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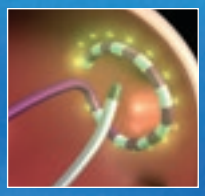
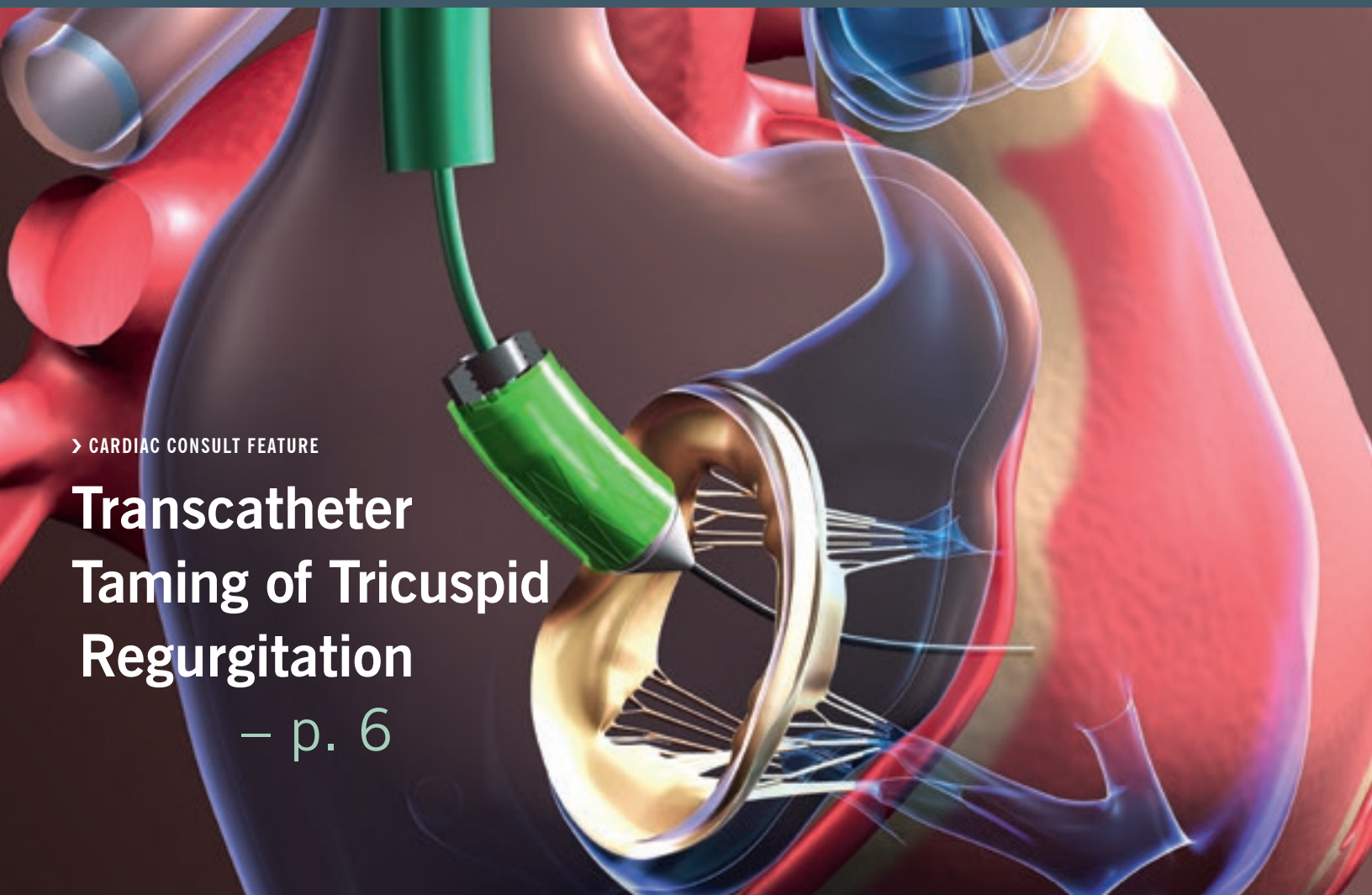


Cleveland Clinic

Cardiac Consult

Heart and Vascular News from Cleveland Clinic | Summer 2018



› CARDIAC CONSULT FEATURE

Transcatheter Taming of Tricuspid Regurgitation

– p. 6

Dear Colleagues,

Cleveland Clinic is honored to share that our Miller Family Heart & Vascular Institute has been recognized as the No. 1 cardiology and heart surgery program in the latest (2018-19) *U.S. News & World Report* "Best Hospitals" rankings. This marks the 24th straight year we've received the top ranking in this specialty area.

