INSIDE THIS ISSUE

Cleveland Clinic

Cardiac Consult

Heart and Vascular News from Cleveland Clinic | Summer 2016

Innovation Unbound:

Case Lessons in Bringing Inventiveness to Every Part of Cardiovascular Practice

– p. 6

Dear Colleagues:

Innovation is a cultural thing. That's the upshot of the cover story of this issue of *Cardiac Consult*, which profiles a few ways in which the ethic of innovation in Cleveland Clinic's Miller Family Heart & Vascular Institute goes beyond realms typically associated with healthcare innovation — like new devices, procedures or technologies — to infuse all aspects of our program's operations. This ethic spans everything from a new way to keep our subspecialists up to speed with each other's fields to enhancements of our STEMI protocol that have trimmed door-to-balloon times to exceptional levels.

As the cover story makes clear, inventiveness tends to be contagious. Innovations in seemingly small or process-oriented matters often foster an atmosphere in which more dramatic innovations flourish, like the development of a novel stented transcatheter mitral valve prosthesis that was implanted successfully in a human for the first time in late 2015. See page 8 for details.

Other stories in this issue are testaments to innovation's contagiousness. Consider the resourceful endovascular strategy devised to address a large pseudoaneurysm on the ascending aorta in an 86-year-old, as outlined on page 3, or the inventive application of remote endarterectomy for occluded arteries in patients with long-standing peripheral vascular disease, as explored on page 12.

Another story (page 14) updates Dr. Stanley Hazen's trailblazing research on the gut microbial metabolite TMAO by detailing new additions to the fast-growing list of cardiometabolic effects now linked to elevated TMAO — namely, platelet hyperreactivity and increased risk for thrombotic events. And page 16 features the latest installment in our "Case Studies in Collaboration" series profiling the innovative Cleveland Clinic Cardiovascular Specialty Network and how we help network partners across the nation improve their clinical and/or operational functions.

The latter example speaks to how the contagion of innovation cannot and should not be restricted by institutional boundaries. Cleveland Clinic always welcomes opportunities to consult with you, our cardiovascular colleagues around the nation, on your most complex and challenging cases. Such interactions provide some of our finest learning opportunities while helping bring highly specialized, volume-based expertise to patients with the rarest conditions. When it comes to innovation, the more is always the merrier.

Respectfully,

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Image of the Issue

By Eric E. Roselli, MD

Stent Grafting for an Ascending Aorta Pseudoaneurysm in an 86-Year-Old

An 86-year-old man who was living independently presented in early 2016 with a large pseudoaneurysm on the ascending aorta (left CT above) in close proximity to widely patent grafts from a previous coronary artery bypass procedure.

Further inspection on CT scan showed the pseudoaneurysm to be immediately adjacent to the back of the sternum (middle CT above), further complicating management of this highly functional but still quite elderly patient.

After weighing options, the surgical team in Cleveland Clinic's Aorta Center devised a plan to address the pseudoaneurysm by placing a stent graft delivered through the right axillary artery. The completed stent graft placement is shown in the right CT above.

After extubation the next morning, the patient was back on his feet and out of the ICU within two days. He continues to fare well.

Cleveland Clinic's ability to develop inventive endovascular strategies like this stems from its unmatched aortic surgery volumes, which consistently approach or exceed 1,200 annually (N = 1,185 in 2015). Its mortality rates for thoracic aorta surgery procedures consistently outperform expected rates (e.g., 2015 observed-to-expected ratio of 0.8) despite an abundance of complex cases like the one profiled here.

For more outcomes and volume information from Cleveland Clinic's Miller Family Heart & Vascular Institute, visit clevelandclinic.org/outcomes. ■

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Heart & Vascular Vitals:
Focus on Cardiothoracic Surgery

A sampling of Cleveland Clinic Miller Family Heart & Vascular Institute volumes and outcomes. This issue's focus is cardiothoracic surgery. For more outcomes data from Cleveland Clinic, visit **clevelandclinic.org/outcomes**.

3★'s in all 3 categories of STS adult cardiac surgery ratings

For the period ending 12/31/15, Cleveland Clinic achieved a 3-star (highest) rating in all 3 categories of adult cardiac surgery in which the Society of Thoracic Surgeons (STS) rates hospitals:

- Coronary artery bypass graft surgery (CABG)
- Aortic valve replacement (AVR)
- Combined CABG + AVR

The rating applies to Cleveland Clinic's main campus and Fairview and Hillcrest regional hospitals.

1.89%

Proportion of programs that achieved this "3 stars in all 3 categories" rating among the 634 U.S. sites that publicly report their STS adult cardiac surgery registry data (see chart)

CABG	AVR+CABG	AVR	Publicly reporting programs w/ this rating
✪ ✪ ✪	✪ ✪ ✪	✪ ✪ ✪	12 (of 634)

Lobectomy too

Cleveland Clinic also scored a 3-star STS rating in lobectomy for lung cancer in the most recent rating period (ending 6/30/15).

Selected procedural volumes (2015)

4,395
Cardiac surgeries

2,943
Valve surgeries

1,508
CABG procedures (isolated + combined)

1,185
Aortic repairs

105
Robotically assisted cardiac surgeries

1,577
Thoracic surgeries

48
Heart transplants (49% bridged from mechanical support)

97
Lung transplants

Outcomes Snapshots

0.1% actual vs. 0.75% expected (STS)
Mortality for isolated mitral valve repairs over 3 years (2013-2015), including 0% mortality in 2015

0.5% actual vs. 2.1% expected (STS)
Mortality for isolated aortic valve surgeries in 2015 (N = 442), including 0% mortality among 89 patients undergoing reoperative procedures

0.9% actual vs. 1.9% expected (STS)
Mortality for isolated CABG in 2015 (N = 511)

0.7% actual vs. 3.4% expected (STS)
Mortality for pediatric congenital heart surgeries in 2015 (N = 140)

1.5% actual vs. 3.0% expected (UHC)
Mortality for adult congenital heart surgeries in 2015 (N = 342)

(UHC = University HealthSystem Consortium)

