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Cardiac Consult

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Dear Colleagues:

At first glance, most biomedical progress seems to follow one of two models: accretion or acceleration. Although accretion — the slow, gradual accumulation of knowledge — is far more common, its flashy sibling, acceleration, often grabs the headlines via a breakthrough surgery or a eureka moment in the lab.

But the cover story (p. 9) of this issue of *Cardiac Consult* reminds us that these two models of progress are not so easy to tease apart. The story profiles fascinating research from the laboratory of Cleveland Clinic's Stanley Hazen, MD, PhD, surrounding the surprising role of gut bacteria in cardiovascular disease. Central to that role is the compound TMAO, which is produced after dietary choline and L-carnitine come in contact with certain intestinal bacteria.

Dr. Hazen's lab has produced a flurry of high-impact papers over the past couple of years documenting how gut flora-dependent TMAO is implicated in various diseases — atherosclerosis, heart failure, chronic kidney disease and possibly more — and laying the groundwork for potential interventions based on these insights. His lab's output seems dizzyingly accelerated, yet the cover story reveals that these insights stem from a methodical approach that tackles one research question after the next in an iterative, carefully planned process. As Dr. Hazen puts it: "One study builds on another." In other words, accretion is at work where the outside world sees breakthroughs.

Similarly, our Image of the Issue (p. 5) spotlights a promising investigational approach to aortic valve replacement using a two-part bioprosthetic valve with an exchangeable leaflet to facilitate eventual leaflet replacement, if needed. While this device is in many ways a breakthrough, it is also a beneficiary of knowledge accumulated over thousands of bioprosthetic aortic valve replacement procedures performed at Cleveland Clinic and other top heart centers, as detailed in the p. 3 story on bicuspid aortic valve disease.

Our lead source for these aortic valve stories is Lars G. Svensson, MD, PhD, who in January was named Chairman of Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute, as reported on p. 8. Dr. Svensson succeeds Bruce Lytle, MD, who left Cleveland Clinic at the end of 2014 after a 36-year career here as a cardiac surgeon and leader (see profile, p. 6).

Drs. Svensson and Lytle have been close colleagues for many years, taking their shared specialty interest of aortic surgery (among many others) to new heights. Now Dr. Svensson looks to build on the foundation and legacy of Dr. Lytle and his predecessors to enhance Cleveland Clinic's world leadership in cardiovascular care. At Cleveland Clinic, we never forget that we stand on the shoulders of the remarkable caregivers and researchers who came before us. Our respect for their cumulative efforts — born of accretive progress accelerated by occasional breakthroughs — only deepens with time.

Respectfully,

Amar Krishnaswamy, MD Staff Cardiologist, Invasive Cardiology

W. Michael Park, MD Staff Surgeon, Vascular Surgery Michael Rocco, MD Medical Director, Cardiac Rehabilitation and Stress Testing

Joseph F. Sabik III, MD Chairman, Thoracic and Cardiovascular Surgery



Cardiac Consult offers updates on advanced diagnostic and management techniques from specialists in Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute. Please direct correspondence to:

Medical Editors

Amar Krishnaswamy, MD krishna2@ccf.org

W. Michael Park, MD parkm3@ccf.org

Michael Rocco, MD roccom@ccf.org

Joseph F. Sabik III, MD sabikj@ccf.org

Managing Editor Glenn R. Campbell

Art Director Michael Viars

Marketing Manager Martha Makar

Photography & Illustrations Cleveland Clinic Center for Medical Art and Photography Russell Lee Photography

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Bringing New Thinking to the Treatment of Bicuspid Aortic Valve Disease

'Lifetime strategy' entails valve repair — or replacement with a bioprosthesis

Bicuspid aortic valve (BAV) is an anomaly occurring in 1 to 2 percent of births. Patients with BAV generally function well until midlife, when symptoms of aortic insufficiency (AI) or aortic stenosis (AS) appear. This generally prompts referral for valve replacement with a mechanical prosthesis.

With extensive experience in treating BAV disease, Cleveland Clinic surgeons recommend a different approach: valve repair for patients with AI, and valve replacement with a bioprosthesis for patients with symptomatic AS and those whose valves cannot be repaired. Both approaches offer excellent short- and long-term outcomes.

"Our overall strategy is to help patients live a long, healthy, active life without the burden of anticoagulation," says Cleveland Clinic cardiothoracic surgeon Douglas Johnston, MD.

Valve Repair for Aortic Insufficiency

Cleveland Clinic is one of few U.S. centers offering repair of BAV in patients with AI. A review of 728 BAV repairs at Cleveland Clinic from 1985 to 2011 (*Ann Thorac Surg.* 2014;97:1539-1548) found the operation to be safe, with low rates of hospital mortality

(0.41 percent) and stroke (0.27 percent). The procedure was also durable, with 78 percent of patients free from AV reoperation at 10 years. Results in recently operated patients are even better.

"Repairs that failed tended to do so within 12 to 18 months," says the review's principal author, Lars G. Svensson, MD, PhD, Chair of Cleveland Clinic's Heart & Vascular Institute. "In these cases, the risks associated with reoperation were low, and there were no deaths from reoperation." The 10-year survival rate was 94 percent.

"Repair is the best option for avoiding anticoagulation," Dr. Svensson adds. "Unfortunately, only 65 to 70 percent of leaky valves can be repaired. Once the leaflets have started to thicken from calcium and the lumen narrows, repair is no longer possible."



Figure 1. A CT with 3-D reconstruction allows surgeons to choose the optimal incision and plan for the safest operation. Here, a sternal-sparing minithoracotomy incision allowed excellent access to the aortic valve.

The Importance of Early Surgery

Often, patients are not referred for aortic valve surgery until they are severely symptomatic. According to Dr. Johnston, it's a misconception that patients must be highly symptomatic to benefit. "Evidence shows that hearts start to develop changes in structure and function before symptoms appear," he says. "Patients who wait until symptoms develop before undergoing surgery do worse than those who have surgery early."

Major barriers to early surgical referral include fear of pain and a difficult recovery with sternotomy, as well as the need for anticoagulation with a mechanical valve. "Although most patients do not have a great deal of pain and difficulty recovering from a sternotomy, minimally invasive surgery makes the recovery easier," Dr. Johnston notes. "However, anticoagulation definitely requires lifestyle changes, which is why we like to avoid mechanical valves whenever possible."

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Figure 2. Many patients needing isolated aortic valve replacement are eligible for a sternal-sparing approach with a 5- to 6-cm incision in the right chest.

A Better Alternative to Mechanical Valves

While mechanical valves are the standard recommendation for AV replacement in younger patients, these valves require lifelong anticoagulation. Anticoagulants are associated with a higher incidence of bleeding complications, and lifelong anticoagulation distresses patients. For patients with symptomatic AS, a biological valve offers excellent durability without the need for anticoagulation.

