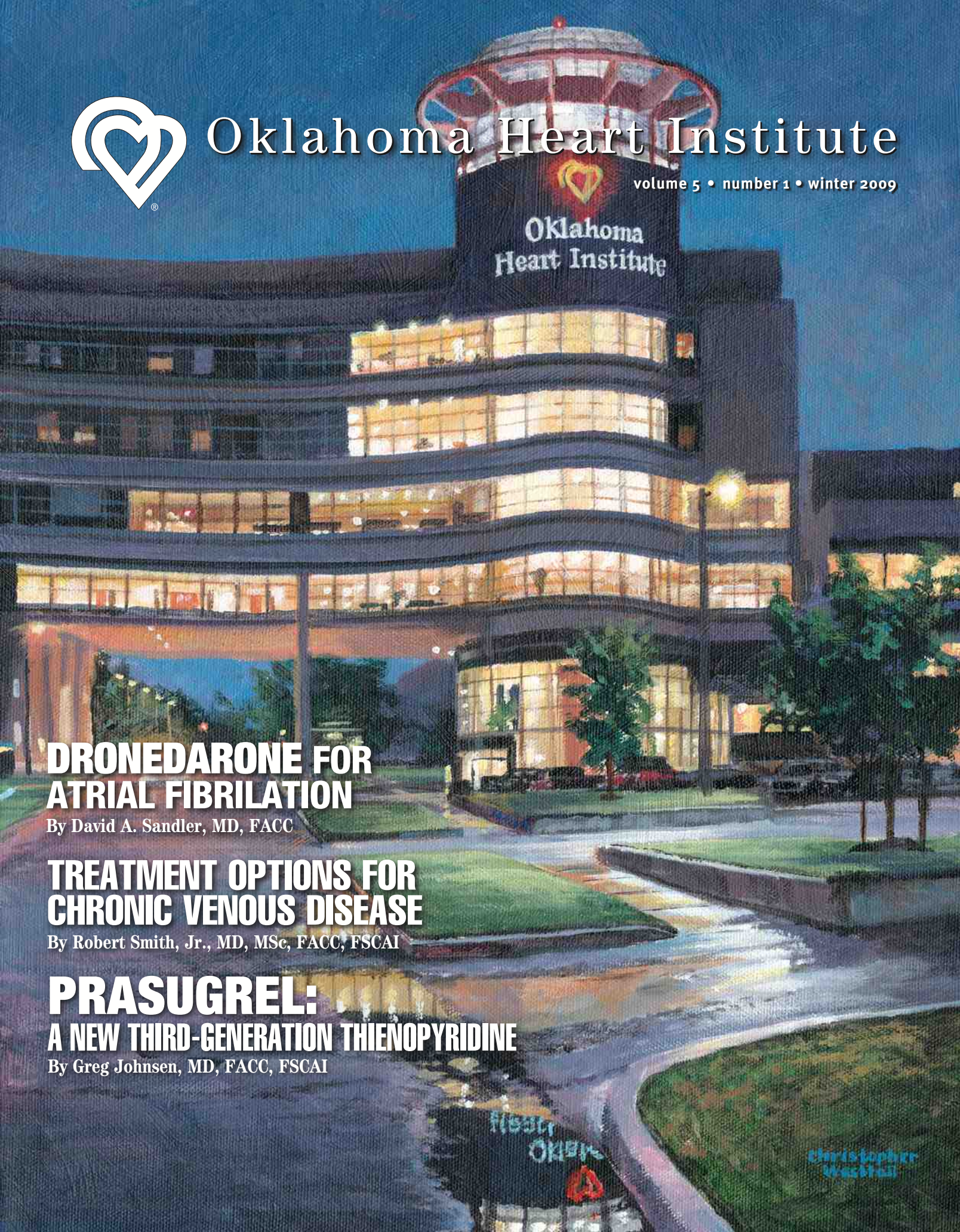

Oklahoma Heart Institute

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DRONEDARONE FOR ATRIAL FIBRILATION

By David A. Sandler, MD, FACC

TREATMENT OPTIONS FOR CHRONIC VENOUS DISEASE

By Robert Smith, Jr., MD, MSc, FACC, FSCAI

PRASUGREL: A NEW THIRD-GENERATION THIENOPYRIDINE

By Greg Johnsen, MD, FACC, FSCAI


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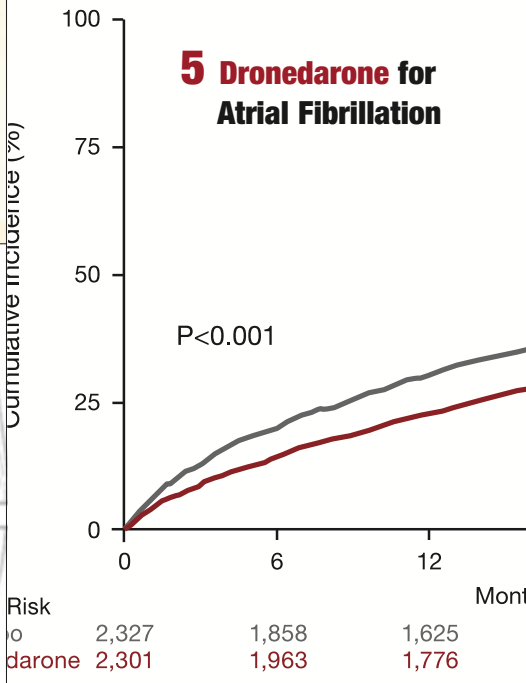
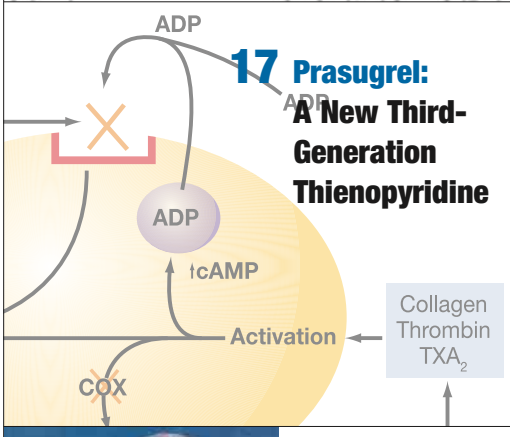
Figure 2
Risk of Death, First Cardiovasc
in the ATHENA T

5 Dronedarone for Atrial Fibrillation





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Edition 16

To Our Readers

ONE OF THE EXCITING THINGS ABOUT THE FIELD OF CARDIOLOGY is the newer treatment options that continue to become available. In this issue of Oklahoma Heart Institute Magazine, some of the newest pharmacologic agents that have been approved, or are expected to be approved, are discussed. Dr. Sandler, Director of Electrophysiology at Oklahoma Heart Institute, discusses the background information, the therapeutic efficacy, and the side effects of the recently approved anti-arrhythmic agent dronedarone. Dronedarone was recently approved for the treatment of atrial fibrillation. Dronedarone has many of the advantages of amiodarone, but without the significant side effects.

Dr. Greg Johnsen, an interventional cardiologist at Oklahoma Heart Institute, discusses the information leading to the approval of prasugrel (Effient), which is a new anti-platelet agent similar to clopidogrel, but without the concerns of patients being resistant to the medication.

Finally, Dr. Robert Smith, an invasive cardiologist at Oklahoma Heart Institute and Director of the Venous Clinic at Oklahoma Heart Institute, describes the treatment options for chronic venous disease. Peripheral venous disease is four to five times more prevalent than peripheral arterial disease. Although peripheral venous disease is less likely to affect mortality, it is a major factor affecting the quality of life for many patients.

We hope you enjoy these articles and welcome any comments or suggestions regarding the magazine content

Sincerely,

Wayne N. Leimbach Jr., MD,
Editor, Oklahoma Heart Institute Magazine

By David A. Sandler, MD, FACC

DRONEDARONE FOR ATRIAL FIBRILLATION

BACKGROUND

On July 2, 2009, the FDA approved dronedarone (Multaq) for prevention of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation associated with cardiovascular risk factors. This new oral anti-arrhythmic agent is the first to be approved by the FDA in 10 years.

Table 1
Oral Antiarrhythmic Medications Listed Alphabetically by Class

Generic Name	Trade Name
Class Ic	
Flecainide	Tambocor
Propafenone	Rythmol, Rythmol SR
Class III	
Amiodarone	Cordarone, Pacerone
Dofetilide	Tikosyn
Dronedarone	Multaq
Sotalol	Betapace, Betapace AF

Note, some drugs (particularly amiodarone, dronedarone and sotalol) share properties of other classes; the drugs are listed by class of their predominant effect.

To understand the role of this drug, it is important to review the current state of AF management. The first branch in the decision tree of AF management is the strategy of rhythm control (ie: anti-arrhythmic medications, cardioversion, AF ablation, etc) versus rate control (leaving the patient in AF and controlling rate alone). AFFIRM was a large multicenter trial demonstrating that these two strategies offered similar outcomes in a population of minimally symptomatic AF patients with an average age of 69. Therefore, a strategy of rhythm control in asymptomatic or minimally symptomatic patients has been discouraged.