1.6% actual vs. 9.9% expected (UHC)
In-hospital mortality for recipients of left ventricular assist devices (LVADs) in 2015 (N = 61)

88.6% 3-year heart transplant graft survival
In most recent SRTR reporting period, compared with 83.7% expected rate and 84.3% national rate

(SRTR = Scientific Registry of Transplant Recipients)

FAST FACTS: Robotic Mitral Valve Repairs

1,355

Number of robotically assisted mitral valve repairs at Cleveland Clinic through April 2016

0.1%

Mortality for robot-assisted mitral valve repairs over 5 years ending 12/31/15 (vs. 1.2% UHC expected rate)

Innovation Unbound:

Case Lessons in Bringing Inventiveness to Every Part of Cardiovascular Practice

If you were told that a leading cardiovascular program developed a way to keep its subspecialists up to speed on the latest capabilities they could offer one another, would you call that an innovative center? How about if they made changes to their STEMI protocol that trimmed door-to-balloon times to 21 or 22 minutes for multiple cases? Or if they launched a platform to connect electrophysiologists around the world in the cause of optimal lead management?

Now what if you were told an academic center discovered cine-coronary angiography, pioneered CABG surgery and introduced IV ultrasound for precise measurement of plaque regression?

Cleveland Clinic knows which description would win plaudits for innovation, because we are in fact *both* of the centers described above. While we may be known for the latter "headline" innovations, we are increasingly convinced of the profound value of the former, less-dramatic types of innovation as well. And we continue to learn how closely the two types of inventiveness are intertwined.

It's a Cultural Thing

"Innovation is about more than developing new devices or procedures or therapies," says Lars Svensson, MD, PhD, Chair of Cleveland Clinic's Miller Family Heart & Vascular Institute. "It's also about delivering care in new ways — for greater efficiency and patient access — and finding better ways to make connections among providers to improve care coordination and disseminate best practices."

For cardiothoracic surgeon Douglas Johnston, MD, who co-chairs the Heart & Vascular Institute's Innovation Committee, innovation is a cultural factor. "I came to Cleveland Clinic several years ago from another academic medical center," he says, "and what struck me as unique here is the fact that we are innovating every day. It parallels our clinical mission and is part of our core business."

The cultural aspect of innovation also resonates with Joseph Cacchione, MD, Chair of Operations and Strategy for the Heart & Vascular Institute, who encounters it in his dealings with the 23 allied or affiliated centers nationwide that make up the Cleveland Clinic Cardiovascular Specialty Network. "Cultural fit is a key attribute we look for in potential network members," he explains. "What's more important than one subpar outcomes metric is an institutional commitment to work with us to find ways to improve that metric. None of us is perfect, but we all need the drive to get better every day. That's a big part of innovation, and that's the culture we foster here and look for in affiliates and allies."

This article profiles a few examples of how that culture goes beyond the headline-grabbing innovations to infuse virtually every aspect of Cleveland Clinic's Heart & Vascular Institute. To show how "traditional" innovation tends to thrive amid these other forms of inventiveness, we've dropped in sidebars on a couple of our recent device innovations for good measure.

A Partner in Innovation

A key partner of the Heart & Vascular Institute in its device- and technology-related innovation is Cleveland Clinic Innovations (CCI), the commercialization arm of Cleveland Clinic. CCI helps caregivers assess, strategize, protect, build and market their solutions for advancing patient care on a global scale. Since its inception in 2000, CCI has acted on approximately 3,400 inventions, resulting in more than 800 issued patents, over 450 licenses and 40 active spinoff companies.

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CASE 1: Innovating Education with 'Tall Rounds'

A few years ago, cardiothoracic surgeon Eric E. Roselli, MD, was grappling with an all-too-common healthcare reality: He worked every day with distinguished experts across many disciplines but found that everyone's schedules were so overloaded that there was almost no time for collegial interaction. "We are all so busy that we simply can't keep up with what each other is doing," says Dr. Roselli, who was frustrated enough to devise a solution.

As Director of Cleveland Clinic's Aorta Center, Dr. Roselli was charged with filling two conference slots each month for internal education in aortic diseases. Although he chose speakers carefully, he felt the routine had grown a bit stale. But then he had an epiphany: Why not give up one of his slots for an interactive, interdisciplinary teaching conference addressing shared patient care issues in a highly streamlined way? With that, Tall Rounds™ was born.

He chose a topic, gathered experts from various cardiovascular subspecialty areas and gave each one about five minutes to provide pearls of information on an aspect of the chosen topic they encounter regularly.

The response was overwhelming. Physicians, surgeons, trainees, midlevel providers, nurses and technicians crammed the room and spilled into the hallway. More than 20 Tall Rounds sessions later, the series is going strong: It's now offered up to twice a month and has moved to a larger space to accommodate up to 180 attendees. Sessions are broadcast live to Cleveland Clinic locations worldwide, with efforts underway to expand access online (with CME credit) to external physicians.

Each session follows the same format: A fellow presents a case and relevant imaging, and four to seven experts from various cardiovascular subspecialties speak to the topic from their vantage points. The final 15 minutes is devoted to discussion.

"No one's too busy to prepare a five-minute talk in their specialty," Dr. Roselli explains. "It's long enough to get one another's focused perspective, and everyone feels they've learned something valuable. The range of issues involved in patient management can be mind-boggling. Tall Rounds represents a fresh approach that promotes better understanding of what everyone on the team can offer."

For more on Tall Rounds, see consultqd.clevelandclinic.org/tallrounds. Contact Dr. Roselli at roselle@ccf.org.

Device Innovation: Novel Stented Transcatheter Mitral Valve Prosthesis

Cleveland Clinic spinoff company NaviGate Cardiac Structures recently announced the first-in-human implant of its stented transcatheter mitral valve prosthesis into a beating heart.