At the 2014 annual meeting of the Society of Thoracic Surgeons, Dr. Johnston and colleagues presented results among 12,569 patients with AV disease who received the Carpentier-Edwards Perimount bovine prosthesis. In this study, the largest series of biological valves ever published (*Ann Thorac Surg.*; in press), mortality was less than 0.5 percent, and short- and long-term outcomes were excellent. In older patients, explantation for structural valve deterioration (SVD) was rare and unlikely to have been affected by valve size or implant technique. SVD was more common in patients under age 60; however, durability was very good, with 55 percent freedom from SVD at 20 years.

"I feel strongly that we must offer patients the option of a valve that does not require anticoagulation, particularly because all evidence says survival is the same with mechanical and tissue valves," says Dr. Johnston. Although the Perimount prosthesis has served patients well for nearly 30 years, newer bovine valves such as Edwards Lifesciences' GLX valve, which is being evaluated in the COMMENCE trial, and new operative techniques are likely to further extend valve life. Dr. Svensson is the national principal investigator of COMMENCE.

Quality of Life Matters

Valve repair and bioprosthetic valve replacement are part of a strategy to ensure patients with BAV get back on their feet as quickly as possible without compromising their future needs.

When valve replacement is performed without another surgery requiring sternotomy, Cleveland Clinic surgeons perform the procedure minimally invasively (Figures 1 and 2).

"With a sternal-sparing right thoracotomy or minimally invasive 'J' incision, patients are back to normal activity faster," Dr. Johnston explains. "Because less scar tissue forms after minimally invasive operations, patients' risk is lower if they need an operation later. Should the patient need reoperation in the future, we know we can do it very safely. In the meantime, they can lead a totally normal life."

Why Biological Valve Use Is Poised to Grow

While avoiding reoperation has been the major impetus to implant mechanical valves in younger patients, decreasing mortality rates for cardiac reoperation and the development of valve-in-valve transcatheter technology have altered this perception.

- "Many younger patients who prefer to avoid lifelong anticoagulation may find the SVD risk reported in our study acceptable," says Dr. Johnston. "Younger, active patients need a valve that will keep up with them and allow them to pursue whatever activities they choose without anticoagulation limiting their lifestyle."
- "Ideally, bicuspid valves should be repaired at centers that have extensive experience repairing these valves," Dr. Svensson adds, "because great care is needed when repairing a valve to achieve an optimal durable result."

The two surgeons expect to see increased use of biological valves for AV replacement in patients for whom repair is not feasible. "Newer valves hold the promise of better long-term durability in younger patients," Dr. Svensson notes. "In addition, we are able to successfully place a new transcatheter aortic valve in a previously replaced valve by remote access via the groin." ■

Contact Dr. Johnston at johnstd3@ccf.org or 216.444.4613 and Dr. Svensson at svenssl@ccf.org or 216.445.4813.

Image of the Issue

BY LARS G. SVENSSON, MD, PhD



IN AORTIC VALVE REPLACEMENT, TWO PARTS MAY BE BETTER THAN ONE

These intraoperative images show essential steps in the implantation of a promising advance in aortic valve replacement: the advent of a two-part aortic bioprosthetic valve — namely, the ValveXchange Vitality[™] aortic bioprosthesis (image at right).

This novel approach involves surgical placement of the valve's base in the aortic root (left image above) followed by installation of a tri-leaflet set (three bovine pericardium tissue leaflets mounted on a circular frame) on top of the base (right image above).

Several objectives drove the two-part valve design, including:

- Greater visibility during implantation of the valve base, with no leaflets blocking the view
- The opportunity for smaller incisions, since the base is half the height of the ultimately assembled valve
- The ability to exchange the initial leaflet set with a new one during re-do valve replacement procedures

The latter objective of leaflet exchangeability becomes increasingly desirable as patients receive tissue valves at ever-younger ages and live increasingly long and active lives (see prior article). In these cases, if a reoperation is eventually needed to replace a worn-out tissue valve, only the leaflet (not the base) needs to be replaced, which can be done less invasively and more quickly than full bioprosthetic replacement.

Cleveland Clinic surgeon Lars G. Svensson, MD, PhD, implanted the first Vitality aortic bioprosthesis in a human in September 2011, and Cleveland Clinic continues to play a lead role in studying the device, which is approved for use in Europe but still investigational in the U.S.

FOR MORE INFORMATION, CONTACT LARS G. SVENSSON, MD, PhD, AT SVENSSL@CCF.ORG.

Saluting a Singular Surgeon, Teacher and Leader: Bruce Lytle, MD

Bruce W. Lytle, MD, Chair of Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute from 2007 to 2014, left Cleveland Clinic at the end of 2014.



The move concluded Dr. Lytle's storied 36-year career as a cardiac surgeon at Cleveland Clinic, one of the longest tenures for an active staff surgeon in the institution's history. During that time Dr. Lytle distinguished himself as one of the most accomplished and respected cardiac surgeons of his generation, excelling in virtually every cardiac and thoracic procedure. Three achievements particularly stand out:

- A mastery of reoperative procedures. Dr. Lytle's willingness to reoperate on scores of patients with multiple prior operations (see sidebar, opposite page) was a prime testament to his skills and courage in the OR.
- **Pioneering work** to expand on the revolutionary 1970s demonstration by his colleague Floyd Loop, MD, of the superiority of the internal thoracic artery over the left anterior descending coronary artery as a bypass graft in CABG.
- Innovations in aortic surgery in the 1980s and 1990s, including introduction and refinement of techniques for retrograde perfusion of the brain and cannulation techniques to extend the safe interval of circulatory arrest and diminish the risk of neurologic complications.

Dr. Lytle joined Cleveland Clinic in 1978 after a surgical internship and residencies at Massachusetts General Hospital

in Boston. He earned his undergraduate degree at Stanford University and his medical degree from Harvard Medical School.

Wearer of Many Hats

Beyond his clinical achievements, Dr. Lytle made his mark as an educator, serving as Professor of Thoracic and Cardiovascular Surgery at Cleveland Clinic Lerner College of Medicine and mentoring countless trainees over the decades. He was honored in 2004 with the Thoracic Surgery Resident Association's Socrates Award for dedication to residency training.

His vision and leadership also shaped the field of cardiothoracic surgery, from his 400+ scholarly publications and presentations to his leadership in the American Association for Thoracic Surgery (AATS), where he served as president in 2006-2007.

That leadership was most influential at Cleveland Clinic, where Dr. Lytle became Chair of the Department of Thoracic and Cardiovascular Surgery in 2004 and then launched the Heart & Vascular Institute in 2007 as a unified team of more than 1,700 medical, surgical and allied health caregivers.

Dr. Lytle was instrumental in the growth of the Heart & Vascular Institute's national affiliation and alliance program (which currently includes nearly two dozen hospitals and health systems nationwide) and the 2014 creation of Cleveland Clinic's Cardiovascular Specialty Network to extend direct-to-employer contracting to the affiliate and alliance network.

