARISMA trial were presented. This trial was designed to test the hypothesis that "long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk."

Patients were eligible to enroll in the trial if they were 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease.

In the study, 15,603 patients with either clinically relevant cardiovascular disease (secondary prevention group) or multiple risk factors (primary prevention group) were randomized to clopidogrel 75 mg/day plus low-dose aspirin (75-162 mg/day) or placebo plus low-dose aspirin. More than three quarters of the patients had established cardiovascular disease and the remaining patients had multiple atherothrombotic risk factors. They were followed for a median of 28 months. The primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. During the study, three quarters of the patients took statins, half took beta-blockers, two thirds took an ACE inhibitor and a quarter took angiotensen II-receptor blocking agents.

The results for the total population revealed no significant benefit associated with clopidogrel plus aspirin, as compared with placebo plus aspirin, in reducing the incidence of the primary end point of myocardial infarction, stroke, or death from cardiovascular causes. There was a moderate, though significant, benefit in reducing the secondary composite end point of myocardial infarction, stroke, and death from cardiovascular causes or hospitalization for unstable angina transient ischemic attack or revascularization.

The rate of severe bleeding was not significantly greater with clopidogrel than with placebo, but a trend prompting concern was noted.

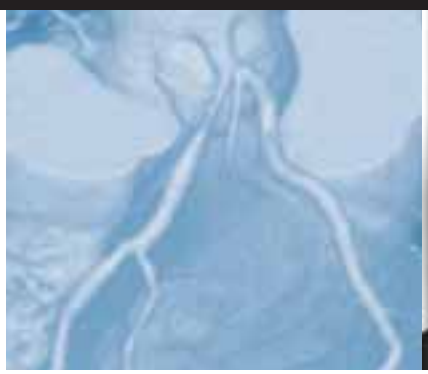
There was benefit in symptomatic patients with established vascular disease (secondary prevention) – the rate of the primary end point among these patients was 6.9% with clopidogrel and 7.9% with placebo (p=0.046). The risk of moderate or severe bleeding in the symptomatic patients was greater in the clopidogrel than with placebo, although there was no increase in intracranial or fatal bleeding.

The rate of the primary end point in the asymptomatic, or primary-prevention, patients was 6.6% with clopidogrel and 5.5% with placebo (p=0.20). Although the primary end point was not significantly different, the rate of death from cardiovascular causes was 3.9% among those receiving clopidogrel and 2.2% in those taking placebo (p=0.01), suggesting possible harm in the asymptomatic primary prevention group.

In conclusion, the authors suggest "the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with multiple cardiovascular risk factors. Furthermore, the risk of moderate-to-severe bleeding was increased. Our findings do not support the use of dual antiplatelet therapy across the broad population tested. There was benefit in symptomatic patients with established vascular disease. Data on mortality rates suggest that dual antiplatelet therapy should not be used in patients without a history of established vascular disease."

(Frank J. Gaffney, MD is an invasive and noninvasive cardiologist with subspecialty expertise in trans-esophageal echocardiography.)

by FWayne N. Leimbach, Jr., MD, FACC, FSCAI, FCCP, FAHAA



Late Breaking Clinical Trials for Cardiology 2006

What's New in Risk Factor Modification?

The practice of cardiology continues to change and rapidly evolve. We are now in the era of evidence-based medicine, and in order to determine the best clinical practice patterns, large randomized clinical trials are being done. Over the past year, several clinical trials have been presented at the national meetings, the results of which were presented at the Oklahoma Heart Research & Education Foundation Spring Symposium. The following is a summary of the outcomes of several of these trials.

What's New in Risk Factor Modification?

We now know that aggressive risk factor modification can dramatically reduce the chances of heart attack and stroke. A major question has always been, how aggressive should we be in risk factor modification? That is, how much should we lower the blood pressure and how much should we lower the cholesterol levels? Five studies have recently addressed this issue.