The device (photo below) was developed by Cleveland Clinic cardiothoracic surgeon José Navia, MD, and licensed to NaviGate in 2012. It is among the first experimental systems designed for catheter-based mitral valve replacement and offers the following innovative features:

- Applicability for heart failure patients with severe mitral or tricuspid valve regurgitation, including inoperable patients with no other treatment options
- A low-profile design that provides superior inflow/outflow performance, eases transfemoral delivery and allows minimally invasive transatrial or transapical implantation
- Preservation using a "dry processed" technology developed at Cleveland Clinic to allow dry storage in the delivery device and avoid the need for toxic glutaraldehyde and rinsing/crimping in the OR

The implantation was performed in Chile in October 2015 in a 53-year-old man with severe mitral regurgitation as part of a feasibility study. The prosthesis was successfully placed in the mitral position via transatrial delivery. The patient has fared well, with no paravalvular leakage and no outflow tract obstruction.

CASE 2: Innovating Care Delivery with a Revised STEMI Protocol

Around the time Dr. Roselli was brainstorming Tall Rounds, cardiologist Umesh N. Khot, MD, was spearheading an effort that shows how innovation often can arise simply from the drive to get better every day.

In mid-2014, Cleveland Clinic implemented enhancements to its protocol for managing patients with ST-segment elevation myocardial infarction (STEMI). "The changes were prompted by an organizational commitment to take our STEMI program from good to exceptional by standardizing the process to reduce variability," explains Dr. Khot, Chief Quality Officer for the Heart & Vascular Institute.

He and others from the Section of Invasive and Interventional Cardiology teamed with colleagues in Cleveland Clinic's Emergency Services Institute on a year's worth of preparatory work, drawing in part on Dr. Khot's extensive experience designing systems of care for MI. Their efforts resulted in four key process improvements:

- Standardization of criteria by which emergency physicians can activate the catheterization lab, enabling the emergency department (ED) and interventional cardiology teams (located in different buildings) to work in a more coordinated way.
- Development of a STEMI handoff checklist delineating clear roles for all caregivers: ED physicians, cardiologists, and nurses in the ED and cath lab. Instructions and contact numbers are provided, accountability is assigned, and a short time-out is required to ensure completion of all tasks.
- Facilitation of immediate transfer of all patients to the cath lab, with the ED attending physician empowered to activate the cath lab (and cardiology staff available for swift consults as needed).
- Round-the-clock cath lab readiness through use of an in-house transfer team and improved organization of nighttime nursing staff.

"Together these process changes were designed to fundamentally structure STEMI management so that patients receive the same care every time with clear consistency," notes Samir Kapadia, MD, Director of the Cardiac Catheterization Laboratory.

The revised protocol yielded improvements in door-to-balloon times — i.e., from ED arrival to percutaneous coronary intervention — within days of its implementation on Cleveland Clinic's main campus in July 2014. These results followed:

- 35 percent of STEMI patients treated in the first year after protocol revision had a door-to-balloon time of 45 minutes or less, nearly double the percentage during the prior six months. Multiple patients were treated in as little as 21 or 22 minutes.
- Median door-to-balloon time during that first year was 52 minutes.
- 100 percent of STEMI patients have had a door-to-balloon time within the American College of Cardiology-recommended 90 minutes for each of the past six quarters.

The revised STEMI protocol is now being deployed in all hospital EDs across the Cleveland Clinic health system. "We want to bring this same consistent delivery of fast, standardized treatment to all STEMI patients," says Dr. Khot.

For more, see consultqd.clevelandclinic.org/stemichanges. Contact Dr. Khot at khotu@ccf.org and Dr. Kapadia at kapadis@ccf.org.

continued next page

100% of STEMI patients have had a door-to-balloon time within the American College of Cardiology-recommended 90 minutes for each of the six quarters since the protocol revisions.

CASE 3: Innovating Collaboration with a Web Community for EPs

As with the STEMI protocol changes, the desire for consistent delivery of optimal care was likewise the impetus for the next case lesson, albeit on a much larger scale.

"Electrophysiologists (EPs) are a community often isolated by geography, language, training and economic systems," says Bruce Wilkoff, MD, Director of Cardiac Pacing and Tachyarrhythmia Devices at Cleveland Clinic. "At the global level, there are so few of us that it can be difficult to have a knowledgeable conversation, and the result can be wide variations in how best practices are incorporated."

After years of hearing about these challenges from colleagues around the world, Dr. Wilkoff grew convinced they could be overcome with online technology. In May 2015, that conviction culminated in the launch of his brainchild: **LEADconnection.org**, an independent web portal that dubs itself "a global community that strives to engage every voice for optimal lead management."

The interactive site provides a forum for conversations, problem-solving and information distribution around the management of patients with transvenous leads, pacemakers, implantable cardioverter-defibrillators and devices for cardiac resynchronization therapy.

It's a go-to resource for EPs worldwide and a clearinghouse for information on EP devices, from updates on clinical trials and registries to conference news to posters and presentations from major medical meetings to educational offerings. And the content is strictly educational: There are no industry links on the site, which is supported by contributions from grateful patients.

More than 350 members in 40 countries to date have registered for the free, password-protected site. It's in the blog section that members scratch their itch for collegial interaction. They post questions, images and videos and receive input from colleagues around the world. "You can have a conversation about a case, images you want help interpreting or questions you're trying to work out," says Dr. Wilkoff. "Discussions are instructional and publicly viewed by members, so hundreds of others are able to gain insights and advance patient care globally."

Although LEADconnection.org was started by Dr. Wilkoff, Cleveland Clinic exercises no editorial oversight and the site operates as a member-directed forum. "The aim is to build a sense of belonging and empowerment among colleagues around the world," Dr. Wilkoff explains. "This can ultimately allow all participants to provide care with the same level of insight as someone in Cleveland."

For more, see consultqd.clevelandclinic.org/leadconnection.
Contact Dr. Wilkoff at wilkofb@ccf.org.

Device Innovation: Whitlow Guide Wires

Veteran Cleveland Clinic innovator Patrick Whitlow, MD, knew from experience how easily guide wires can get twisted in the course of an interventional procedure. So he came up with a new guide wire design with a strong torque response so that rotating one end results in simultaneous rotation of the opposite end. The design also aims to increase flexibility over existing guide wires and features a flexible bend in the tip to help penetrate arterial occlusions.