"Dr. Lytle is an extraordinary surgeon who was devoted, above all, to ensuring the best outcomes for his patients," says new Heart & Vascular Institute Chair Lars G. Svensson, MD, PhD, a longtime colleague. "His compassion for his patients and colleagues was exceptional, as was his commitment to sharing his vast knowledge and wisdom with trainees. All of us who follow in his footsteps in the Heart & Vascular Institute are well-served by the superb foundation he laid. We miss him, fondly remember his collegiality and wish him the very best."



Dr. Lytle in a few of his many roles: Surgical team leader in the 1980s (above), trusted mentor and educator (opposite page), nationally renowned surgical thought leader (below left) and judicious clinician and administrator (below right).

A Master of Reops

15,000

Number of cardiac surgeries Dr. Lytle performed at Cleveland Clinic

4,000

Number of those surgeries that were reoperations

53

Number of his reop patients who had 4+ prior operations

15

Number of his reop patients who had 6 to 8 prior operations



"Cardiac surgeons are personally and identifiably responsible for outcomes. The position of the cardiac surgeon has been and will continue to be that of the patient's last chance. In the end, there is no one else to whom we can pass the ball."

- Dr. Lytle in his presidential speech to the AATS

Lars G. Svensson, MD, PhD Named New Heart & Vascular Institute Chair

In January 2015, Cleveland Clinic announced the appointment of cardiothoracic and vascular surgeon Lars G. Svensson, MD, PhD, as Chairman of its Sydell and Arnold Miller Family Heart & Vascular Institute.



In this role, Dr. Svensson will oversee the institute's more than 1,700 employees, including its team of 227 heart and vascular surgeons, cardiologists, and other staff physicians.

"Our distinguished physicians and caregivers are fully committed to patient care and discovering innovative treatments to help patients locally, nationally and from around the world," Dr. Svensson says. "It's a tremendous honor to have the chance to lead the best heart and vascular program in the world."

He succeeds Bruce Lytle, MD, who left Cleveland Clinic at the end of 2014 (see previous story).

A Broad Base of Leadership Experience

Prior to his appointment, Dr. Svensson, a 14-year veteran of Cleveland Clinic, served in various key roles in Cleveland Clinic's Heart & Vascular Institute, including:

- Director of the Aorta Center
- Director of the Marfan Syndrome and Connective Tissue Disorder Clinic
- Director of Affiliate Cardiothoracic Surgery Programs
- Co-Director of the Transcatheter Valve Program
- Director of Quality and Process Improvement in the Department of Thoracic and Cardiovascular Surgery

His efforts in the latter role contributed to Cleveland Clinic's three-star (highest) score in all three categories of the Society

of Thoracic Surgeons' risk-adjusted quality ratings — CABG, aortic valve replacement (AVR), and a composite of CABG and AVR — placing Cleveland Clinic among just 3 percent of U.S. hospitals to achieve that distinction.

Additionally, Dr. Svensson serves on the Council of the American Association for Thoracic Surgery and chairs its Guidelines Committee. He is also a professor of surgery at Cleveland Clinic Lerner College of Medicine.

"Lars Svensson is an exceptional leader and surgeon who is committed to providing the highest quality of care to his patients," says Brian G. Donley, MD, Cleveland Clinic's Chief of Staff. "He brings to this position a wealth of clinical expertise along with excellence in research and education."

Renowned for Clinical and Research Expertise

Dr. Svensson is internationally recognized for his acumen in cardiac and thoracic reoperations and aortic surgeries. He has contributed to advances in protecting the brain, spinal cord and kidneys during major cardiac and aortic surgery and has been instrumental in developing minimally invasive keyhole procedures. He is the principal investigator for a number of clinical research trials.

His areas of clinical expertise include adult cardiac surgery, cardio-aortic and aortic surgery (including combined valve and aneurysm surgery), minimally invasive mitral and aortic valve surgery, mitral and aortic valve repairs (including bicuspid valve repairs and the modified David reimplantation operation), blood-sparing surgery, prevention of stroke and paralysis after aortic surgery, Marfan syndrome, peripheral vascular surgery, percutaneous valve surgery and the maze procedure.

From South Africa to Ohio

Dr. Svensson received his undergraduate degree at Treverton College in Mooi River, South Africa, and his medical degree and PhD in blood flow pathophysiology from the University of Witwatersrand in Johannesburg, where he won numerous awards.

He trained in cardiology and general surgery at the Johannesburg Hospital before coming to Cleveland Clinic for training in cardiothoracic surgery. He completed a cardiovascular surgery fellowship and residency at Baylor College of Medicine in Houston.



New studies extend the gut flora-dependent compound's reach beyond the arteries to the heart and kidney

> There's been another shake-up in our understanding of the causes of cardiovascular disease. Cholesterol is still king. But it now shares explanatory power with a swarm of bacteria resident in the digestive tract. The first studies of these bacteria found direct links between the chemical product of their metabolism and the vascular events leading to heart attack. Now studies are linking these bacteria to heart failure and even chronic kidney disease.



he concept that gut flora contribute not only to atherosclerosis, but also to heart failure and chronic kidney disease, opens up exciting new nutritional and interventional prospects," says Stanley Hazen, MD, PhD, Chair of Cellular and Molecular Medicine and Section Head of Preventive Cardiology and Rehabilitation at Cleveland Clinic.

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"The metabolic pathway is not separate from cholesterol. It affects heart disease through and in addition to cholesterol. It's another piece to the puzzle of how cholesterol causes heart disease." — Stanley Hazen, MD, PhD

Dr. Hazen served as principal author of key clinical studies published in *The New England Journal of Medicine* and *Nature Medicine* in April and May 2013. These studies showed how certain bacteria found primarily in the intestines turn choline — a byproduct of lecithin, found in meat and eggs — into trimethylamine (TMA), which is absorbed into the bloodstream and metabolized by the liver. There, it is transformed into the substance that appears to be a key player in a number of disease processes: TMAO. These studies also showed a clear link between higher TMAO levels and elevated three-year risk of heart attack, stroke and death.

Gut Bacteria and TMAO: The Basics

Gut bacteria may affect the progress of cardiovascular disease by influencing appetite, fat creation and insulin sensitivity. But the key process involves how the host digests two key nutrients, choline and L-carnitine. Choline is abundant in animal cell membranes, egg yolk and high-fat dairy products; L-carnitine is found mostly in red meat. They also are marketed as nutritional supplements, with L-carnitine being a frequent ingredient in energy drinks.

When dietary choline and L-carnitine come in contact with certain bacteria in the intestine, they are metabolized into TMA, which makes its way to the liver through the portal circulation, where an enzyme converts it to TMAO (trimethyl-amine-*N*-oxide). TMAO ends up in the bloodstream, where it participates in changes in whole-body cholesterol metabolism, vascular inflammation and formation of unstable plaques in the arterial walls.

Additional Metabolite Newly Identified

A new study from the Hazen lab, published in *Cell Metabolism* (2014;20:799-812), has revealed an additional metabolite of L-carnitine that may be involved in atherosclerosis development. Known as γ -butyrobetaine, it is a newly discovered intermediate that is formed in large amounts by gut microbes and ultimately gets turned into TMAO. After being produced in the proximal gut by one set of microbes, the γ -butyrobetaine is converted into TMA lower in the gut by a distinct set of microbes. These studies are of interest, Dr. Hazen notes, because they identify a new set of microbial targets to help curb the TMAO generation in response to dietary L-carnitine.