Table 2
Side-Effects of Dronedarone Requiring Discontinuation in the ADONIS/EURYDIS Trials

	Placebo (n=2875)	Dronedarone (n=3282)
Gastrointestinal		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
General		
Asthenic conditions	5%	7%
Cardiac		
Bradycardia	1%	3%
Skin and subcutaneous tissue		
Rashes, pruritis, eczema, dermatitis	3%	5%

On the other hand, restoration of sinus rhythm in patients with AF has been demonstrated to improve left ventricular ejection fraction, left atrial size, and quality of life both in patients with congestive heart failure and normal ejection fraction, even when optimal ventricular rate control during AF has been achieved.

In fact, review of AFFIRM demonstrates a mortality benefit in patients who were able to maintain sinus rhythm. This benefit, however, was negated by the increased mortality associated with anti-arrhythmic medications. In other words, the medications used to treat AF seem to carry side effects, which counteract any benefit obtained from maintaining sinus rhythm.

continued on page 6

The current ACC/AHA/ESC AF Management Guidelines for maintaining sinus rhythm are summarized in Figure 1. A list of anti-arrhythmic medications recommended for AF (with generic and trade names) is listed in Table 1. Each of these agents has limitations.

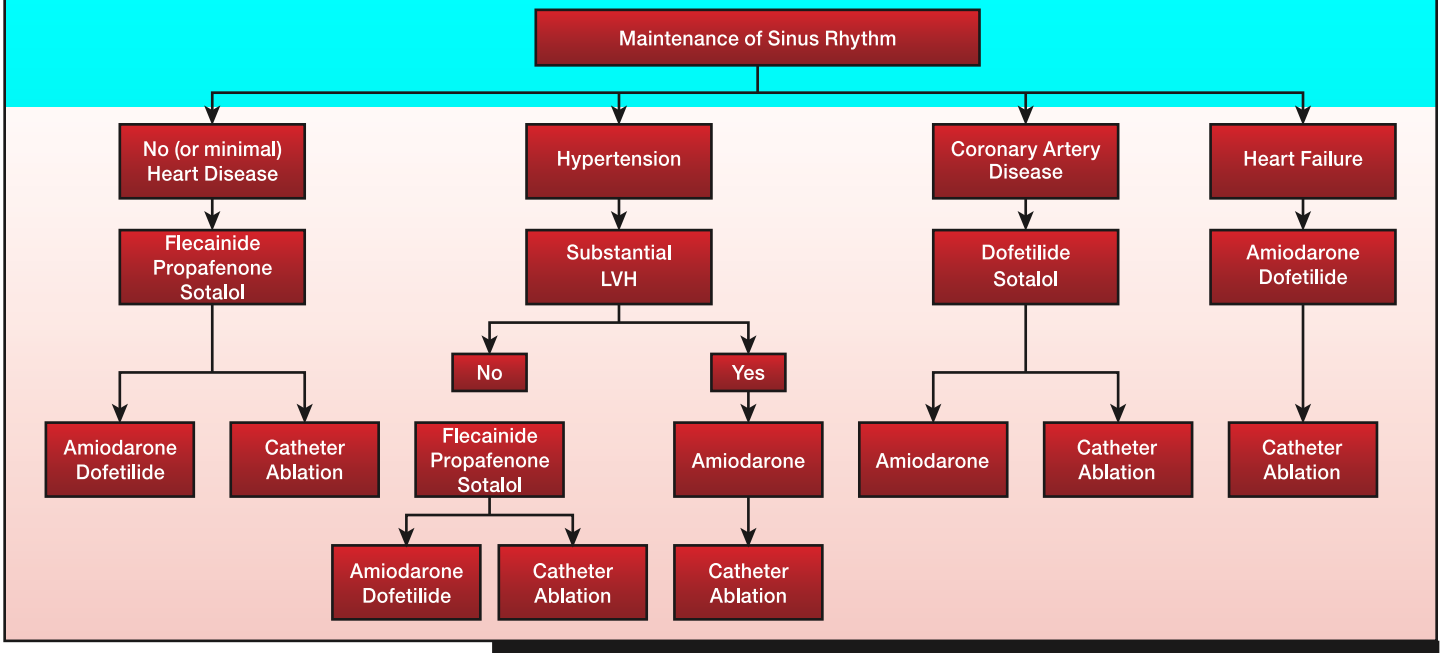
Propafenone and flecainide have limited use due to risk of increased mortality in patients with coronary artery disease or congestive heart failure. Sotalol and dofetilide each carry a risk of QT prolongation leading to torsades de pointes. In addition, each of these medications is contraindicated in patients with renal insufficiency.

The most effective anti-arrhythmic for AF is amiodarone (ironically, without an FDA indication for AF). Unfortunately, this medication is limited by its side effects. Specifically, pulmonary fibrosis, thyroid dysfunction, liver failure and skin discoloration result in significant rates of withdrawal. Each of these side effects is attributed to the iodine moiety in the chemical composition.

Dronedarone has a chemical composition similar to amiodarone, but lacks the iodine moiety. The goal, of course, is to harness the efficacy of amiodarone without the side effects. This drug has been the subject of numerous clinical studies evaluating efficacy and safety.

Figure 1

Strategy for Maintaining Sinus Rhythm in Patients Treated with a Strategy of Rhythm Control (ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation 2006)



Large randomized trials have demonstrated that dronedarone is a safe alternative to the more commonly prescribed antiarrhythmic agents on the market. The trade-off of this safety is lower efficacy in preventing AF recurrence.

THE TRIALS

The ATHENA Trial was the largest dronedarone trial and included 4,638 patients with risk factors for stroke (age ≥ 75 or age ≥ 70 with hypertension, diabetes, left atrial enlargement, ejection fraction < 40 percent or prior TIA/stroke) randomized to dronedarone or placebo. In these patients dronedarone was associated with a 24 percent reduction in death or cardiovascular hospitalization (Figure 2). Oklahoma Heart Institute was a participant in ATHENA, and we are grateful to our patients for partnering with us in this landmark trial.

The ANDROMEDA Trial was designed to evaluate potential benefit of dronedarone on all-cause mortality or hospitalization for worsening heart failure. The study enrolled 627 patients with relatively severe heart failure who had been hospitalized or referred to a specialty

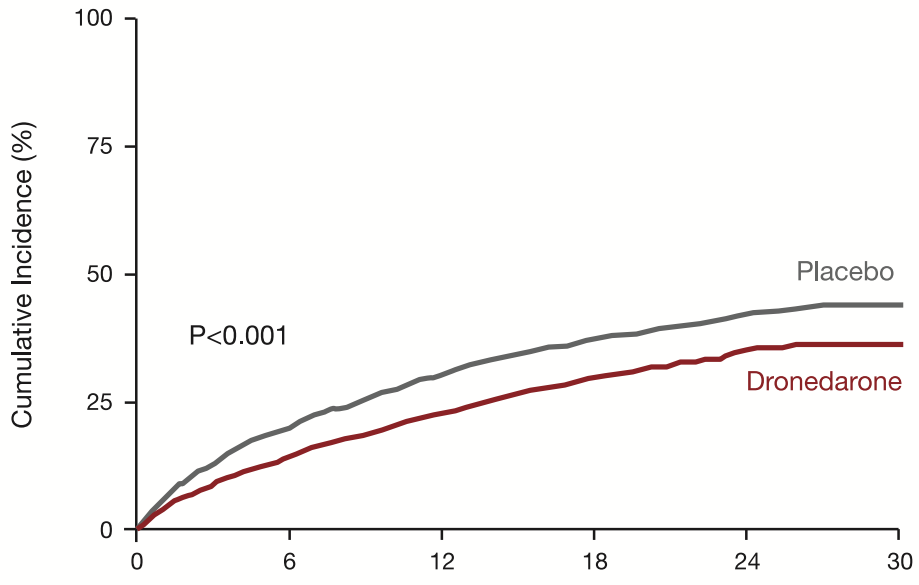
clinic for worsening symptoms of heart failure. This trial was terminated prematurely when the Data Safety and Monitoring Board detected a greater than two-fold increase in mortality in dronedarone

studies of dronedarone or amiodarone. Amiodarone was shown to reduce AF recurrence more effectively than dronedarone. However, adverse effects were higher with amiodarone, and a

Adverse reactions of dronedarone are listed in Table 2. Notably, gastrointestinal complaints appear common with this medication. Fortunately, serious side effects such as pulmonary fibrosis, torsades de pointes and hepatic failure appear to be extremely rare.

Figure 2

Risk of Death, First Cardiovascular Hospitalization in the ATHENA Trial



No. at Risk						
Placebo	2,327	1,858	1,625	1,072	385	3
Dronedarone	2,301	1,963	1,776	1,177	403	2

group. For this reason, dronedarone should not be prescribed to patients with NYHA Class IV heart failure or patients with Class II-III with a recent decompensation.