His invention — known by the trade name PW Guidewires ("Whitlow wires") — was licensed to Cleveland Clinic spinoff firm Tatara Vascular and received 510(k) premarket approval from the FDA in January 2016 for use in percutaneous coronary intervention. Sadly, Dr. Whitlow died two months later (see "In Memoriam," page 15), but this latest invention is the capstone of a long Whitlow legacy of innovation at Cleveland Clinic that is likely to endure for decades.

Innovating Abroad: Cleveland Clinic Abu Dhabi

When Cleveland Clinic Abu Dhabi opened in 2015, Cleveland Clinic's U.S. facilities gained a unique partner that promises to accelerate cardiovascular innovation at home and abroad.

This new multispecialty hospital, a partnership with Abu Dhabi's Mubadala Development Company, is an extension of Cleveland Clinic's model of care and specifically designed to address complex and critical care needs in the Middle East region.

Its Heart & Vascular Institute has attracted a world-renowned staff from the U.S. and Europe, including five cardiothoracic surgeons with extensive expertise across the spectrum of robotically assisted heart surgery: mitral valve repair, CABG, hybrid coronary interventions and atrial septal defect repair.

These services are complemented by the full range of cardiovascular medicine activities and a wealth of other minimally invasive surgical and procedural offerings that are new to the region, including:

- Multivessel totally endoscopic coronary bypass surgery (TECAB) (first in region)
- Quintuple coronary revascularization using double robotic TECAB and triple PTCA/stenting in a simultaneous session (first in region, perhaps first worldwide)
- Transcatheter mitral valve repair with MitraClip® (first in region by an interdisciplinary team of interventional cardiologists and cardiac surgeons)
- Transcatheter aortic valve replacement with guidance by intracardiac echo and using monitored anesthesia care (first in region)

The match of these services to the region is a good one in at least two ways. First is the region's traditional cultural emphasis on preserving bodily integrity, which means minimally invasive cardiac surgery may be preferable to open-chest surgery among some patients in the region.

Second is the fact that Cleveland Clinic Abu Dhabi specialists can use some innovative devices and approaches sooner than their colleagues in Cleveland can, including products that have received the CE mark but are still pending FDA approval. For instance, Cleveland Clinic Abu Dhabi has treated three cases of in-stent restenosis using a cutting balloon followed by a drug-eluting balloon to avoid the conventional stent-in-stent approach. These cases, the first in the region, will offer useful experience for practice in Cleveland if this approach gains FDA approval.

Such examples show how innovation can be a two-way street between the U.S. and Abu Dhabi. The relationship is a two-way exchange in a more literal sense as well. "As Cleveland Clinic becomes a more global healthcare entity, this requires some surgeons to be mobile on a global level," says Johannes Bonatti, MD, Chief of Cleveland Clinic Abu Dhabi's Heart & Vascular Institute. "We plan to bring fellows and colleagues here to share methods, to ensure our techniques can be identified as Cleveland Clinic methods."

One more way that Cleveland Clinic is well matched to Abu Dhabi is a shared culture of innovation. "New approaches to medicine are very welcome here," says E. Murat Tuzcu, MD, Chief Academic Officer and Chief of Cardiovascular Medicine at Cleveland Clinic Abu Dhabi.

Dr. Tuzcu, an interventional cardiologist who relocated from Cleveland, says Abu Dhabi is a modern, multicultural city whose young leaders have a vision for research, innovation and education. He notes that the new multispecialty hospital has encountered no cultural resistance and was approved in May 2016 as a research institute by Abu Dhabi's health authority, paving the way for clinical trials and other research activities. "Our first phase was setting up a clinical environment allowing us to undertake programs safely," he says. "Innovation is next." ■

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Remote Endarterectomy: The Third Pathway for Arterial Revascularization

Patients with limb-threatening ischemia have a forgotten third option.

By W. Michael Park, MD

As patients with long-standing peripheral vascular disease live longer with their condition, we are increasingly referred patients who are at the end of the line due to artery occlusion, having exhausted bypass and endovascular options. These patients face the prospect of limb loss or worse.

Three approaches to an occluded artery

There are a finite number of ways to deal with an occluded artery. One option is to bypass the artery using either the patient's own veins, tubes of artificial graft materials or, as a last resort, donor arteries and veins.

A second option is to open the arteries by pushing aside the occlusive plaque with balloons, stents or the more recently developed stent grafts, which consist of graft material mated to stents. Newer therapies include devices to drill through the plaque by pulverizing, cutting or burning it.

Before the advent of bypass surgery and endovascular therapy, endarterectomy represented the only option for revascularization. Endarterectomy and its modern incarnation, remote endarterectomy, offer an important third option in revascularization, especially when the first two alternatives have been exhausted.

Endarterectomy has the advantage of not relying on artificial materials, which makes it suitable for application in cases of infection. The procedure involves removing the obstructive plaque surgically, thereby reopening the previously occluded artery (Figure 1).

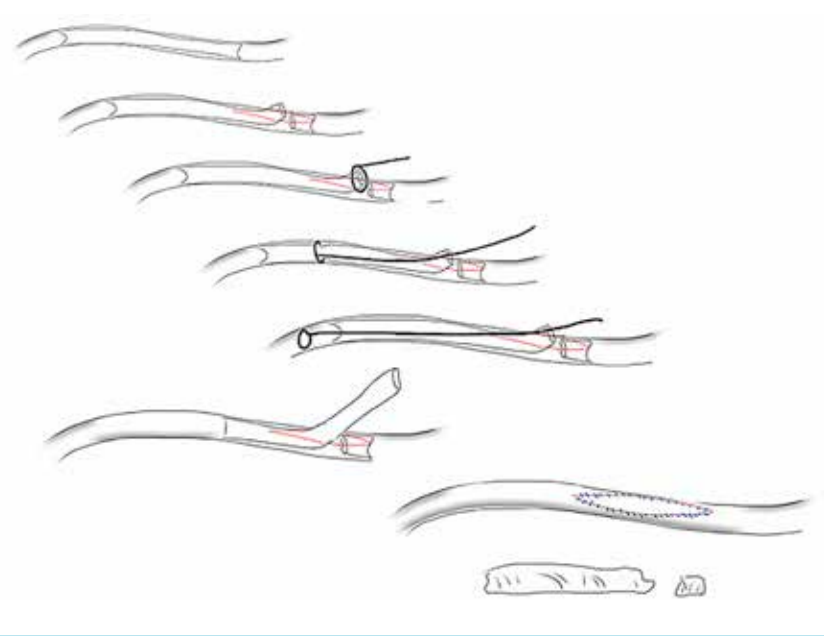

Figure 1. The steps involved in endarterectomy.