An Assay in the Wings

Dr. Hazen and his team have developed a test that can help assess cardiac risk by measuring plasma TMAO. It has already been used in several clinical studies of well over 5,000 subjects collectively, which have shown it to predict increased cardiovascular risk. Although the test is currently available only for research purposes, several diagnostics companies are expressing interest in making it more widely available, perhaps as early as this year.

"TMAO is readily measured using mass spectrometry, which is a widely used platform for diagnostic testing available at larger reference labs," explains Dr. Hazen. "We expect that testing for TMAO may one day help us individualize dietary recommendations and also facilitate monitoring of gut microbe-targeted therapies."



How Does TMAO Contribute to Heart Disease?

Among the goals of the Hazen lab is to establish the mechanisms by which TMAO promotes atherosclerotic disease.

"Data show that TMAO and this pathway are centrally involved in cholesterol and sterol metabolism, both by impacting how cholesterol is taken up by cells in the artery wall and by inhibiting removal of cholesterol from the artery wall, reducing what is called reverse cholesterol transport," Dr. Hazen notes. "The net effect is buildup of cholesterol in cells of the artery wall. But it is clear that this is not the complete story: TMAO seems to foster changes in cellular metabolism that make a person more susceptible to cardiovascular events such as heart attack, stroke and even death. We and others have many studies on this subject in the pipeline."

Dr. Hazen is particularly excited about a study his group just published in the *Journal of Biological Chemistry* (2014 Dec 30 [Epub ahead of print]). "It demonstrates for the first time that we can fulfill Koch's postulate of causation, showing that microbial transplantation can transfer susceptibility for development of atherosclerosis in an animal model," he explains. Studies such as these firmly establish a mechanistic link between gut microbes and cardiovascular disease.

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TMAO and Chronic Kidney Disease

Chronic kidney disease is increasing in prevalence and represents a major healthcare cost burden. It's also strongly linked to cardiovascular disease risk.

"We've found that the TMAO pathway seems to be mechanistically linked not only to atherosclerosis but also to the development of chronic kidney disease, based on animal model data and some human studies," says Dr. Hazen.

In a new paper in *Circulation Research* (2014 Nov 5 [Epub ahead of print]), Dr. Hazen, along with W.H. Wilson Tang, MD, and other Cleveland Clinic colleagues, showed in animal models that chronic consumption of dietary choline (the precursor for forming TMAO) or TMAO itself appears to directly contribute to progressive renal fibrosis and dysfunction. They also examined 3,166 subjects with normal kidneys, plus



Drugging the Microbiome, the 'Largest Endocrine Organ'

"Our gut bacteria serve as a filter of our largest environmental exposure — the food we eat," says Dr. Hazen. "It's reasonable to think of the intestinal microbiome as our largest endocrine organ. Just consider that the gut microbiome makes biologically active compounds that circulate in the body and impact end-organ physiology just like a hormone does. But it's a flexible endocrine organ, and what it's fed over time can influence what it becomes. Once we work out the chemical language of this organ, we can develop drugs to manipulate it and reduce the risk of cardiovascular disease, heart failure, kidney disease and possibly a host of other conditions."

Dr. Hazen has studies underway to "drug" the microbiome with medications and perhaps with probiotics or other substances that may be able to suppress specific bacteria to safely inhibit their endocrine effect on distant organs. another 521 subjects with chronic kidney disease, and followed their medical history over five years. They confirmed that high blood levels of TMAO at baseline were associated with chronic kidney disease and also with poorer outcomes and higher five-year mortality among subjects with and without kidney disease. TMAO was found to predict worse outcome particularly among those with less than normal kidney function.

"People with chronic kidney disease and end-stage renal disease tend to die of heart disease," says Dr. Hazen. "Even when their kidney function is replaced, they still die of heart disease. In fact, traditional risk factors don't adequately account for the heightened cardiovascular risks observed in subjects with kidney disease. Recent animal model studies and human clinical studies collectively indicate that elevated TMAO may contribute to renal functional impairment, which further raises TMAO levels, and is associated with progressively worse cardiovascular risks."

TMAO and Heart Failure

New studies by Dr. Hazen, Dr. Tang and colleagues also link TMAO to both systolic and diastolic heart failure. One paper (*J Am Coll Cardiol.* 2014;64:1908-1914) examined the relationship between gut flora-dependent TMAO and all-cause mortality in 720 patients with stable heart failure over five years. It found that these patients had elevated TMAO — and that the higher the TMAO, the higher the long-term mortality risk, independent of traditional risk factors, renal function and markers of heart strain like B-type natriuretic peptide (BNP). In patients with both high TMAO and high BNP, the five-year mortality rate was greater than 50 percent.

The findings imply that testing for TMAO may help identify which patients are at higher risk from heart failure. And while this concept is not yet tested, they also suggest that new dietary strategies to prevent TMAO elevation may be beneficial for patients with heart failure or kidney disease.

More to Come

Dr. Hazen believes we are only at the beginning of our understanding of the complex relationships among our gut bacteria and our organ systems. The future need will be to identify specific metabolites that are relevant to disease and the gut microbial enzyme systems involved in generating these compounds — along with their host receptor systems.

"This field is moving fast," he says. "One study builds on another. And many groups are jumping into the field. There is still much to be told — and much, much more to learn." ■

Direct comments or inquiries to Dr. Hazen via makarm@ccf.org.

PCSK9 Inhibitors:

With Likely Approval Imminent, What Should We Make of Them?

he investigational lipid-lowering agents known as PCSK9 inhibitors have come a long way in a short time — especially in terms of their potential for use in combination with statins for:

- Patients with heterozygous familial hypercholesterolemia
- Those prescribed maximal doses of statins but still experiencing cardiac events or unable to achieve treatment goals
- Individuals unable to tolerate statin therapy

"This drug class is moving rapidly from bench to bedside," says Steven Nissen, MD, Chairman of Cleveland Clinic's Department of Cardiovascular Medicine. "The target (see "Fast Facts" sidebar, next page) was identified just a few years ago, and now large outcomes trials are underway." "Even with the different [PCSK9 inhibitor] products, the studies have been very consistent in the degree of LDL-C lowering across a broad range of patients."

- Michael Rocco, MD

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2014 was a pivotal year for presentations of PCSK9 inhibitor studies demonstrating promising results in a broad spectrum of patients with hyperlipidemia and mixed dyslipidemia, according to Michael Rocco, MD, Medical Director of Cardiac Rehabilitation and Stress Testing in Cleveland Clinic's Section of Preventive Cardiology. "In these studies, many of which spanned a year or more, consistent lowering of LDL cholesterol (LDL-C) was achieved, with sustained benefits over time, excellent tolerability and very few serious side effects," he says.