The EURIDIS/ADONIS Trials enrolled a total of 1,237 patients with ≥ 1 documented episode in the prior three months. In these patients, there was a 25 percent reduction in the risk of recurrent AF.

The DIONYSIS Trial pit dronedarone against amiodarone in 504 patients. This as-of-yet unpublished trial demonstrated a significantly higher rate of AF recurrence with dronedarone (63 percent vs 42 percent) with a trade-off of fewer adverse effects.

A recent meta-analysis reviewed trend towards improved mortality was seen with dronedarone.

CONTRAINDICATIONS/ADVERSE REACTIONS

Dronedarone is contraindicated in patients with NYHA Class IV heart failure or Class II-III with recent decompensation (based on the ANDROMEDA Trial). Severe liver failure, bradycardia (<50 bpm), QTc >500ms are also reasons to avoid dronedarone. Drugs that prolong QT or inhibit CYP 3A should be avoided with dronedarone. Digoxin should be avoided, or at least halved. (As always, please review package insert prior to prescribing any new drug).

SUMMARY

Dronedarone is a new antiarrhythmic drug indicated for prevention of cardiovascular hospitalization in patients with AF and risk factors for stroke. Large randomized trials have demonstrated that dronedarone is a safe alternative to the more commonly prescribed antiarrhythmic agents on the market. The trade-off of this safety is lower efficacy in preventing AF recurrence.

Whether this new, safer agent will shift the paradigm of rate control versus rhythm control will be tested in the future.

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Dr. David Sandler is a cardiologist with specialty expertise in electrophysiology, complex ablation and atrial fibrillation management.

By Robert Smith, Jr., MD, MSc, FACC, FSCAI

Treatment Options for Chronic Venous Disease

ALTHOUGH RECENT YEARS have brought about a greater awareness of the importance of diagnosing and treating peripheral arterial disease, pathology of the venous system has received little attention. Peripheral venous disease was first mentioned in the medical literature in 500 BC, when Hippocrates described an association between leg ulcers and varicose veins.[1] Despite longstanding recognition, understanding of issues surrounding venous hypertension and resultant venous incompetence has lagged.

Peripheral venous disease is four to five times more prevalent than peripheral arterial disease,[1] and the clinical presentation of lower extremity venous incompetence spans a broad clinical spectrum from telangiectasias (spider veins) to long-standing and recalcitrant venous stasis ulcers. This spectrum of disease manifests from cosmetically displeasing lesions on the legs to threats of serious secondary illnesses such as DVT/PE and infection from chronic ulceration. Venous disease has a hereditary component, and children of patients with varicose veins are more likely to develop problems related to venous reflux.[2] Occupations characterized by inactivity, such as standing or sitting for long periods of time, also place patients at risk.[3]

Traditionally, treatment of venous incompetence has consisted mainly of surgical "vein stripping" procedures,

Figure 1

Veins of the Deep and Superficial Venous Systems of the Lower Extremity

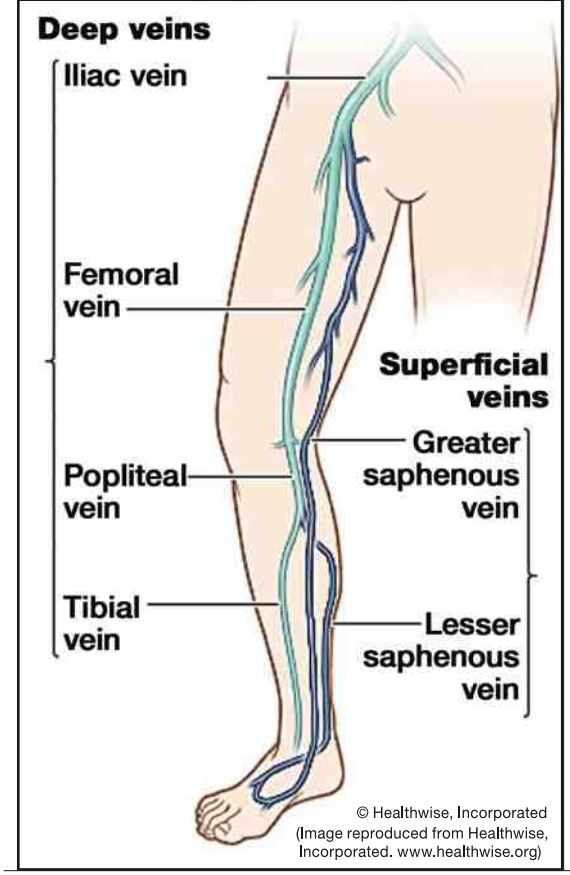
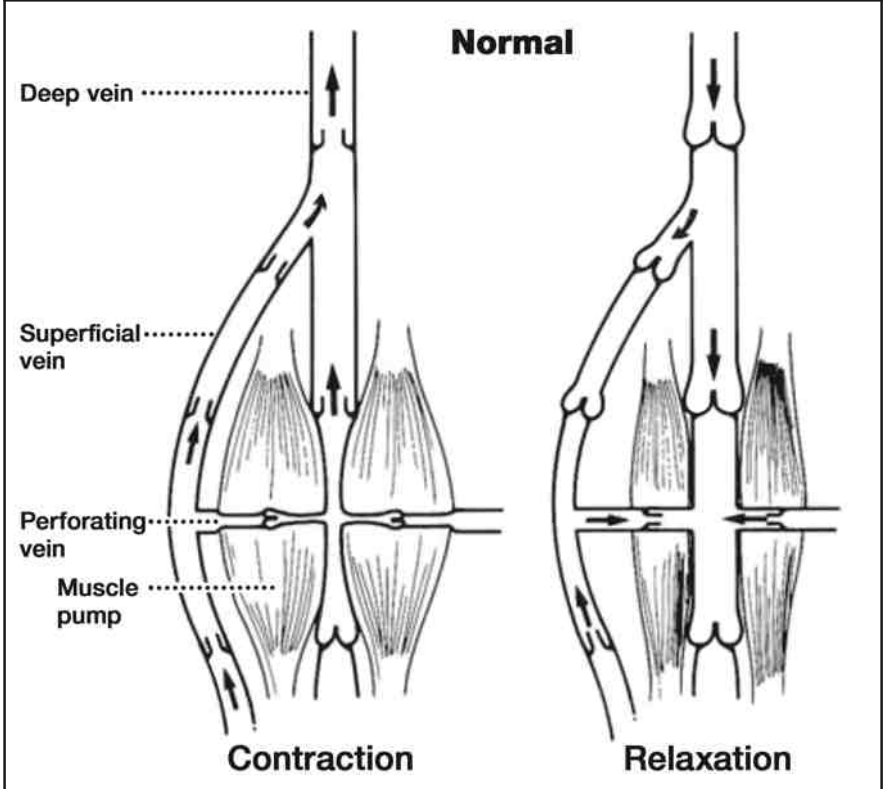


Figure 2

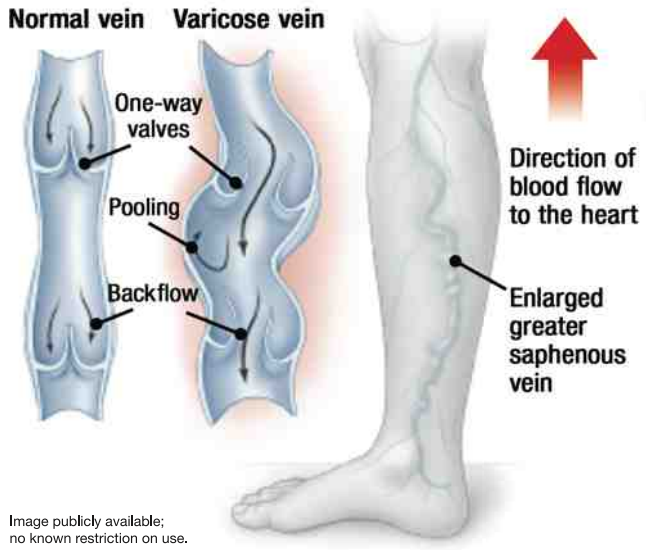
Flow of Venous Blood from the Deep System to the Heart is Aided by the Pumping of the Calf Muscles, Which Actively Propel Blood Against Gravity with Each Contraction.