The TROPHY study looked at how much blood pressure in patients at risk should be lowered. The TROPHY study is a trial targeting the prevention of hypertension. In this trial, patients with pre-hypertension were randomized to either treatment with the angiotension receptor blocker, candasartin, or a placebo.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (the JNC 7 Report) defined normal blood pressure as blood pressures less than 120 mm Hg, systolic and diastolic less than 80 mm Hg. Systolic blood pressures between 120 and 139 mm Hg and diastolic blood pressures between 80 and 89 mm Hg were defined as pre-hypertension. The TROPHY study randomized 772 patients with pre-hypertension to either candasartin 16 mgs a day for two years or a placebo. After two years, all the patients were treated with placebos. The study lasted a total of four years. The population was relatively young, with the mean age being 48 years. The mean systolic blood pressures for the candasartin and placebo groups at baseline were 133.9 mm Hg and 134 mm Hg respectively. At the end of two years, 154 patients taking placebo and 53 patients taking candasartin developed hypertension. This represented a 66.3% reduction in the development of hypertension at 2 years in the candasartin group. Over the four-year duration of the study, the candasartin-treated patients had their risk of developing hypertension reduced by 15.6%. This was a significant reduction. During the four-year period, stage one hypertension developed in nearly two thirds of the patients with untreated pre-hypertension (the placebo group). Treatment of pre-hypertension with candasartin appeared to be well tolerated and reduced the risk of incident hypertension during this study group. This study would therefore suggest that there may be significant value to treating patients with pre-hypertension with an angeotension receptor blocker in order to prevent the development of hypertension. Further studies will need to be done to confirm this.

Just as blood pressure target levels are decreasing, so are the target goals for LDL cholesterol. A major question has been how low should LDL cholesterol be in patients at risk of coronary artery disease. The IDEAL study randomized 8,888 patients with a history of a myocardial infarction to either moderate LDL lowering with simvastatin 20 to 40 mgs a day versus more aggressive lipid lowering, with atorvastatin 80 mgs a day. The median follow-up was 4.8 years. The mean LDL cholesterol for the simvastatin treatment group was 104 mg/dl. The mean LDL cholesterol for the atorvastatin group was 81 mg/dl. At the end of 4.8 years, the more aggressive LDL lowering with atorvastatin reduced major cardiac events by 11% with the more aggressive therapy. Non-fatal myocardial infarctions were reduced 17%, and any coronary heart disease event was reduced 16%. These findings correlate with previous findings in the TNT trial, which looked at the use of atorvastatin 10 mg a day versus atorvastatin 80 mg a day. In that study, significant reductions in cardiac events were also found with more aggressive

lowering of the LDL cholesterol.

The recent ASTERIOD trial used a technique called intravascular ultrasound to accurately measure plaque volume in coronary artery disease. Patients were treated with rosuvastatin 40 mgs a day (Crestor) for twenty-four months. Patients received coronary angiograms and intravascular ultrasound studies at baseline and at follow-up two years later. Three hundred forty nine patients completed the study with good baseline and follow-up intravascular ultrasound studies. LDL cholesterols dropped from a mean of 130.4 to 60.8 mg/dl. This represented a 53% reduction in LDL cholesterol. Importantly, the group as a whole had their mean LDL cholesterol decreased to 60.8 mg/dl. HDL cholesterol increased from 43 to 49 mg/dl. Triglycerides decreased from 152 to 121 mg/dl.

After two years, the intensive treatment with rosuvastatin 40 mgs per day reduced the atheroma volume of the indexed vessel and also produced a significant reduction in the atheroma volume in the most diseased subsegment of the vessel. Both IVUS efficacy parameters showed a highly significant regression at two years for the group. Thus, very intensive treatment with rosuvastatin 40 mgs per day in a group of patients with coronary artery disease successfully reduced the LDL cholesterol to 60.8 mg/dl and raised the HDL cholesterol by 14.7%, resulting in a significant regression in the atheroma plaque burden in the coronary artery. Regression occurred in 64% to 78% of subjects treated, depending on the efficacy parameter used. The adverse events observed were low. This study raises the question as to whether fixed LDL cholesterol goals should be followed, or whether the lowest level of LDL cholesterol achievable without adverse events should be the optimal strategy for treating patients at risk. The study does provide scientific evidence supporting the newer guidelines for LDL cholesterol target goals of LDL cholesterol less than 70 mg/dl for patients with known coronary artery disease,