How Low Can (and Should) Lipid Levels Go?

Several PCSK9 inhibitors are in the development pipeline. "Even with different products, the studies have been very consistent in the degree of LDL-C lowering across a broad range of patients," Dr. Rocco notes. These include patients who are high-risk, those with familial hypercholesterolemia and those who are statin-resistant. The reductions have ranged from about 48 percent to 70+ percent, depending on the study, with LDL-C levels reaching the range of 20 to 50 mg/dL in some cases.

"Unprecedented" is how Dr. Nissen characterizes PCSK9 inhibitors' ability to lower LDL-C, adding: "We have not seen any evidence in emerging trials that the LDL-C levels achieved are producing any harm. Even the very, very low levels appear to be safe."

Fast Facts on PCSK9 Inhibitors

- What are they? Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). They increase liver surface LDL receptors and cholesterol clearance by preventing the newly identified PCSK9 protein from degrading LDL receptors.
- How are they administered? Subcutaneously every two to four weeks.
- How much do they lower LDL-C? From about 48 percent to more than 70 percent in studies to date.
- Who benefits? Nearly all patients studied have responded to PCSK9 inhibitors, although a few people with certain rare genetic types of dyslipidemia with few or no functioning LDL receptors may not benefit.
- What about safety? Few serious side effects have been reported so far. There have been limited reports of myalgia and creatine kinase elevation signals. Ongoing phase 3 trials are assessing long-term safety.

He notes, however, that it will take a few years of outcomes trials to demonstrate whether these very low LDL-C levels yield important reductions in morbidity and mortality.

Will 2015 See an FDA Approval?

Dr. Nissen says researchers are "cautiously optimistic" that one or more PCSK9 inhibitors will be approved by the FDA as add-on therapy in 2015, for indications related to the specific high-need patient groups mentioned above. At press time, the two agents that appeared closest to potential approval were Amgen's evolocumab and Sanofi and Regeneron's alirocumab.

Positive results were reported last year for both evolocumab and alirocumab at major cardiology meetings. While favorable clinical results also have been reported for Pfizer's bococizumab, it falls in the middle of the development pack, followed by Lilly's LY3015014, which may offer a different dosing regimen, and PCSK9 inhibitors from Roche and Alnylam.

2015 should bring additional safety and durability results from ongoing open-label trials with longer follow-up than previous studies. More patient subgroup study results are also likely this year.

Initial Indications Will Target Unmet Needs ...

There's a growing need for new options like PCSK9 inhibitors in difficult-to-treat and statin-intolerant patients, according to Dr. Rocco. "One in 250 to 500 people have familial hypercholesterolemia," he says. "Large numbers of patients are at least partially intolerant of statins. And myalgia is reported in substantial numbers of patients on statin therapy — 2 to 3 percent in clinical trials and as many as 10 to 20 percent in observational studies. This represents a large population for which there are limited treatment options."

Dr. Nissen says studies are showing that even patients previously intolerant of statins may be able to tolerate them at lower or less-frequent doses when used with a PCSK9 inhibitor — while still realizing the benefits of significantly lower LDL-C levels. He adds that patients who previously could not reach LDL-C targets on maximal statin therapy also are seeing significant reductions with PCSK9 inhibitor add-on therapy.

... But Broader Use Likely if Outcomes Studies Pan Out

FDA approval of PCSK9 inhibitors for these targeted indications would likely be a gateway to broader use, according to Dr. Rocco. He expects that additional indications would follow pending results of large outcomes trials gauging whether PCSK9 inhibitors' LDL-C reductions translate to fewer major cardiac events, including cardiac-related deaths. "We have not seen any evidence in emerging trials that the LDL-C levels achieved are producing any harm. Even the very, very low levels appear to be safe."

Steven Nissen, MD

The three major outcomes studies underway for evolocumab, alirocumab and bococizumab collectively include 50,000 to 60,000 higher-risk patients, so the results will be reflective of large patient populations.

Meanwhile, a post hoc analysis presented at the American Heart Association's 2014 scientific sessions suggested that PCSK9 inhibitors' LDL-C-lowering abilities may ultimately be shown to reduce major cardiac events, Dr. Rocco says. The analysis pooled results of five alirocumab trials, which included 3,500 patients followed for at least a year, to retrospectively assess cardiac endpoints, including cardiac death. The 65 percent hazard ratio represented a robust reduction, although the finding did not quite reach statistical significance, due in part to the low number of events.

"While larger prospective controlled outcomes trials are needed, this post hoc analysis supports the notion that this degree of LDL-C reduction may be associated with long-term outcomes benefits," Dr. Rocco says. "It suggests we're headed in the right direction."

Other Considerations: Cost, Potential Monotherapy

Demonstrating positive outcomes with optimal LDL-C control also will be important for convincing payers to cover PCSK9 inhibitors, since these monoclonal antibodies are expected to be much more costly than statins and other dyslipidemia therapies.

While the FDA is currently considering PCSK9 inhibitors only as combination therapy with statins, not as monotherapy, Dr. Nissen notes they may ultimately have a role as monotherapy in certain settings. "It's an evolution," he says. "It will take time to figure it all out."

Contact Dr. Nissen at nissens@ccf.org or 216.445.6852 and Dr. Rocco at roccom@ccf.org or 216.444.9353.

PCSK9 Inhibitor Research Continues

"PCSK9 inhibitors are very promising molecules, so we want to maintain a strong presence in their development," says Dr. Rocco. Here's a profile of major studies of these agents conducted at Cleveland Clinic.

GLAGOV — Cleveland Clinic is the national leader and initiator of the international multicenter GLAGOV trial, with Dr. Nissen serving as principal investigator (PI). This long-term phase 3 trial is studying the effect of evolocumab on regression of coronary atherosclerosis, as measured by intravascular ultrasound, in 950 patients undergoing cardiac catheterization. Results are expected in approximately two years.

GAUSS and **OSLER** — Dr. Rocco serves as site PI of the GAUSS studies of evolocumab in patients with hyperlipidemia who cannot tolerate statins, as well as the open-label OSLER investigation studying evolocumab's long-term safety profile.

- GAUSS-2, which reported positive results at the 2014 American College of Cardiology meeting, included more than 300 patients with hyperlipidemia who were intolerant of two or more statins due to muscle symptoms. At 12 weeks, evolocumab (given every two weeks or every four weeks) reduced LDL-C by 53 to 56 percent, representing a treatment difference of 37 to 39 percent over the reductions achieved with ezetimibe. The PCSK9 inhibitor was likewise welltolerated, with a discontinuation rate lower than that in the ezetimibe group.
- GAUSS-3, which recently closed to enrollment, aims to address the issue of "truly statin-intolerant" patients head-on. The study randomized patients who failed multiple statins to receive placebo or atorvastatin and then be crossed over to the opposite arm to assess possible myalgia symptoms. "Only individuals who pass that test are then randomized to the comparison of the PCSK9 inhibitor vs. ezetimibe," Dr. Rocco explains. "The hope is that this will ensure truly proven statin intolerance. It's the only study so far to be that rigid."