(Image reproduced from "Chronic Venous Insufficiency" ASUM Ultrasound Bulletin, 2004 August. 7:4: 14–21)

Figure 3

Normal and Incompetent Venous Valves



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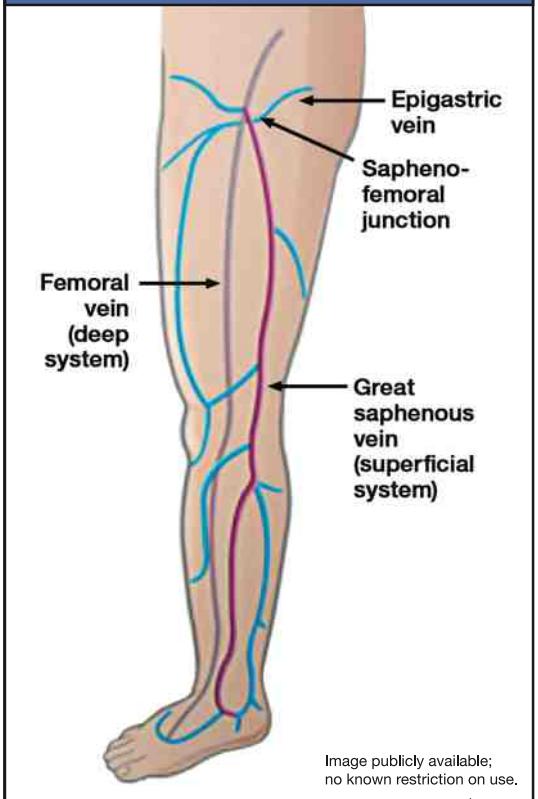
during which large veins from the superficial collecting system of the legs are ligated and/or removed under general anesthesia. These surgical procedures, while effective, are associated with the risks of general anesthesia, infection of surgical wounds, long recovery times, and considerable patient discomfort. Perhaps for these reasons, surgical treatment of venous disease has occupied a rather small niche, and many patients have chosen to live with the condition rather than opt for surgery.

In order to understand the physiology of venous reflux disease, one must understand that there are two distinct venous systems in the lower extremities: the deep venous system is comprised of veins that run parallel to the arteries. These veins are surrounded by muscle and encased in fascia, providing them with good mechanical support. The deep veins are responsible for returning >95 percent of the venous blood from the lower extremity back to the heart. The superficial system, comprised of the saphenous veins, perforator veins, and tributaries, lies just beneath the skin and is without the mechanical support of the deep system. These superficial veins collect blood from surrounding tissues and, in a healthy system, route blood into the deep system so that it may be returned to the heart (Figure 1). It is typically incompetence of the superficial system that gives rise to the clinical sequelae of venous reflux disease.

It is widely accepted that the genesis of common manifestations of venous disease relates to incompetence of the greater saphenous vein, the largest superficial vein. In some cases, the small saphenous vein (previously referred to as the lesser saphenous vein) is also involved. These superficial veins are located about a centimeter beneath the skin and should be less than 3mm in diameter in a healthy patient, though they can dilate to greater than 10mm in a patient with venous reflux disease. Unlike the deep venous system, where contraction of the leg muscles plays an important role in "pumping" the venous blood back to the heart, the return of venous blood in the superficial systems is passive and depends entirely upon a series of one-way valves that aid the flow of the superficially collected blood on its route back to the deep venous system. Once in the deep system, venous blood is actively propelled against gravity back to the heart, primarily through the action of the calf muscles (Figure 2). In a healthy system, the superficially collected blood enters the deep venous system at two critical anatomic locations: the small saphenous vein deposits blood into the deep system at the sapheno-popliteal junction (near the knee) and the greater saphenous vein deposits blood into the deep system at the sapheno-femoral junction (near the groin). Additionally, smaller veins (called perforator veins) communicate between the superficial and deep systems throughout the length of their parallel course. These smaller perforator veins also have one-way valves that assist in the return of superficially collected blood back to the deep system. If the series of one-way valves in the superficial veins (and/or perforator veins) become incompetent (Figure 3), the superficial system becomes congested, and the flow of blood into the deep system (and subsequently toward the heart) stalls, resulting in edema, pain, and other clinical sequelae. When valvular function in the superficial system

continued on page 10

Figure 4



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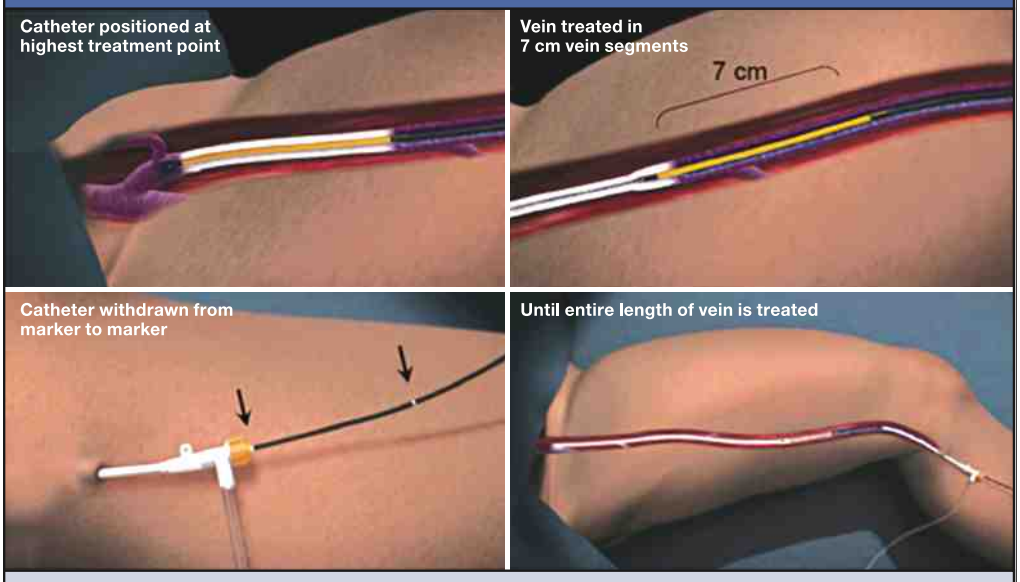
The most common site of venous incompetence is the sapheno-femoral junction, where blood from the deep system is diverted from its route back to the heart and flows into the superficial system in a retrograde fashion, resulting in a blind loop, where oxygen and nutrient poor blood cycles endlessly from the deep system into the superficial system and back again, never returning to the heart.

Figure 5

The VNUS Closure Procedure

Using the ClosureFAST™ Catheter



In minimally invasive radiofrequency (RFA) ablation of the greater saphenous vein, a small incision is made near the knee (lower left panel), and the RFA catheter is advanced to a level just distal to the sapheno-femoral junction (upper left panel). Radiofrequency waves are then applied in a segmental fashion, treating 7 centimeters of the vein at a time. Pullback of the catheter is performed and the treatment is repeated until the entire length of the desired segment of vein is treated (right panels).

(Image provided by VNUS Medical Technologies, Inc.)

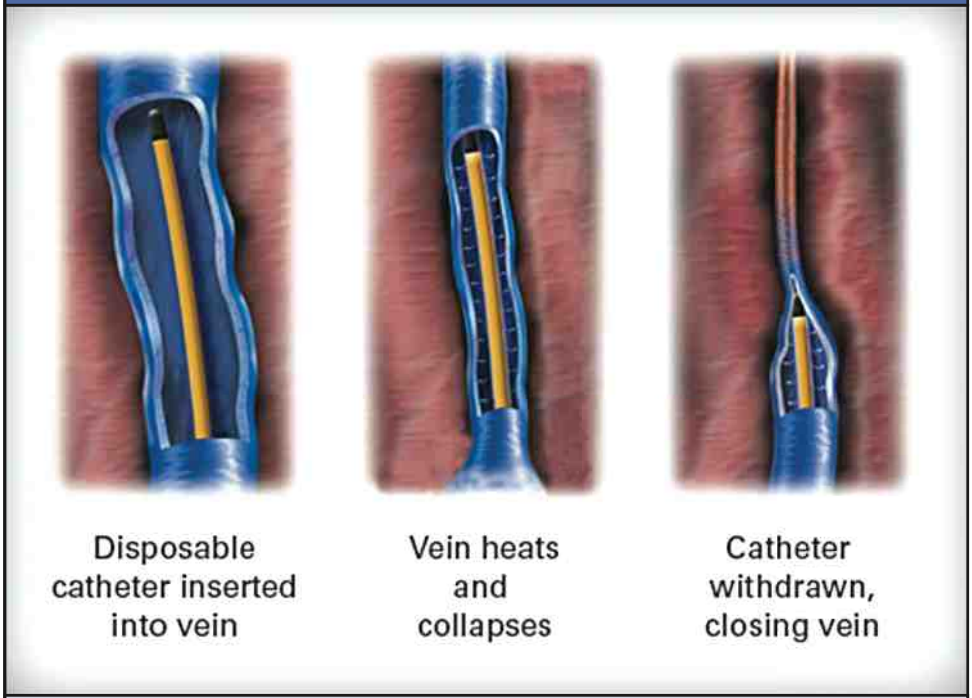
venous blood from the deep system, en route to the heart, is diverted from the (deep) femoral vein back into the (superficial) greater saphenous vein. This is typically the starting point of the pathologic cycle, and causes the greater saphenous vein to become increasingly engorged, setting off a cascade of events where superficial valves, unaided by the pumping function of the leg muscles, fail in a proximal to distal fashion until clinical manifestations develop. Surgical removal of a diseased greater saphenous vein is effective in the treatment of venous reflux disease because the most common site of retrograde flow from the deep to superficial system is eliminated and the blood has nowhere to go but up (and back to the heart). Experience with surgical removal of the greater saphenous vein goes back many decades. Surgical literature on the topic indicates that, regardless of the

continued on page 15

becomes sufficiently compromised, deoxygenated venous blood flows backwards, *from the deep system into the superficial system*, at these critical anatomic points, resulting in a blind loop, where deoxygenated blood cycles endlessly from the deep system to the superficial system, back to the deep system, and so forth, never making it back to the heart. Common clinical manifestations of these events are edema, heaviness, throbbing, pain, varicosities (bulging tributaries of the overloaded superficial veins), and skin changes that occur as a result of the endless loop of oxygen and nutrient poor blood circulating throughout the lower extremity network of veins. At the extreme, refractory and painful venous ulcers develop.