When discussing cholesterol risk factor modification, another significant issue is how aggressive we should be in the relatively low risk patient. The MEGA study, presented at the American Heart Association in November 2005, looked at primary prevention of cardiovascular disease in Japan, using mild to modest reductions of LDL cholesterol with pravastatin in low risk patients. The disease burden of ischemic heart disease is substantially lower in Japan than in the United States for many different reasons, including diet. The question was whether use of statin therapy in patients at low risk will produce any significant reduction in cardiovascular events.

8,214 patients were randomized to either diet therapy or diet plus pravastatin therapy, 10 to 20 mgs per day. The average follow-up was 5.3 years. The mean LDL cholesterol in the two groups was approximately 156 mg/dl; the mean HDL cholesterol in the two groups was elevated at 56 mg/dl. The primary end point of cardiovascular events was decreased by 33% at 5 years for the statin treatment group. This represented a significant reduction. All cardiovascular events were decreased by 26%. Total mortality was significantly decreased by 28% at 5 years. In this low risk population, a 33% risk reduction in coronary heart disease events was found, even though patients had higher HDL cholesterol levels and lower triglyceride levels at baseline than the average American population.

The MEGA trial raises the very intriguing question as to how aggressive we should be in treating our low risk population in the United States. Low risk is defined as a less than 5% risk of a cardiovascular event over 10 years. The 33% risk reduction in cardiovascular events in the MEGA trial using a statin therapy in a low risk population, when applied to the twenty-five million low risk patients in the United States, would predict that 125,000 cardiovascular events could be prevented over a ten-year period by using statin therapy. Interestingly, for any other disease, 125,000 events over ten years would be considered an epidemic problem. The MEGA trial, therefore, will require re-analysis as to who should and who should not be treated with lipid-lowering agents.

High homocysteine blood levels have been correlated with an increased risk of cardiovascular disease. While the use of folic acid and B vitamins will decrease homocysteine levels, there have been conflicting reports as to the clinical value of lowering homocysteine levels for the prevention of cardiovascular events.

The HOPE-2 trial looked at the value of homocysteine-lowering in patients with vascular disease, using folic acid and B vitamins. 5,522 patients were randomized in this study. The study demonstrated that supplements containing folic acid, vitamin B-6 and B-12 did not reduce the risk of major cardiovascular events in patients with vascular disease. This finding was confirmed by another recent trial called the NORVID trial, which looked at homocysteine-lowering for the prevention of subsequent cardiovascular events after an acute myocardial infarction. This study also found that treatment with B vitamins and folic acid did not lower the risk of recurring cardiovascular disease after an acute myocardial infraction. In fact, there was a trend towards possible harm. Therefore, it was felt that routine lowering of homocysteine levels with high does folic acid and B vitamins should not be routinely recommended. Lower is better for the management of blood pressure and cholesterol, but the concept does not apply to the treatment of elevated homocysteine levels.

References:

For TROPHY Trial:
Julius S, et al; *NEJM* 2006; 354:16: 1685 – 1697

For ASTERIOD Trial:
Nissen, S, et al; *JAMA* 2006; 295: 1556-1565

For NORVIT Trial:
Bonaa, K, et al; *NEJM* 2006; 354:1578-1588, Apr 13, 2006
For HOPE Trial:

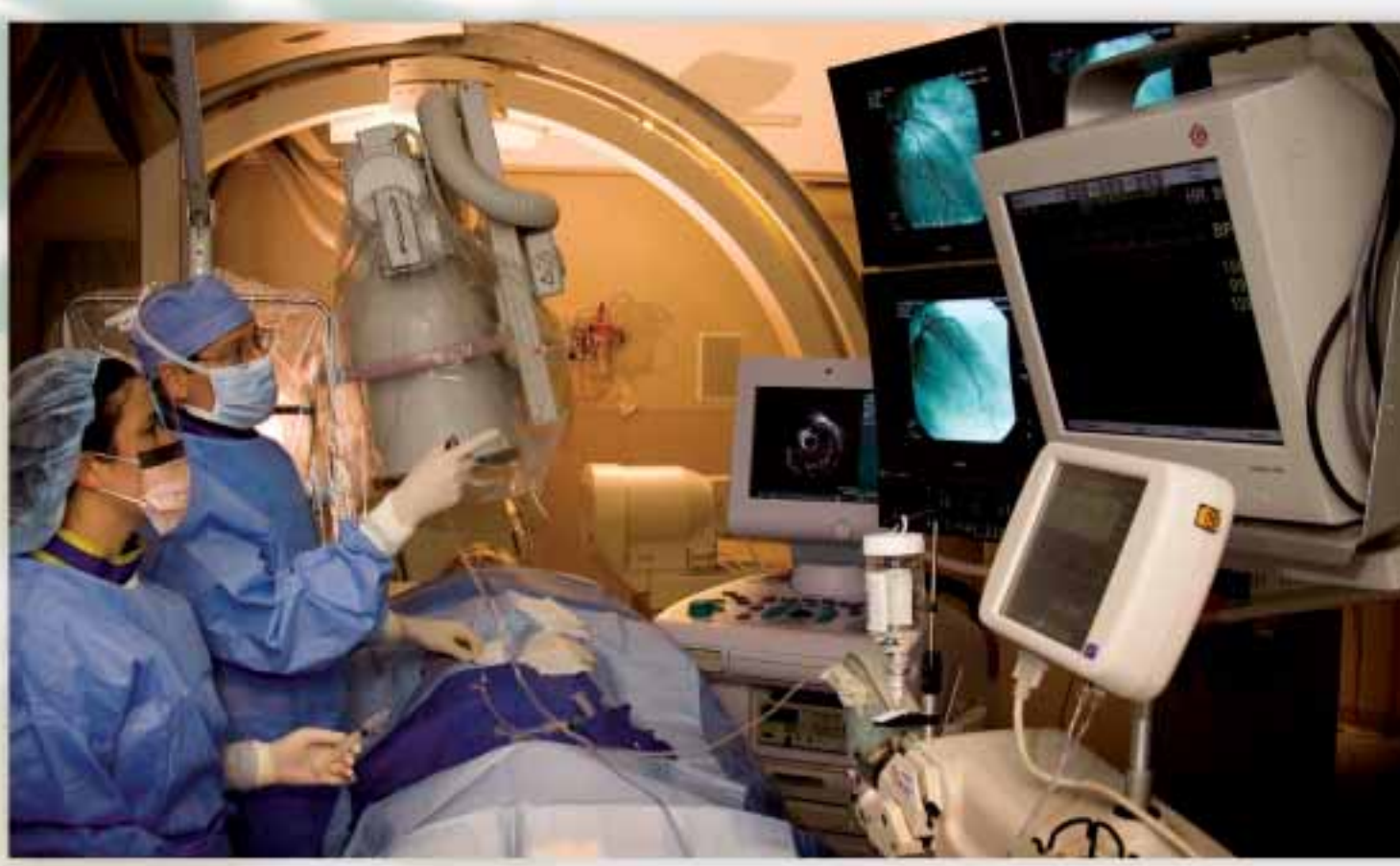
Lonn, E, et all; *NEJM* 2006; 354:1567-1577, Apr 13, 2006

(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.)

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

THE FUTURE OF CARDIOLOGY IS HERE.

918.592.0999 / 1265 SOUTH UTICA AVE. / 9228 SOUTH MINGO / www.oklahomaheart.com

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