Cleveland Clinic researchers are also gearing up to take part in the **SPIRE** trials program assessing bococizumab. Specific studies include the SPIRE long-term outcomes trial and a study in patients with statin intolerance.

Pushing the Envelope to Prevent Device-Related Infections

One of the largest-ever device trials is launched to thoroughly assess new antibiotic delivery system

As more and more older patients with comorbidities receive cardiovascular implantable electronic devices (CIEDs), recognition of associated complications has risen, and infection has emerged as perhaps the most important. Device-related infections are associated with significant morbidity and mortality. They cannot be cleared while the device or its leads remain in the body, and device and lead removal is indicated.

Absorbable Antibacterial Envelope: Can It Do the Trick?

At this time, little can be done to minimize or reduce infection risk: Only preoperative or perioperative antibiotics have been shown to help. Cleveland Clinic electrophysiologists are hoping an antibiotic-permeated, bioabsorbable, implantable CIED envelope will be effective in reducing infection. The FDA approved Medtronic's TYRX[™] antibacterial envelope in June 2013 based on retrospective and prospective nonrandomized studies. Since then, adoption of the envelope has been slow. Cleveland Clinic has worked with Medtronic to launch an international randomized controlled trial that will enroll up to 7,000 subjects at 225 sites, making it one of the largest medical device trials ever.

"Previous case-control and single-arm studies suggest this absorbable antibacterial envelope may be effective at preventing CIED infection," says Cleveland Clinic electrophysiologist Bruce Wilkoff, MD, the study chair and president of its steering committee. "However, there may be unrecognized problems that would show up in a randomized controlled trial."

WRAPping Up the Evidence

The study — known as the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) — is a randomized, prospective, single-blind, multisite, post-market interventional trial with important outcome measures. Its primary purpose is to evaluate the antibacterial envelope's ability to reduce major CIED infections within 12 months after either replacement, upgrade or revision of the CIED generator or de novo defibrillator implant.

"Nobody wants to do a device change or upgrade and have the patient return with infection," says Khaldoun Tarakji, MD, MPH, who serves as global principal investigator of WRAP-IT. "It's frustrating when you do everything by the book and this continues to happen."

The trial will also serve as a post-approval study for the FDA and other regulatory bodies around the world requiring it.

The design of WRAP-IT allows physicians to use the envelope in standard device implantation procedures, in the hope of determining how real-world situations contribute to infection rates.

> "Different institutions use different techniques and measures to minimize infection, and there are no clear guidelines that say one approach is better than another," Dr. Tarakji explains. "We're hoping WRAP-IT will enable us to examine the correlation between different practices and rates of infection."

The antibacterial envelope is woven from filament (left) that holds the CIED in place (right) while eluting antibiotics for several days before eventually being absorbed by the body. Images courtesy of Medtronic



How the Envelope Works

The antibiotic envelope is woven from fully bioabsorbable filament similar to resorbable sutures and coated with a bioabsorbable polymer containing two antibiotics, minocycline and rifampin. A nonrandomized observational study presented at the Heart Rhythm Society's 2013 scientific sessions showed a reduction in infections of up to 90 percent with use of these same two antibiotics.

The pulse generator and residual leads are placed into the envelope, which is then placed into the tissue pocket. The envelope elutes the antibiotics over a minimum of seven days, delivering less than 10 percent of the recommended daily oral dose of each agent. The envelope is fully absorbed by the body about nine weeks after implantation.

Full Results Expected by Late 2017

Enrollment is expected to begin in early 2015 and continue through the first half of 2016. The final study report is expected in December 2017.

"In addition to wreaking havoc clinically, infections are expensive," says Dr. Wilkoff. "This trial will reveal the true rate of infection around the world, as well as whether this device reduces that rate and is cost-effective. If the study shows a reduction in infections by 50 percent or more, the envelope will be incorporated into practice guidelines and be adopted on a wide scale."

Contact Dr. Wilkoff at wilkofb@ccf.org or 216.444.4975 and Dr. Tarakji at tarakjk@ccf.org or 216.445.9225.





A Different Tack: Eliminating Leads to Eliminate Infection

About 60 percent of device infections involve the device pocket. Antibiotics alone will not cure these infections: Both the device and the leads must be removed.

Leadless pacemakers now in clinical trials have no leads and — because they are implanted endovascularly directly into the heart — require no pocket. These design features should eliminate both of these common sources of infection.

Cleveland Clinic is participating in clinical trials of two investigational leadless pacemakers: St. Jude Medical's Nanostim[™] and Medtronic's Micra[™]. The Nanostim trial was launched in February 2014. In October 2014, two Cleveland Clinic patients received the Micra device; both patients were discharged the next day and were problem-free at their six-week checkup.

The Nanostim is tipped with a small screw that secures the device into the heart muscle. The Micra anchors to the myocardium with three curved prongs. Both leadless devices adjust to the patient's changing activity level and have an estimated battery life of seven to 10 years.

"There's no question leadless pacemakers are the future," says Dr. Tarakji, who serves as co-principal investigator (with Dr. Wilkoff) of the Micra trial at Cleveland Clinic. "There's less risk of infection, no need for lead extraction, and no issues with vascular access, occlusion or lead malfunction. We don't know the risk of infection with endovascular placement of leadless pacemakers, but we'll find out with these trials."

At this time, the Nanostim and Micra devices are restricted to pacing a single chamber.

Robotic Hybrid Revascularization Can Offer the Best of Both Worlds but Only for Carefully Selected Patients

By Stephanie Mick, MD

Hybrid coronary revascularization combines minimally invasive coronary artery bypass grafting (CABG) with a catheter-based intervention as an alternative to open CABG with sternotomy and percutaneous coronary intervention (PCI). The aim is to bring the most favorable aspects of both cardiac surgery and interventional cardiology to bear for patients with multivessel coronary artery disease.

The approach typically involves anastomosis of the left internal mammary artery (LIMA) to the left anterior descending (LAD) artery — the most durable aspect of CABG — in conjunction with stenting of non-LAD target lesions. When used in appropriate lesions, stents have been shown to provide long-term patency equivalent to that of vein grafts.

Enter the Robots

The surgical component of this approach can be offered either partially or entirely endoscopically using robotic technology, thereby avoiding sternotomy or large thoracotomy. However, hybrid revascularization is still in its infancy, with only about 1,200 reported cases performed nationwide. The procedure is restricted to a handful of medical centers where surgeons have mastered less-invasive CABG and have a close association with interventional cardiologists committed to the hybrid approach.

In the largest reported series of robotic hybrid revascularization procedures to date (N = 226) (*Ann Thorac Surg.*



Figure. Catheterization image showing a totally occluded left anterior descending artery with right coronary artery stenosis — a combination that may prompt consideration of robotic hybrid revascularization.