Although incompetence of the one-way valves can occur at any point in the network, the most common site of incompetence is the sapheno-femoral junction (Figure 4), where superficially collected blood in the greater saphenous vein should drain into the femoral vein (of the deep system). When incompetence of the sapheno-femoral junction occurs,

Figure 6



Using a radiofrequency ablation catheter, the diseased vein is cannulated and energy is applied from within, resulting in fibrotic obliteration of the vein. The result is functionally identical to surgical "vein-stripping" procedures, during which the vein is surgically removed under general anesthesia.

(Image provided by VNUS Medical Technologies, Inc.)

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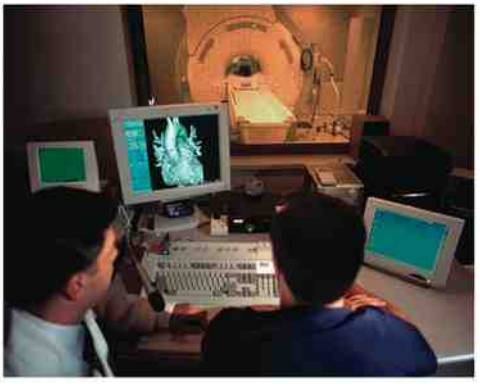

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THE DOCTORS OF OKLAHOMA HEART INSTITUTE

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

Dr. Leimbach is a specialist in interventional cardiology, including cardiac catheterization,

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

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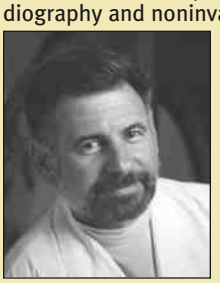
Robert C. Sonnenschein, MD, FACC, ASE, RVT

Dr. Sonnenschein specializes in echocardiography and noninvasive peripheral vas-



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

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Registered Vascular Technologist

Robert E. Lynch, MD, FACC

Dr. Lynch is a specialist trained in noninvasive and invasive cardiology with a special interest

in the prevention of cardiovascular disease. 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. Dr. Lynch is also a Clinical Assistant Professor at the University of Oklahoma College of Medicine – Tulsa. He completed his Cardiology Fellowship, as well as his Internal Medicine Internship and Residency, at the University of Oklahoma Health Sciences Center. Dr. Lynch received his medical degree from the University of Oklahoma School of Medicine and his Bachelor of Science degree from the University of Tulsa. Before establishing his practice in Tulsa, he served as Chief of Medicine at the U.S. Army Hospital, Bangkok, Thailand.

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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.

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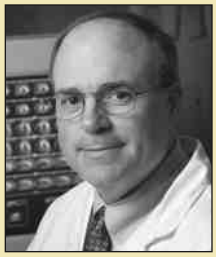

Board certified in Internal Medicine, Cardiovascular Disease, Echocardiography, Pediatrics and Nuclear Cardiology

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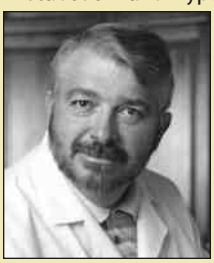
Dr. Hanson is a specialist in Endocrinology, Metabolism and Hypertension at Oklahoma Heart Institute with expertise in diabetes, lipids and hypertension. He also serves as Clinical Associate Professor of Medicine in the College of Osteopathic Medicine – Oklahoma State University. He completed a Fellowship 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, Endocrinology, Diabetes and Metabolic Diseases

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Dr. Smith is a noninvasive cardiologist with subspecialty expertise in transthoracic echocardiography, transesophageal echocardiography, intraoperative echocardiography, stress and pharmacological echocardiography and contrast echocardiography. 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.

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

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Dr. Aspenson is a specialist 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.

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Dr. Flesner-Gurley is a specialist 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.

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Dr. Smith specializes in interventional cardiology including cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures. He completed an Interventional Cardiology Fellowship at the University of Florida College of Medicine in Jacksonville, FL. Dr. Smith performed his Clinical Cardiology Fellowship at Vanderbilt University School of Medicine in Nashville, TN and Tulane University School of Medicine in New Orleans. He received his medical degree from the University of Oklahoma College of Medicine in Oklahoma City and then completed his Internal Medicine Internship and Residency at Emory University School of Medicine in Atlanta, GA. Dr. Smith received his Bachelor of Science, Bachelor of Arts, and Master of Science degrees at the University of Oklahoma in Norman, OK.

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Dr. Cameron is a cardiologist with subspecialty expertise in electrophysiology, including the implantation and management of cardiac pacemakers, defibrillators, and cardiac resynchronization devices, as well as catheter ablation. He completed his Cardiac Electrophysiology Fellowship and his Cardiovascular Disease Fellowship at Baylor University Medical Center in Dallas, TX. Dr. Cameron's Internship and Internal Medicine Residency were performed at Baylor College of Medicine in Houston. He earned his medical degree from the University of Kansas School of Medicine in Kansas City, KS. Dr. Cameron received his Bachelor of Science degree at Pittsburg State University in Pittsburg, KS.

Board certified in Internal Medicine and Cardiovascular Disease

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Dr. Ichinose specializes in interventional cardiology including cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound and peripheral vascular interventional procedures. He earned his Bachelor of Science degree from Texas Christian University in Fort Worth, TX and his medical degree from Louisiana State University in New Orleans. He then completed his Internal Medicine residency, general cardiology and interventional cardiology fellowships at the University of Massachusetts Memorial Health Care Center in Worcester, MA.

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Dr. Bruns is a specialist in endocrinology, diabetes and metabolism at Oklahoma Heart Institute, with expertise in diabetes, thyroid disease (including thyroid cancer) and polycystic ovary syndrome. She completed her Internal Medicine Internship and Residency and Endocrinology Fellowship at the University of Wisconsin Hospital and Clinics in Madison, WI. Dr. Bruns earned her medical degree from Saint Louis University School of Medicine in St. Louis, MO and her Bachelor of Arts and Bachelor of Science degrees in biology from Truman State University in Kirksville, MO. Prior to joining Oklahoma Heart Institute, Dr. Bruns worked as a clinical endocrinologist at the Dean Clinic in Madison, Wisconsin.

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

Gregory A. Cogert, MD

Dr. Cogert is a cardiologist who specializes in electrophysiology, including catheter ablation of arrhythmia, as well as the implantation and management of cardiac pacemakers, defibrillators, and cardiac resynchronization devices. He completed his Cardiac Electrophysiology Fellowship at Mayo Clinic in Rochester, MN and his Cardiovascular Fellowship at Cedars-Sinai Medical Center in Los Angeles, CA. Dr. Cogert's Internal Medicine Internship and Residency were completed at UCLA Medical Center in Los Angeles. He earned his medical degree from the University of California in Irvine and received his Bachelor of Science degree in microbiology and molecular genetics from the University of California in Los Angeles.

Board certified in Internal Medicine, Cardiovascular Disease, Echocardiography and Nuclear Cardiology

John S. Tulloch, MD

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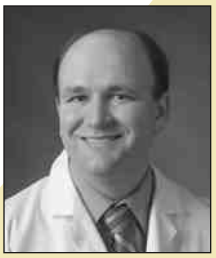
Board certified in Internal Medicine

Anthony W. Haney,MD

Dr. Haney is a noninvasive cardiologist with expertise in nuclear cardiology, echocardiography, peripheral vascular imaging, cardiac computed tomography and MRI. He completed his Cardiovascular Fellowship at the Medical College of Virginia in Richmond. Dr. Haney's Internal Medicine Internship and Residency were completed at the Mayo Clinic in Scottsdale, AZ. He earned his medical degree from the University of Oklahoma School of Medicine.