Endarterectomy has the advantage of not relying on artificial materials, which makes it suitable for use in cases of infection.

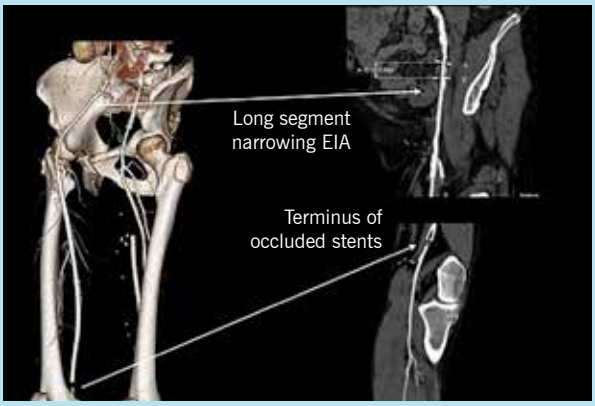

Figure 2. Patients with prior stenting commonly return with stent occlusion, as seen in this example.

Figure 3. Photo of occluded stenting removed from the superficial femoral artery (SFA) in a remote endarterectomy.

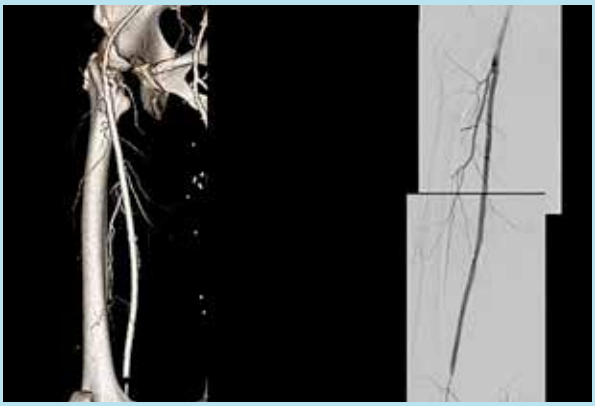

Figure 4. A 3-D reconstruction image and angiograms of the superficial femoral artery in a patient following remote endarterectomy.

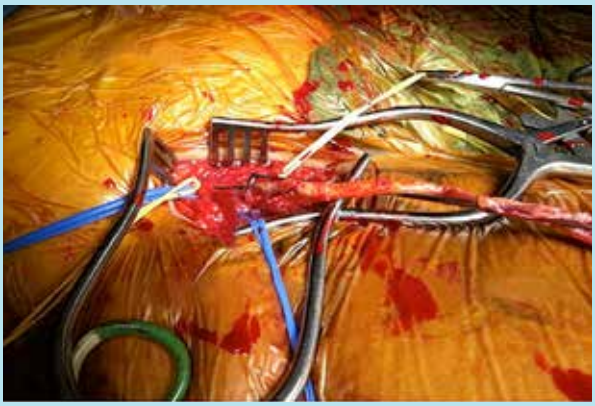

Figure 5. Remote endarterectomy is accomplished with a single groin incision approximately 4 inches in length.

A feasible option for occlusive stents

Removal of occlusive stents is often technically feasible. For example, it is common to see patients who have undergone prior stenting return with these stents occluded (Figure 2). If these patients do not have an available vein for use in bypass, their options can be limited, but with this third option of remote endarterectomy, the occlusive plaque and stents can be removed (Figure 3). This restores patency of the previously occluded artery (Figure 4), with all accomplished from a single groin incision approximately 4 inches in length (Figure 5).

A useful fallback strategy

Remote endarterectomy provides a less-invasive revascularization option. It is durable relative to endovascular intervention for TransAtlantic Inter-Society Consensus (TASC) II D lesions (long-segment occlusions)[1] and compares favorably to bypass with prosthetic grafts with acceptable patency rates.[2]

While endarterectomy is not suitable for all cases or as a primary revascularization option, it remains a useful part of the vascular surgery armamentarium. ■

Dr. Park is a surgeon in the Department of Vascular Surgery. Contact him at parkm3@ccf.org.

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Gut Microbe-Dependent TMAO Promotes Platelet Hyperreactivity, Raises Thrombosis Risk

Study raises prospect of a new mechanism for preventing thrombotic events.

Add two more entries to the fast-growing list of cardiometabolic effects of elevated levels of the gut microbial metabolite TMAO: platelet hyperreactivity and increased risk for thrombotic events.

In a new paper published in *Cell* (2016;165:111-124), researchers in the Cleveland Clinic lab of Stanley Hazen, MD, PhD, report in vivo studies that collectively show that gut microbes, through generation of TMAO (trimethylamine-*N*-oxide), directly contribute to platelet hyperreactivity and increased thrombosis potential.

"Our findings reveal a previously unrecognized mechanistic link between specific dietary nutrients, gut microbes, platelet function and thrombosis risk," says Dr. Hazen, Chair of Cellular and Molecular Medicine and Section Head of Preventive Cardiology and Rehabilitation at Cleveland Clinic.

Hypothesis-generating data from a large human cohort

The new findings build on multiple clinical studies — many by Dr. Hazen's research team — linking elevated blood levels of TMAO with heightened risk of cardiometabolic diseases in humans, including atherosclerosis, heart failure and chronic kidney disease. Central to this link are the dietary nutrients choline, lecithin and carnitine (all abundant in animal products), which are ultimately metabolized into TMAO after they come in contact with microbes in the gut.