2012;94[6]:1920-1926), hospital mortality was 1.3 percent and the average length of stay was six days. Patients were able to resume normal household chores within 14 days and full activity at 42 days. Five years post-procedure, the survival rate was 92.9 percent and 75.2 percent of patients were free from major adverse cardiovascular events. In this series, 2.7 percent of the bypass grafts and 14.2 percent of PCI lesions required reintervention.

Evaluation for Suitability

Hybrid revascularization has been performed at Cleveland Clinic for several years, generally with the surgical portion of the case performed first and the PCI procedure occurring at a separate time afterward. Hybrid revascularization is not appropriate for the patient who would benefit from all-arterial grafting.

We remain conservative, reserving the technique for patients with specific indications, as discussed further below.

Evaluation of a patient's suitability for robotic hybrid revascularization is done by a team including interventional cardiologists and cardiothoracic surgeons specializing in robotically assisted procedures. All team members must understand the benefits and limitations of the procedure. Our overarching goal is to offer every patient the best procedure for his or her individual case. When considering hybrid revascularization, we seek to ensure the technique will provide revascularization quality equivalent to that of open CABG.

Not Necessarily a Matter of Reduced Risk

Although patients at high risk from CABG are often referred for hybrid revascularization, the robotic approach is not necessarily less risky than open revascularization. Complicated patients with widespread disease are not amenable to stenting. Patients with a low ejection fraction and comorbidities that increase the risk of open surgery are poor candidates for a minimally invasive procedure. Those with significantly reduced forced expiratory volume may not tolerate the procedure and have an increased risk of requiring conversion to an open procedure.

Who's Not a Candidate

Candidates for robotic hybrid revascularization must be able to undergo off-pump surgery with single-lung ventilation. Therefore, patients with severely impaired lung function and those with cardiogenic shock or hemodynamic instability are not appropriate candidates. Additionally, obesity, chest deformities, pleural adhesions and reoperation are generally contraindications, due to the technical difficulties they create.

The LAD artery must be accessible and not embedded in the myocardium. The patient must have a patent LIMA and no dialysis catheter or fistula in the left arm.

Hybrid revascularization is not appropriate for the patient who would benefit from all-arterial grafting, such as a 49-year-old male diabetic with a 90 percent lesion in the circumflex and LAD artery and 100 percent occlusion in the right coronary artery. Such a patient could benefit from bilateral internal mammary artery grafts and a radial graft, and it would be a disservice to perform PCI, which does not outperform arterial grafts.

The Profile of a Good Candidate

To be eligible for robotic hybrid revascularization, the patient must be a candidate for both PCI and minimally invasive CABG. Ideally, this is a patient with multivessel disease, a complex LAD lesion and relatively simple non-LAD lesions that are amenable to PCI.

For instance, an active 70-year-old with LAD occlusion and right coronary artery stenosis (Figure) would be a suitable candidate. In such a case, we could perform a minimally invasive LIMA-to-LAD graft placement and stent the right coronary artery, producing revascularization likely to be equivalent in quality to open CABG.

What the Future May Hold

Due to the complexity of the procedure, robotic hybrid revascularization may remain in the domain of a handful of medical centers where surgeons have mastered lessinvasive CABG and have a late-generation da Vinci® robot in a cardiac surgery suite. Nevertheless, as skills in robotic surgery improve and surgeons continue to refine minimally invasive CABG, we can expect to push the boundaries of the procedure to include patients with broader indications.

Contact Dr. Mick at micks@ccf.org or 216.444.5410.

Preventing Restenosis After Percutaneous Vascular Intervention: Three Takes on Three Emerging Strategies

Three decades after the advent of percutaneous intervention for treatment of various forms of atherosclerotic vascular disease, optimal methods of preventing the most common complications after treatment — restenosis and thrombosis — are still under active investigation.

Although these complications have become less frequent with newer technology and pharmacotherapy, a number of recent developments promise further improvements. These include:

- Approval of the first drug-coated angioplasty balloon catheters for treatment of peripheral artery disease (PAD)
- The re-emergence of vascular brachytherapy as an option for preventing restenosis in carefully selected patients
- Improved understanding of the appropriate duration of dual antiplatelet therapy in recipients of coronary stents

Cardiac Consult caught up with three Cleveland Clinic interventional cardiologists for their perspectives on how these developments are shaping therapy.

Drug-Coated Balloon: Lessons from Real-World Use Begin

In October 2014, the FDA approved a paclitaxel-coated angioplasty balloon catheter — the Lutonix® 035 DCB — for percutaneous transluminal angioplasty, after predilatation, for the treatment of de novo or restenotic stenoses in superficial femoropopliteal arteries as a result of PAD. The paclitaxel-coated balloon is approved for treating stenoses up to 150 mm long in these arteries.

The dose of paclitaxel used is 300 times lower than the dose used as chemotherapy, and only about 10 percent of that is delivered to the vessel wall, says Mehdi Shishehbor, DO, MPH, PhD, Director of Endovascular Services in the Department of Cardiovascular Medicine. FDA approval was supported by results of the international LEVANT 2 pivotal trial, which included 476 patients — including some enrolled at Cleveland Clinic — with angiographically significant stenoses in the superficial femoral or popliteal artery and a patent tibial artery to the foot. Patients were randomized in a 2-to-1 ratio to treatment with the paclitaxelcoated balloon or conventional balloon angioplasty. Only those who had successful predilatation with an undersized standard balloon were randomized.

At 12 months, patency rates were 73.5 percent in patients randomized to the paclitaxel-coated balloon and 56.8 percent in those randomized to standard balloon angioplasty. Greater improvements in Rutherford class and walking distance scores were also observed with the paclitaxel-coated balloon.

The benefits of the drug-coated balloon are less clear in patients with longer stenoses with moderate to heavy calcification, notes Dr. Shishehbor. "While this new technology is exciting and may help patients, questions remain, such as its efficacy, safety and cost-effectiveness for longer lesions," he says. "In my practice, I will be using drug-coated balloons in selected patients with short lesions that have only mild to moderate calcification. In the near future, we may learn that we get better results by removing some of the plaque and then delivering the drug."

In January, the FDA approved a second paclitaxel-coated balloon, Medtronic's IN.PACT Admiral Drug Eluting Balloon, for treating PAD in the upper leg. Both devices are now available for routine clinical use.

The benefits of the drug-coated balloon are less clear in patients with longer stenoses with moderate to heavy calcification.

Vascular Brachytherapy Redux

Vascular brachytherapy (VBT), which fell out of favor for the prevention of restenosis following percutaneous coronary intervention after drug-eluting stents (DESs) entered the market, is being reintroduced into practice for selected patients at Cleveland Clinic.

Stent restenosis is still a problem for some high-risk patients who receive a DES, explains Stephen Ellis, MD, Section Head of Invasive and Interventional Cardiology. The presence of diabetes, implantation of longer stents and multiple stents, and small blood vessels are risk factors that may increase the likelihood of stent restenosis.

VBT is usually considered only in patients who have experienced multiple bouts of restenosis, according to Dr. Ellis. "The approach to addressing restenosis is highly individualized," he notes. "It includes a number of options based on the principal cause of the restenosis, the blockage size, whether the patient has restenosis in multiple spots and the number of stents the patient may already have in one area. The way the blockage comes back partly determines the likelihood that it will become a recalcitrant problem — and, to a certain extent, guides therapy."