Board certified in Internal Medicine, Cardiovascular Disease and Nuclear Cardiology

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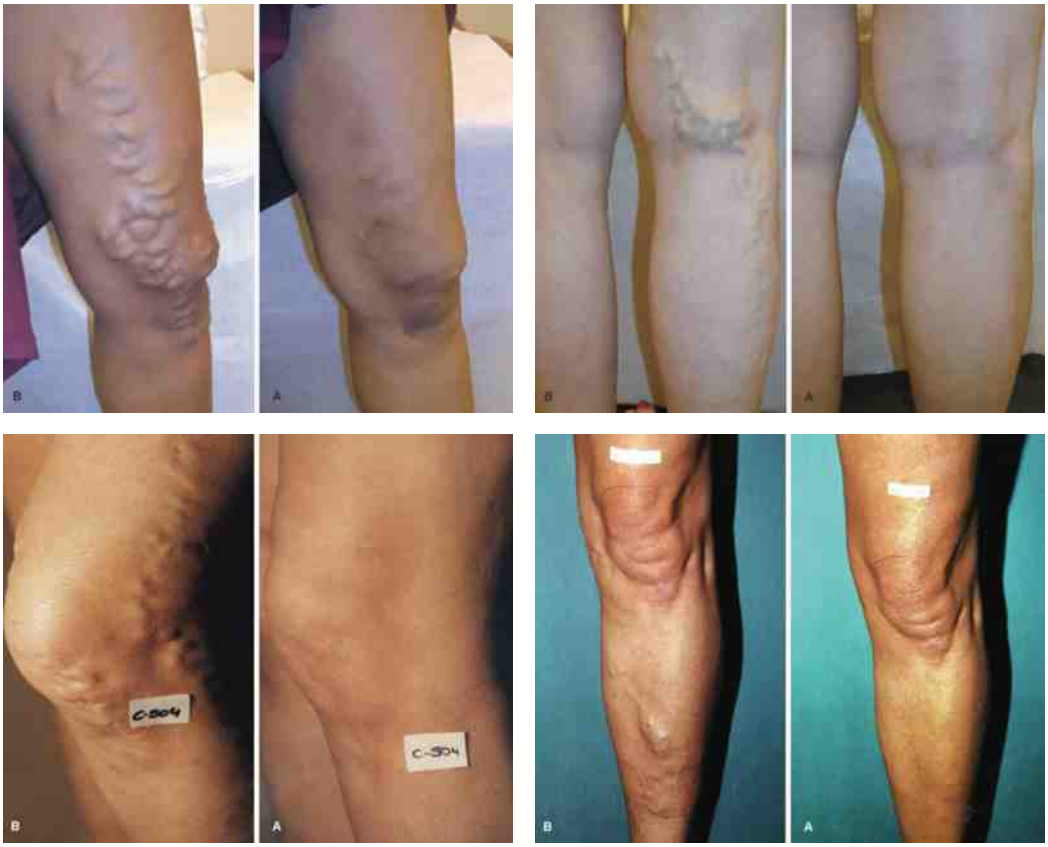
extent of disease in the superficial systems, doing away with the retrograde flow at the sapheno-femoral junction alone (by removing the greater saphenous vein) will provide dramatic clinical results in most patients.[4,5,6]

Figure 7
Images from Before and After RFA Ablation of the Greater Saphenous Vein



Images publicly available; no known restriction on use.

When the offending greater saphenous vein is removed, the superficial blood it collects reroutes and finds alternative pathways directly into the deep system, and the stress on the superficial system is alleviated, if not altogether reversed. With removal of a diseased greater saphenous vein, varicosities often shrink, edema improves, and skin changes and ulcers begin to heal. For patients who fail to experience complete relief from removal of the greater saphenous vein, a host of other treatments are available, including removal of persistent varicosities through tiny incisions under local anesthesia (stab phlebectomies), removal of the small saphenous vein, and sclerotherapy, which is often reserved for small telangiectasias and recalcitrant perforator vein disease. Except for surgical vein stripping, each of these procedures can be performed on an outpatient basis under local anesthesia with good results.

During the last several years, less invasive alternatives to surgical vein stripping procedures have been developed, and have targeted treatment of greater saphenous and small saphenous veins. Endovenous laser ablation and radiofrequency ablation of diseased greater and small saphenous veins have largely replaced the more painful surgical procedures. In several trials, these minimally invasive procedures, which can be performed on an outpatient basis, have proven to be as effective as the surgical alternatives.[7,8,9,10] While laser endovenous ablation of the greater saphenous vein and radio-frequency ablation of the greater saphenous vein are both as effective as surgery, radiofrequency ablation causes the least amount of patient discomfort, and is emerging as the minimally invasive procedure of choice.[11,12]

During radiofrequency ablation of the greater saphenous vein, a tiny incision is made near the knee (Figure 5). Under ultrasound guidance, the greater saphenous vein is cannulated and a radiofrequency ablation catheter is advanced from the knee to the sapheno-femoral junction near the groin. Radiofrequency waves are then applied to the vein, causing the vein to fibrose and permanently close (Figure 6). In a matter of minutes, the vein is ablated, and the same functional outcome of the more painful surgical treatments is achieved. Although the benefit to the patients is the same as the surgical approach, patients may have this procedure performed on an outpatient basis and will walk out of the office afterward, often experiencing dramatic results in hours to days after the procedure. When done properly, radiofrequency ablation of the saphenous vein is associated with little pain, speedy recovery time, and lasting results.[11,12] Complications, which include infection, paresthesias, DVT/PE, skin burns, and lymphedema, are exceedingly rare.[11,12]

Several clinical scenarios may lead to the recommendation of minimally invasive saphenous vein ablation, but the presence of reflux must be confirmed by ultrasound prior to consideration of any treatment. Venous duplex and mapping studies are performed in order to rule out deep venous thrombosis in the deep venous

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system and to evaluate for dilation and reflux in the superficial system. If a saphenous vein is greater than 3mm in diameter and doppler evidence of physiologically significant reflux exists (greater than 0.5s of reflux is pathologic), the patient with clinical manifestations such as edema, pain, and varicosities may be considered for treatment. Prior to minimally invasive saphenous vein ablation, conservative measures should be tried. These include compression with graded elastic stockings, leg elevation, exercise, and symptomatic pain management with NSAIDS. If the patient demonstrably fails a 3-6 month trial of conservative therapy, they may be considered for minimally invasive saphenous vein ablation. In cases where isolated saphenous vein ablation fails to entirely treat the problem, a host of adjunctive therapies, such as stab phlebectomy and sclerotherapy, are available.

Venous reflux disease results in painful and cosmetically displeasing derangements of normal venous anatomy. At the extreme, it leads to recalcitrant venous ulcers, which can themselves cause secondary health issues. In the modern era, this common disease can be effectively treated with a minimally invasive, office-based procedure, with pleasing results (Figure 7). Radiofrequency saphenous vein ablation results in less discomfort and risk to the patient than surgical alternatives, and is proven to have lasting benefit.

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Dr. Robert Smith specializes in interventional cardiology including cardiac catheterization, coronary angioplasty and related interventional procedures such as coronary stents, atherectomy, intravascular ultrasound, and peripheral vascular interventional procedures. ***Dr. Smith is the Director of the Oklahoma Heart Institute Center for the Treatment of Venous Disease.***

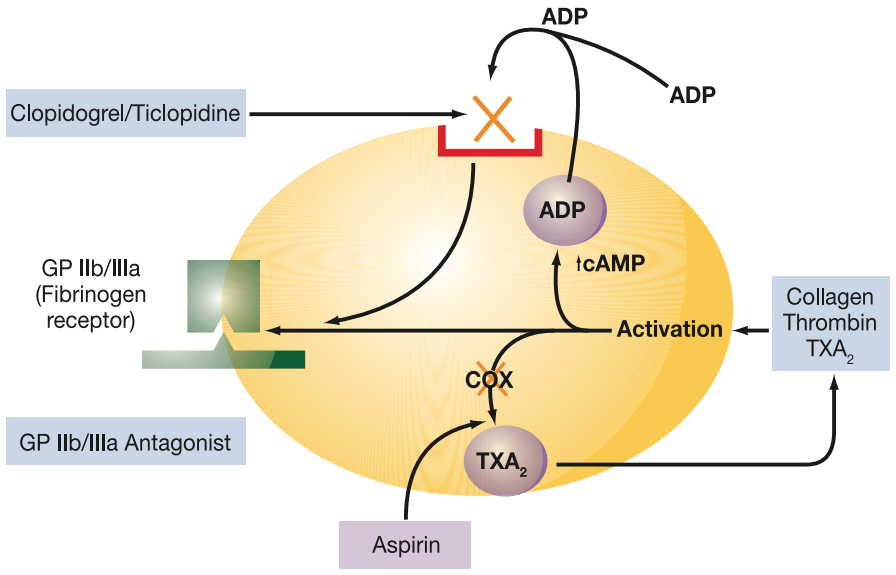
By Greg Johnsen, MD, FACC, FSCAI

PRASUGREL:
A New Third-Generation Thienopyridine

DUAL ANTIPLATELET THERAPY with aspirin and thienopyridine is a crucial element of treatment to prevent thrombotic complications in acute coronary syndromes and in percutaneous coronary interventions. Thienopyridines inhibit platelet aggregation, increase bleeding time and reduce blood viscosity by inhibiting adenosine diphosphate (ADP) action on platelet receptors. They inhibit the binding of ADP to the P2Y12 component of the ADP receptor (Figure 1). Blockade of this receptor inhibits ADP-induced platelet activation and subsequent platelet aggregation, and also decreases platelet activation by other outside stimuli.