Yet while these prior studies showed mechanistic links between TMAO and atherosclerosis development through changes in tissue sterol metabolism as well as arterial macrophage and endothelial cell activation, no studies had explored the strong association between TMAO and acute cardiovascular events or vulnerable plaque triggered by acute thrombotic events. Nor had there been exploration of the potential involvement of gut microbes and TMAO in the modulation of platelet function or in any resulting effects on risk for thrombotic events.

Suspecting such involvement, Dr. Hazen's team reanalyzed data from its landmark study in the *New England Journal of Medicine* (2013;368:1575-1584) of the relation between TMAO and cardiovascular events in over 4,000 patients. Their new analysis, reported now in *Cell*, tested specifically for an association between plasma TMAO levels and incident risk for thrombotic events (MI or stroke). The analysis revealed such an association and that it remained significant even after adjustment for cardiovascular disease history, traditional cardiovascular risk factors, renal function and medication use. Specifically, it found a 1.64-fold increase in thrombotic events in patients whose TMAO levels were in the highest quartile versus those with levels in the lowest quartile, even after adjustments ($P < .001$).

"We found that a high TMAO tracks with heightened risk for thrombotic MI and stroke in a large human sample," says Dr. Hazen. "The effect was seen across a large, dynamic range of TMAO levels."

> The paper suggests that therapeutic targeting of the gut microbial TMAO pathway has the potential to temper TMAO-related platelet hyperresponsiveness without promoting bleeding.

Testing the hypothesis in animal models

These findings prompted the Hazen lab to undertake a series of animal model studies to test the notion that TMAO directly modulates platelet function. The studies used dietary choline or TMAO, germ-free mice and microbial transplantation to collectively demonstrate the following:

- TMAO directly promotes human platelet responsiveness by enhancing stimulus-dependent release of Ca^{2+} from intracellular Ca^{2+} stores and activation in the setting of submaximal agonist stimulation.
- This effect is not stimulus-specific but applies to several distinct agonists, including ADP, thrombin, collagen and arachidonic acid.

- The effect of TMAO on platelet reactivity and in vivo thrombosis is both rapid and reversible.
- Dietary choline enhances platelet responsiveness and in vivo thrombosis potential.
- Gut microbes play an essential role in choline diet-dependent enhancement of thrombosis potential.
- Specific gut microbial taxa are associated with TMAO levels and thrombosis potential.
- Thrombosis potential is a transmissible trait, as shown in gut microbial transplantation studies conducted with microbes producing low versus high levels of the TMAO precursor TMA.

"These studies show that gut microbes modulate thrombosis potential in vivo," says Dr. Hazen. "Importantly, they show that TMAO's effect on platelet function is dose-dependent across the physiological range of TMAO concentrations in humans and animal models alike."

Remaining questions — and potential clinical payoffs

At the same time, he notes, the existence and identity of molecular receptors that sense TMAO within platelets remain uncertain and a focus of intense research interest.

Despite these uncertainties, the new study holds great clinical relevance. "While antiplatelet medications are a cornerstone of treatment and prevention of acute complications of cardiovascular disease, they are hampered by the potential for bleeding," Dr. Hazen observes. "Our paper suggests that therapeutic targeting of the gut microbial TMAO pathway has the potential to temper the platelet hyperresponsiveness associated with elevated TMAO, and to do so without promoting bleeding."

The new findings also underscore the potential utility of TMAO levels as a clinical tool for better identifying subjects who may benefit from antiplatelet therapy to prevent thrombotic events. That utility is especially relevant in light of the recent commercial availability of a plasma TMAO assay through Cleveland HeartLab (and potentially other labs soon) and the availability of TMAO testing throughout the Cleveland Clinic health system. "This is an area of considerable interest," Dr. Hazen notes. ■

To contact Dr. Hazen about this article, email campbeg@ccf.org.

In Memoriam: **Patrick Whitlow, MD**

Cleveland Clinic mourns the passing of Patrick L. Whitlow, MD, who died in March 2016. In addition to founding Cleveland Clinic's interventional cardiology program three decades ago, he was an internationally recognized physician who trained an entire generation of interventional cardiologists and treated thousands of patients.

Dr. Whitlow practiced at Cleveland Clinic from 1986 until early this year, and his expertise spanned multiple subspecialty areas within interventional cardiology, from directional atherectomy to rotational atherectomy. He pioneered the first chronic total occlusion devices and was known to take on the most difficult cases with confidence.

Despite battling lifelong diabetes, Dr. Whitlow "remained passionate about his patients, passionate about education and tremendously loyal to Cleveland Clinic," says Steven Nissen, MD, Chair of Cardiovascular Medicine.

A longtime innovator (see page 10), Dr. Whitlow continued to invent and collaborate on new devices until he was too ill to work, and he has innovations in the pipeline today.

How Market Research Helped MedStar Maximize Benefits of Heart Program Alliance

Cobranding with Cleveland Clinic adds value for cardiovascular leader.

MedStar Heart & Vascular Institute is the largest heart program in the Washington, D.C., metropolitan area. It cares for one out of every four heart patients in Washington and suburban Maryland. It's the only heart program in the region nationally recognized by *U.S. News & World Report.* And it boasts one of the largest cardiac catheterization programs in the nation.

To say MedStar is a leader in cardiovascular care is an understatement. Yet, in 2013, MedStar further elevated its heart program and positioned itself for future growth by aligning with Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute.

It was one of the first health systems to join Cleveland Clinic's Cardiovascular Specialty Network. This network shares best practices to help affiliated and allied provider organizations across the U.S. enhance their cardiovascular programs strategically, clinically and operationally.

Since then, Cleveland Clinic has helped MedStar implement a robust data and informatics program, shared marketing insights and provided other support.

As part of the alliance agreement, MedStar Heart & Vascular Institute began cobranding with Cleveland Clinic — referencing both organizations and showing both logos in communications online, in print, on TV and elsewhere.