A standard antithrombotic regimen of aspirin and clopidogrel is used after VBT. In the short term, this regimen reduces the rate of restenosis by about 50 percent, but long-term durability of the effect in patients with a DES is not known.

Duration of Dual Antiplatelet Therapy After DES Placement

For patients with a DES who tolerate one year of dual antiplatelet therapy with aspirin and a thienopyridine (clopidogrel or prasugrel), an additional 18 months of dual antiplatelet therapy reduces the risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events compared with stopping therapy at one year. This was the major finding of the recent international Dual Antiplatelet Therapy (DAPT) trial (*N Engl J Med.* 2014;371:2155-2166), in which 9,961 patients were randomly assigned to continue their thienopyridine and aspirin or to receive placebo and continue aspirin. Specifically, patients assigned to 30 months of dual antiplatelet therapy experienced the following relative to those assigned to 12 months of dual therapy:

- 71 percent reduction in stent thromboses (P < .001)
- 53 percent reduction in myocardial infarctions (MIs) (*P* < .001)
- 29 percent reduction in risk of death, MI or stroke (*P* < .001)

"For patients who have tolerated dual antiplatelet therapy for one year and don't seem to be at an excess risk for bleeding, there may be benefit to continuing for at least another 18 months," says A. Michael Lincoff, MD, Vice Chair of the Department of Cardiovascular Medicine.

The optimal duration of dual therapy is still unknown, Dr. Lincoff adds, because the event curves were diverging until dual therapy was stopped, and an additional three months of follow-up showed that rates of stent thrombosis and MI started to increase after cessation of dual therapy at 30 months.

Although the trial was started when earlier generations of DESs were in use, the benefit of prolonged dual therapy was apparent in patients treated with newer-generation DESs.

While extended dual therapy increased the risk of moderate or severe bleeding, the benefit-to-risk ratio was still firmly on the side of extending therapy, Dr. Lincoff notes.

Contact Dr. Shishehbor at shishem@ccf.org or 216.636.6918; Dr. Ellis at elliss@ccf.org or 216.445.6712; and Dr. Lincoff at lincofa@ccf.org or 216.444.2367.

Teaming Up to Take on Severe Pulmonary Embolism

Of the 300,000 to 600,000 pulmonary embolism (PE) cases in the U.S. each year, 10 to 30 percent result in death within a month of diagnosis, according to data from the Centers for Disease Control and Prevention. In cases of severe PE — involving abnormal vital signs, right ventricular strain, central or saddle PE, or a large embolism and contraindications to anticoagulation — complex decision-making is often required in a narrow time window if death is to be averted.

In response to these stark realities, Cleveland Clinic has taken an "all hands on deck" approach in the form of a new multidisciplinary Pulmonary Embolism Response Team (PERT) to expedite and streamline the care of patients with severe PE.

"The goal is to enable coordinated, real-time consultation by a multidisciplinary team that's empowered to rapidly make complex therapeutic decisions and mobilize the needed management resources," says John R. Bartholomew, MD, Section Head of Vascular Medicine and a leading PERT member.

The PERT's hallmark is its multidisciplinary makeup, with specialists in vascular medicine, cardiothoracic surgery, cardiology, interventional radiology, pulmonary/ critical care medicine, emergency medicine and internal medicine. "The idea is to virtually bring together a diverse team of experts for these complex cases rather than having just one expert making all the decisions in the field," says pulmonary and critical care specialist Gustavo Heresi-Davila, MD, another PERT member.

As soon as a case of severe PE is identified, the team is activated via a dedicated pager number for an online meeting (via email or instant messaging platform) followed by a bedside meeting with PERT members joining in person (if needed) or virtually. The team jointly devises recommended management — drawing on resources in the OR, catheterization or interventional radiology labs, electrophysiology lab, vascular ultrasonography suite and beyond — for targeted implementation within 180 minutes (or less) of patient presentation.

PERT implementation began in summer 2014, with the team managing over 20 cases by year's end.

Contact Dr. Bartholomew at barthoj@ccf.org and Dr. Heresi-Davila at heresig@ccf.org.

Save the Date for CME

2015 Preceptorship in Carotid Ultrasound Interpretation

March 2-6 | June 22-26 | Aug. 31-Sept. 4 Nov. 30-Dec. 4, 2015

Cleveland Clinic Noninvasive Vascular Laboratory Cleveland

This intensive 4½-day training program features lectures, preceptored interpretation sessions with physicians from Cleveland Clinic's noninvasive vascular lab, hands-on screening sessions and extensive case reviews with angiographic correlations. Class size limited to six participants.

Information/registration: ccfcme.org/carotid15

Controversies in the Prevention and Management of Ischemic Heart Disease

Friday, March 13, 2015

An independent certified session at ACC.15 7-9:30 p.m. (complimentary dinner program)

Marriott Marquis San Diego Marina San Diego

See this issue's back cover for details on this independent dinner symposium at the American College of Cardiology's Annual Scientific Session.

Information/registration: ccfcme.org/ACC.15

Fundamental to Advanced Echocardiography in 2015

April 17-19, 2015

Cleveland Marriott Downtown at Key Center Cleveland

This 2½-day course explores practical issues in echo salient to today's cardiology practices. Emphases include new imaging technologies and multimodality imaging, with a focus on the role of new products and innovations. Features several breakout workshops and sessions offering guidance on the optimal use of echo in various practice settings. Preceded the evening of April 16 by an optional Maintenance of Certification Learning Session on the ABIM 2015 Update in Cardiovascular Disease knowledge module.

Information/registration: ccfcme.org/GoEchoCardio

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The Cleveland Clinic Way By Toby Cosgrove, MD, CEO and President,

Cleveland Clinic

Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ ClevelandClinicWay for details or to order a copy.

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2014, Cleveland Clinic was ranked one of America's top four hospitals in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 20th consecutive year) and urologic care.



The Cleveland Clinic Foundation 9500 Euclid Ave./AC311 Cleveland, OH 44195

Cardiac Consult

Carve Out Time at ACC.15 for an IHD Update

Controversies in the Prevention and Management of Ischemic Heart Disease

Friday, March 13, 2015 | 7-9:30 p.m. (complimentary dinner program) Marriott Marquis San Diego Marina, San Diego

This independent dinner symposium at the American College of Cardiology's Annual Scientific Session provides an in-depth discussion of the current state of prevention and management of ischemic heart disease. Among the focus areas:

- The latest recommendations for hyperlipidemia therapy and risk modification
- Appropriate-use criteria for PCI
- Decision-making in revascularization: Beyond the STICH trial

This CME-certified program is jointly provided by Cleveland Clinic and the North Shore-LIJ Health System and features expert faculty from both institutions.

Information/registration: ccfcme.org/ACC.15 Registration questions: 216.932.3448

Cleveland Clinic