Ticlopidine (Ticlid), clopidogrel (Plavix) and prasugrel (Effient) are the three available thienopyridines that are used in clinical practice. Ticlopidine (Ticlid) was the first thienopyridine used in the stent era, but was associated with a high rate of gastrointestinal side effects and bone marrow suppression.

Figure 1
Mechanisms of Action of Antiplatelet Therapies



ADP= adenosine diphosphate; cAMP=cyclic adenosine monophosphate; COX=cyclooxygenase; GP=glycoprotein; TXA_2=thromboxane A_2

Adapted from Schafer AI: Antiplatelet Therapy. Am J Med 101:199, 1996.

Ticlopidine is associated with neutropenia, thrombocytopenia, and in one percent of cases with TTP which can be fatal in 25-40 percent of cases. Thus, a CBC should be checked every two weeks while on ticlopidine. In the past few years, ticlopidine has been used only on rare occasions, mostly in patients who are allergic to clopidogrel.

Clopidogrel (Plavix) was developed to avoid the hematological complications associated with ticlopidine. In clinical trials, clopidogrel has not been associated with an increased incidence of these hematological side effects. Clopidogrel quickly replaced ticlopidine as the preferred thienopyridine in the late 1990s. There are several limitations to clopidogrel therapy, including significant interpatient variability of effectiveness[1,2] and a delayed onset of action.[3]

Despite treatment with dual anti-platelet therapy, a significant percentage of patients have recurrent thrombotic events. Patients with a reduced pharmacological response to clopidogrel are at an increased risk for coronary stent thrombosis and myocardial infarction.[4] Coronary stent thrombosis can be a devastating complication with mortality rates ranging from 32-45% in patients with drug-eluting stent thrombosis.[5] There is a significant genetic variability of pharmacological response to clopidogrel, which makes some patients less responsive to

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clopidogrel, increasing their risk for coronary stent thrombosis.

Prasugrel (Effient), a new third-generation thienopyridine, was recently approved by the FDA as an alternative to clopidogrel for the treatment of patients having percutaneous coronary intervention and acute coronary syndromes. Both clopidogrel and prasugrel are products requiring conversion to their active metabolite by liver enzymes; however, prasugrel uses a single, rather than a multiple-step process for activation, which provided a higher potency and a faster onset of action than clopidogrel.[5] Prasugrel inhibits ADP-induced platelet aggregation more quickly, more consistently and to a greater degree than clopidogrel in patients with coronary artery disease.

The TRITON-TIMI-38 trial was designed to test the hypothesis that using an agent with a higher level of inhibition of ADP-induced platelet aggregation and a more consistent response than clopidogrel reduces ischemic events.[7] TRITON-TIMI 38 enrolled 13,608 patients with acute coronary syndromes who were scheduled for PCI and were randomized to either prasugrel or clopidogrel. 26 percent of the patients had ST elevation MI and 74 percent had unstable angina or Non-ST elevation MI (Table 1). 94 percent of the patients received at least one coronary stent, and 47 percent received at least one drug-eluting stent. A loading dose of study medication (60mg of prasugrel or 300mg of clopidogrel) was given in a randomized, double blind manner followed by maintenance doses of prasugrel (10mg) or clopidogrel (75mg) daily (Figure 2).

Prasugrel, a new third-generation thienopyridine can be used as an alternative to clopidogrel in patients with acute coronary syndromes who are scheduled to have PCI.

The primary efficacy end point in the TRITON-TIMI 38 trial was a composite of the rate of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke during the follow-up period. Key secondary endpoints were stent thrombosis and a composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke or rehospitalization for cardiac ischemia.

Figure 2

ACS (STEMI or UA/NSTEMI) and Planned PCI

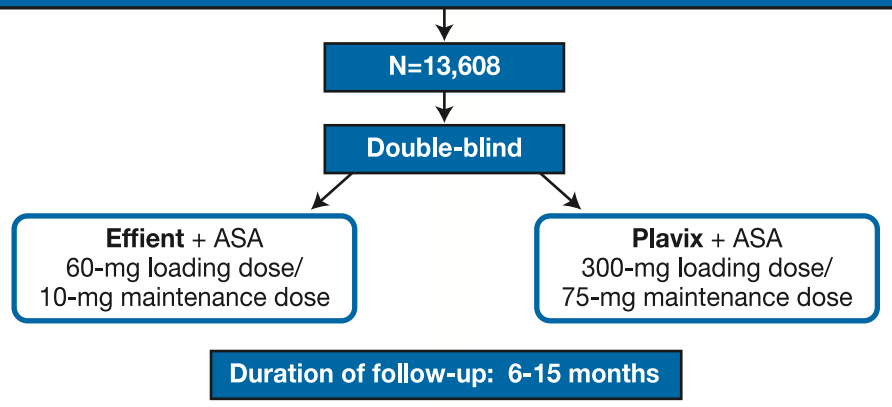
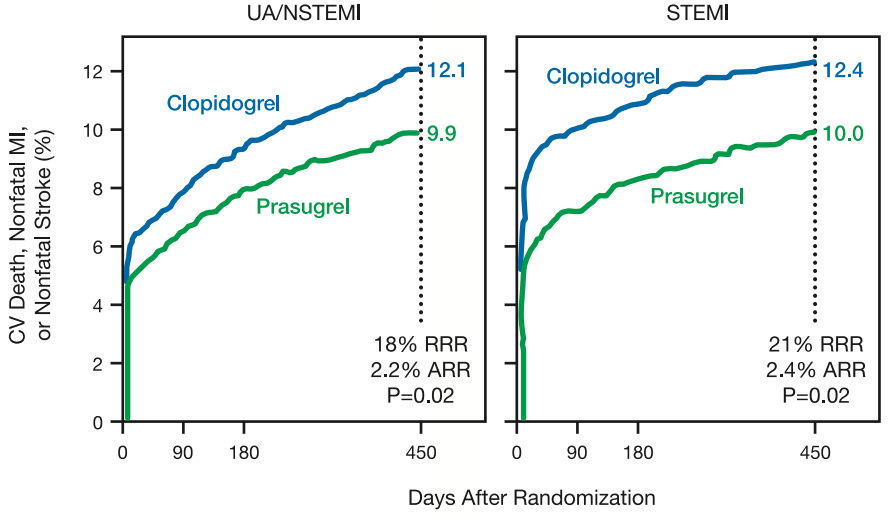


Figure 3

Primary Endpoint Events at End of Trial: UA/NSTEMI and STEMI Patients



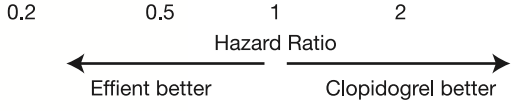
Based on Kaplan-Meier estimates.

Effient Full Prescribing Information.
Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Figure 4

Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke (HR and 95% CI; TRITON-TIMI 38)–UA/NSTEMI Patients

Baseline Characteristics		N	Percent Events	
			Effient	Clopidogrel
Overall – UA/NSTEMI		10,074	9.9	12.1
Age	<65 yr	5,987	7.5	10.0
	≥65 yr	4,087	11.9	13.1
	<75 yr	8,672	8.2	10.5
	≥75 yr	1,402	15.8	16.2
Gender	Female	2,724	10.3	11.4
	Male	7,350	8.9	11.2
Body Weight	>60 kg	503	9.2	9.8
	≥60 kg	9,458	9.2	11.1
Region	North America	3,538	9.6	11.9
	United States	3,382	9.7	12.2
	South America	534	13.3	15.2
	Western Europe	2,527	8.8	9.8
	Eastern Europe	2,300	8.5	10.0
	Rest of world	1,175	9.1	13.1
Diabetes Mellitus	Yes	2,472	10.8	15.0
	No	7,602	8.8	10.0
Metabolic Syndrome	Yes	4,511	9.1	11.5
	No	5,563	9.5	11.1
Previous MI	Yes	2,075	12.9	15.8
	No	7,999	8.3	10.1
Previous PCI	Yes	1,597	12.0	14.8
	No	8,477	8.8	10.6
Previous CABG	Yes	957	16.0	18.2
	No	9,117	8.6	10.5
Previous TIA/Stroke	Yes	405	18.3	12.5
	No	9,669	8.9	11.2
Time from Symptom Onset	≤24 hr	3,902	8.3	10.8
	>24 hr	5,976	10.1	11.5
Stent Type	Drug-eluting ≥1	5,225	9.2	10.9
	Bare metal only	4,362	9.2	11.6
	None	401	11.7	14.9
GP IIb/IIIa Inhibitor Use	Yes	5,183	9.9	11.9
	No	4,891	8.7	10.5



Key safety end points involved TIMI major or minor bleeding.

The results of the study demonstrated that 12.1 percent of the patients in the clopidogrel group had the primary endpoint, as compared to 9.9 percent in the prasugrel group (a 19 percent relative risk reduction and a 2.2 percent absolute risk reduction, which is highly statistically significant) (Table 2 and Figure 3). This difference was driven largely by a significant reduction in myocardial infarction in the prasugrel group (9.7 percent in the clopidogrel group vs 7.4 percent in the prasugrel group). The prasugrel group also had lower rates of urgent target vessel revascularization (3.7 percent vs 2.5 percent) and lower rates of stent thrombosis (2.4 percent vs 1.1 percent). Table 3 demonstrates hazard ratios and rates of the primary end point according to selected subgroups. The benefit of prasugrel is clearly greater in patients with diabetes than in those without diabetes.