But just how valuable was the name "Cleveland Clinic" on MedStar marketing materials? That's what MedStar intended to learn from a consumer awareness study.

What consumers think about MedStar

Studying Cleveland Clinic's impact on MedStar marketing was anything but simple, says Donna L. Arbogast, Vice President of Public Affairs & Marketing at MedStar Washington Hospital Center.

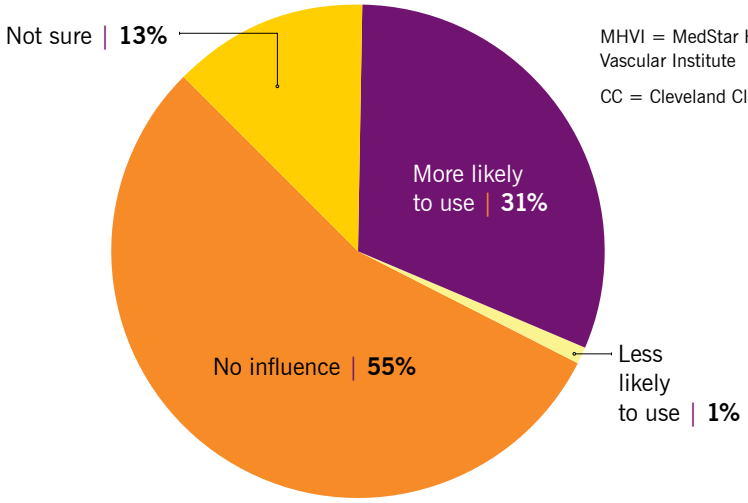
"A year before we launched the alliance with Cleveland Clinic, all 10 hospitals in the MedStar system had discrete names," says Arbogast. "Consumers tended to associate our top heart program with 'Washington Hospital Center.' But then we shifted to a unified branding strategy, and all hospital names began with 'MedStar.' For our heart program, we then created the name 'MedStar Heart & Vascular Institute' and used 'Cleveland Clinic' in conjunction with that. It was very important to us to determine how those changes affected our perception as a cardiovascular leader."

Approximately 1,000 consumers across central and southern Maryland, Greater Washington and northern Virginia were surveyed online.

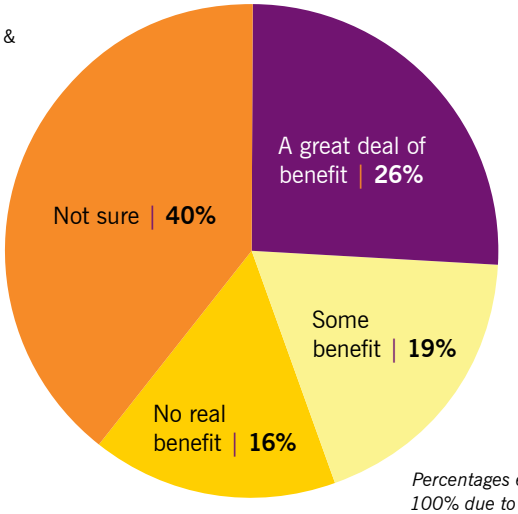
"We learned that while people weren't as familiar with 'MedStar Heart & Vascular Institute,' they *were* connecting it with Washington Hospital Center and our region's top heart care," says Arbogast. "Using 'MedStar' was favorable."

> Research showed that consumers needed more — yet simple — explanation of the MedStar-Cleveland Clinic alliance.

Does this relationship between MHVI and CC make you more or less likely to use MHVI for heart care?



Based on what you know, do you see added benefit to patients receiving heart care at MHVI?



Percentages exceed 100% due to rounding

How Cleveland Clinic enhances consumer perception

Survey participants also favorably recognized the name "Cleveland Clinic." When asked for their feedback on a simple advertisement with both the MedStar and Cleveland Clinic logos — and no explanation of the alliance — consumers' verbatim comments included the following:

- "Great combination"
- "Local system and a national leader with a great reputation"
- "Great choice"

"Later, we tested an ad that included a descriptor of Cleveland Clinic, 'the nation's #1 heart program,'" says Arbogast. "That simple addition was so effective with consumers that we decided to start using it as much as possible."

When consumers were asked about the value of MedStar's alliance with Cleveland Clinic:

- 31 percent of respondents claimed they were more likely to seek cardiovascular care at MedStar Heart & Vascular Institute because of the alliance (see graph on left above).
- 45 percent said that Cleveland Clinic provided some or a great deal of benefit to patients receiving care at MedStar (see graph on right above).
- Only 14 percent thought MedStar didn't need to align with Cleveland Clinic because its position in heart care was strong enough.

Next steps: Maintaining dominance

Research findings assured MedStar of its high regional brand equity in heart care and the added value of Cleveland Clinic. It learned that consumers needed more — yet simple — explanation of the MedStar-Cleveland Clinic alliance. Awareness could be increased, although the benefit of a Cleveland Clinic connection was already apparent.

Awareness efforts are continuing in the Greater Washington area, including building relationships with referring physicians, who have significant influence over heart care decisions. MedStar's *Cardiovascular Physician* publication, which consistently promotes the alliance with Cleveland Clinic, is mailed quarterly to 16,000 physicians in the mid-Atlantic region.

"In a very, very competitive cardiovascular market, we have remained dominant," says Arbogast of MedStar's market share.

The next focus will be in central Maryland, including Baltimore, where MedStar Union Memorial Hospital's heart program competes for awareness with nationally known healthcare brands.

"We will continue to leverage our relationship with Cleveland Clinic to help differentiate MedStar across Maryland and Greater Washington," says Arbogast. ■

For information on forming an alliance or affiliation with Cleveland Clinic's Miller Family Heart & Vascular Institute, see affiliatenetwork.clevelandclinic.org.

Research Roundup

Quick Takes on Studies Presented at Recent Cardiovascular Meetings

GAUSS-3: At Last, Robust Evidence of Muscle-Related Statin Intolerance

For the first time, a major randomized trial has shown that muscle-related statin intolerance is reproducible using a blinded, placebo-controlled statin rechallenge in patients with a history of muscle symptoms associated with statin use. The multicenter GAUSS-3 trial also found that two statin alternatives — ezetimibe and the PCSK9 inhibitor evolocumab — are about equally unlikely to cause muscle symptoms in statin-intolerant patients, although evolocumab yielded significantly greater reductions in LDL cholesterol.

"GAUSS-3 has important implications for guidelines and regulatory policy, as it provides strong evidence that muscle-related statin intolerance is a real and reproducible phenomenon," says Cleveland Clinic Cardiovascular Medicine Chair Steven Nissen, MD, who presented the findings at the American College of Cardiology's 2016 annual meeting. For more on GAUSS-3, see **consultqd.clevelandclinic.org/gauss3**.

STAMPEDE: Glycemic Benefits of Bariatric Surgery Persist to 5 Years

The beneficial effects of bariatric surgery on glycemic control in obese patients with type 2 diabetes are durable out to at least five years, and surgery's advantage over intensive medical therapy appears to widen over time. Those are key takeaways of the final, five-year report from the pivotal STAMPEDE trial presented by Cleveland Clinic bariatric surgeon Philip Schauer, MD, at the American College of Cardiology's 2016 annual meeting.

Final results from the randomized trial of 150 Cleveland Clinic patients confirm those from prior interim STAMPEDE reports. "Our findings show continued durability of glycemic control after metabolic surgery as well as persistent weight loss and reductions in diabetes and cardiovascular medications at five years," Dr. Schauer notes. For more on STAMPEDE, see **consultqd.clevelandclinic.org/stampede5.**

Pacemaker Matchup Finds Leadless Safer than Transvenous

A new analysis shows that a leadless cardiac pacemaker may hold safety advantages over traditional transvenous pacemakers. The analysis, presented at the Heart Rhythm Society's 2016 annual meeting, compared acute and mid-term adverse event rates from the multicenter LEADLESS II clinical trial of St. Jude Medical's Nanostim™ leadless pacemaker with those for transvenous pacemakers from a large U.S. insurance claims database. Patients receiving the leadless device developed significantly fewer infectious and lead-related complications than did those receiving transvenous pacemakers in real-world settings.

Complication rates in the real-world claims data were considerably higher than previously reported for transvenous devices. "This analysis debunks the argument that leadless pacing is unnecessary because complications with transvenous systems are very low across the board," says Cleveland Clinic electrophysiologist and LEADLESS II investigator Daniel J. Cantillon, MD, who co-authored the analysis. "Leadless pacing can potentially eliminate the most common sources of complications, which are the surgical pocket and the lead." For more, see **consultqd.clevelandclinic.org/leadless**.

Robust Success with Robotics in 1,000-Case Mitral Valve Series

Robotic surgery, the least invasive approach to mitral valve (MV) repair, yields a procedural success rate of 99.7 percent and operative mortality of just 0.1 percent (1/1,000) when performed at an expert center. So reveals an analysis of the first 1,000 robotically assisted MV surgery cases performed at Cleveland Clinic, presented at the American Association for Thoracic Surgery's 2016 annual meeting by Cleveland Clinic cardiothoracic surgeon A. Marc Gillinov, MD.

"Despite reports documenting the safety and efficacy of robotically assisted MV surgery, it has not become the standard of care for managing MV disease," says Dr. Gillinov. "These results may help change that, especially since we found that procedural safety and effectiveness improved with experience and with application of algorithm-driven patient selection." For more, see **consultqd.clevelandclinic.org/1000robots**.

RESOURCES FOR PHYSICIANS

Stay Connected with Cleveland Clinic's Heart & Vascular Institute

Consult QD — Heart & Vascular

A blog featuring insights and perspectives from Cleveland Clinic experts. Visit today and join the conversation.

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On the web
clevelandclinic.org/heart

24/7 Referrals

Referring Physician Center and Hotline
855.REFER.123
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Physician Referral App

Download today at the App Store or Google Play.

Available on the App Store

Google play

Physician Directory
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Same-Day Appointments
216.444.CARE (2273) or 800.223.CARE (2273)

Track Your Patients' Care Online
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Critical Care Transport Worldwide
216.448.7000 or 866.547.1467
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Outcomes Books
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About Cleveland Clinic
Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,400 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 18 full-service family health centers and three health and wellness 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 2015, Cleveland Clinic was ranked one of America's top five 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 21st consecutive year.

Cleveland Clinic

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

Cardiac Consult

CME Calendar

17th Annual Intensive Review of Cardiology

Sat.-Wed., Aug. 20-24, 2016

InterContinental Hotel & Conference Center | Cleveland

Information/registration: ccfcme.org/CardioReview

Prevention 360: Strategies for Managing Cardiovascular Risk

A complimentary satellite lunch symposium at the European Society of Cardiology meeting

Sun., Aug. 28, 2016, 12:45-1:45 p.m.

Nicosia – Village 1 | Rome, Italy

Information/registration: ccfcme.org/ESC2016_Prevention

CVD Risk Reduction and Lipid Management: State of the Science

A complimentary satellite lunch symposium at the European Society of Cardiology meeting

Mon., Aug. 29, 2016, 12:45-1:45 p.m.

Nicosia – Village 1 | Rome, Italy

Information/registration: ccfcme.org/ESC2016_Lipids

1st Annual Advances in Pediatric and Congenital Heart Care: From Single Ventricle to Failing Fontan

Fri.-Sat., Sept. 16-17, 2016

Cleveland Clinic main campus | Cleveland

Information/registration: ccfcme.org/pediatric-congenital

Fundamental to Advanced Echocardiography

Fri.-Sun., Sept. 16-18, 2016

Global Center for Health Innovation | Cleveland

Information/registration: ccfcme.org/echocardio

Current Management of Prevalent Cardiovascular Diseases

Fri., Oct. 7, 2016, 7:30 a.m.-5 p.m.

Time Warner Center | New York

Offered in partnership with Northwell Health.

Information/registration: northwell.edu/cme

These activities have been approved for *AMA PRA Category 1 credit™*.