Patients treated with prasugrel had a higher rate of TIMI major bleeding not related to CABG (2.4 percent in the prasugrel group vs 1.8 percent in the clopidogrel group). Patients who required CABG also had higher bleeding rates in the prasugrel

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Table 1

Baseline Characteristics of the Patients

Characteristic	Prasugrel (N=6,813)	Clopidogrel (N=6,795)
Unstable angina or NSTEMI (%)	74	74
STEMI (%)	26	26
Age		
Median (yr)	61	61
25th percentile, 75th percentile (yr)	53, 69	53,70
≥75 yr (%)	13	13
Female sex (%)	25	27

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antiplatelet agents including aspirin, clopidogrel, and abciximab have been associated with increased rates of bleeding. Thus, it is not surprising the prasugrel has lower rates of ischemic events, and also higher rates of bleeding when compared with clopidogrel.

In the subgroup analysis of patients with unstable angina/ Non-ST elevation MI, the patients demonstrating the most benefit from prasugrel compared to clopidogrel were the patients with diabetes mellitus, metabolic syndrome and previous MI (Figure 4).

Prasugrel has a black box warning. Prasugrel is contraindicated in patients with active pathological bleeding or in those with a propensity to bleed.

Table 2

Major Efficacy End Points in the Overall Cohort at 15 Months

End Point	Prasugrel (N=6,813)	Clopidogrel (N=6,795)	Hazard Ratio for Prasugel (95% CI)	P Value
	no of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73-0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70-1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67-0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71-1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78-1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73-0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75-0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54-0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76-0.92)	<0.001
Stent thrombosis	68 (1.1)	142 (2.4)	0.48 (0.36-0.64)	<0.001

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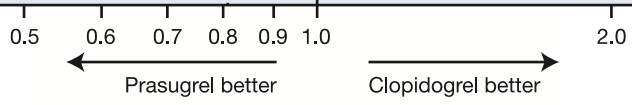
group (13.4 percent vs 3.2 percent). Subpopulations at increased risk for non-CABG bleeding included those patients less then 60kg body weight and age 75 and above. Patients with a previous TIA or stroke had no evidence for clinical benefit from prasugrel as compared with clopidogrel and had a strong trend toward a greater rate of TIMI major bleeding, including an increase in intracranial hemorrhage.

The reduction in ischemic events by several well-established

Prasugrel is not recommended in patients age 75 and older. Prasugrel is contraindicated in patients with a previous history of TIA or stroke. Prasugrel is not recommended in patients on coumadin or NSAIDS. Ideally, prasugrel should not be used

Table 3

Baseline Characteristics	Hazard Ratio for Prasugrel Efficacy (95% CI)	Total No. of Patients	Prasugrel %	Clopidogrel %	Reduction in Risk (%)
Overall		13,608	9.9	12.1	19
Unstable angina or non–ST-elevation MI		10,074	9.9	12.1	18
ST-elevation MI		3,534	10.0	12.4	21
Sex					
Male		10,085	9.5	11.9	21
Female		3,523	11.0	12.6	12
Age					
<65 yr		8,322	8.1	10.6	25
65-74 yr		3,477	10.7	12.3	14
≥75 yr		1,809	17.2	18.3	6
Diabetes mellitus					
No		10,462	9.2	10.6	14
Yes		3,146	12.2	17.0	30
Stent placement during index procedure					
Bare metal stent only		6,461	10.0	12.2	20
≥1 Drug-eluting stent		6,383	9.4	11.6	18
Glycoprotein IIb/IIIa receptor–antagonist use					
Yes		7,414	10.4	12.9	21
No		6,194	9.3	11.0	16
Creatinine clearance					
<60 ml/min		1,490	15.1	17.5	14
≥60 ml/min		11,890	9.0	11.1	20



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in patients less than 60kg body weight. If it is used in these patients, a 5mg maintenance dosage is recommended. Ideally, the coronary anatomy should be known before initiating prasugrel because of the significant risk of bleeding associated with CABG. If CABG is needed, prasugrel should be stopped for at least seven days prior to CABG if possible. If bleeding occurs, platelets can be given; however platelet transfusions within six hours of the loading dose or four hours of the maintenance dose may be less effective.

In summary, prasugrel can be used as an alternative to clopidogrel in patients with acute coronary syndromes who are scheduled to have PCI. Certain high risk patients, such as those with diabetes, metabolic syndrome and previous MI who are greater then 60kg in body weight and less than age 75 are the patients who are most likely to receive greater benefit with prasugrel as compared to clopidogrel. This difference is driven primarily by a reduction in nonfatal MI. Prasugrel is contraindicated in patients with a previous history of TIA or stroke.

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Dr. Greg Johnsen is a an interventional cardiologist with expertise in cardiac catheterization, angioplasty and related interventional procedures, such as stents and atherectomy.

By Dan Robey

THE POWER OF POSITIVE HABITS

Did you know that habits are incredibly powerful tools for personal growth and success? Let me ask you a question. When is the last time you made a conscious decision to add a new habit to your life? If you are like most people you probably answered…never!

THE REASON FOR THIS is that most people only think of habits as something bad. If you ask ten people on the street what the word habit means, nine out of ten will tell you that a habit is a negative action that people do over and over again, like smoking, or procrastinating or eating too much. But the truth is that positive habits hold the keys to success in virtually everything you do. What are positive habits you ask? A positive habit is simply a habit that produces positive benefits, action and attitudes. Why is there such great power in positive habits to effect change? Because habits, by their very nature, are automatic, and after a period of time they can also become permanent. This is a very powerful combination.

So how do we go about adding new positive habits to our life? It's really quite easy. You simply begin repeating an action, attitude or thought process every day for at least 21 days. Research has shown that an action that is repeated for a minimum of 21 days is likely to become a permanent habit.

Remember that positive habits have positive benefits and you will reap those benefits for as long as you maintain that habit. So now that we know what positive habits are, and how to acquire them, let's look at some simple positive habits for success.

POSITIVE HABIT #1 – Make it a Habit to Set Goals

Did you know that the most successful people all share the common positive habit of goal setting? A study was done to determine the importance of goal setting. College students who had gone on to achieve great success in business were asked to list their habits. The students who had made a habit of setting goals were in the top 3 percent of earnings in the population! It is almost impossible to overestimate the value of goal-setting as a positive habit. Goal setting is simple, yet 97 percent of the population never do it. By making goal setting a positive habit, you can start placing yourself in the top 3 percent of the population of successful people.

Here are some steps to help you make goal setting a positive habit:

Step 1. Define your goals, write them down, and be very specific; capture your goals on paper. It is amazing how many people never take the time to write down exactly what it is they want in life. Remember, you can't hit a target if you don't have one

Step 2. Determine what the time line is for reaching your goals; set specific deadlines for each goal.

Step 3. Identify any obstacles that may stand in your way, list them, and state how you plan to overcome them.

Step 4. Make a list of the people and/or organizations who will help you reach your goals.

POSITIVE HABITS #2 – Be more Productive with the 4-D Habit

May of us are stressed out by the negative effects of work overload in our careers. The 4-D habit is a very simple positive habit that will help you to prevent work overload. Every time you are faced with a new task to perform, apply the 4-Ds as listed below. You will find that your workload will be reduced as you apply this screening and decision making tool to each task you are confronted with. Decide on the most appropriate choice — and take action.

Do it Now. Take immediate action, do the task right away, don't procrastinate.

Dump it Now. Make a quick decision and dump the task.

Delegate it. Give the task to someone else. This is a very critical aspect of time management. Your time is valuable; make it a habit to work on tasks that you do best and delegate the tasks that can be performed by someone else.

Defer the Task. Make an immediate decision to postpone the task to a later time. Make sure to schedule a time to complete it.

POSITIVE HABIT #3 – Create and Repeat Positive Attitude Phrases

A positive attitude is perhaps the most important ingredient to success and a surefire way to maintain a positive attitude is to make a habit to repeat positive attitude phrases. Choose or create a positive attitude phrase and repeat it aloud many times each day. In a few days you will notice that your attitude will become more positive. Here are some examples:

- "I am reaching my success goals every day."
- "I am getting stronger and stronger every day."
- "I can overcome any obstacle."
- "Every day I am getting closer and closer to my goals in life."
- "If I believe it, I can achieve it."
- "Every day, my mental attitude is becoming more positive.

Positive habits can truly change your life, I know from personal experience. I am now constantly aware of the habits I have and the new positive habits I am acquiring; I am also aware of the benefits I am receiving. Positive habits are now second nature to me and soon they will be second nature to you.

Put your mind and body on autopilot and reach your goals automatically with the new book that is changing the lives of readers all around the world … The Power of Positive Habits … now with over 80 positive habits for health, success and better relationships.

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