Unsurpassed outcomes in complex cases play an essential role in that achievement. An example of such outcomes can be found in the latest Adult Cardiac Surgery Database analysis from the Society of Thoracic Surgeons, for the period January 2015-December 2017. In that report, Cleveland Clinic achieved the maximum three-star rating in all five categories — including the two newly reported categories of mitral valve repair and replacement surgery with or without coronary artery bypass surgery — as detailed in the graphic on the right. Only two out of 1,012 database participants achieved these results.

A sampling of additional outcome and volume statistics from our Heart & Vascular Institute is the focus of the special insert to this issue of *Cardiac Consult*. The rest of the issue is devoted to aspects of our mission that may be less tangibly linked to rankings but are just as critical to our tradition of leadership. These range from the innovation showcased in the cover story on transcatheter tricuspid valve replacement to new research grants reported on pages 12 and 13 that promise to yield key insights into atrial fibrillation prevention and heart transplant survival. We remain committed to sharing with the cardiovascular care community these and other insights our program has gained over the past 24 years and beyond. I always welcome your inquiries and outreach.

Respectfully,

Lars G. Svensson, MD, PhD

CHAIRMAN | Sydell and Arnold Miller Family Heart & Vascular Institute

Cleveland Clinic's Composite Quality Ratings in STS Adult Cardiac Surgery Database, 01/2015 – 12/2017

★ ★ ★ CABG

★ ★ ★ AVR

★ ★ ★ AVR + CABG

★ ★ ★ MVRR

★ ★ ★ MVRR + CABG

Only 2 out of 1,012 database participants achieved three-star (highest) ratings in all five categories.

STS = Society of Thoracic Surgeons; CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVRR = mitral valve repair/replacement

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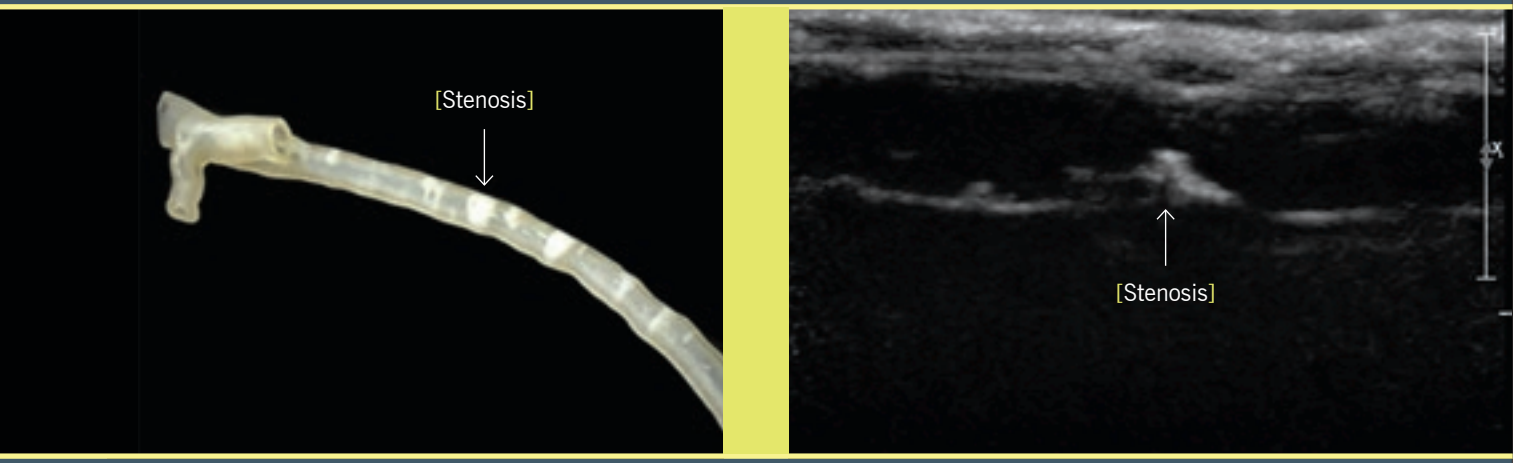


Stenosis in a 3D-printed superficial femoral artery model (left) is matched with its corresponding appearance on ultrasound (right).

ULTRASONICALLY REALISTIC 3D-PRINTED MODEL OF THE SUPERFICIAL FEMORAL ARTERY

A 3D-printed model of an atherosclerotic superficial femoral artery (SFA) can be used to provide realistic-appearing ultrasound characteristics at very low cost. So concludes a study by Paul Bishop, MSEE, RVT, and his colleagues in Cleveland Clinic's Department of Vascular Surgery and Department of Biomedical Engineering.

Using commercially available 3D printing materials and equipment, the researchers created a 3D model of an atherosclerotic SFA based on geometry derived from a CT scan reconstructed and segmented using semi-automated methods and commercial software. Multiple 3D print materials were selected to simulate normal artery wall tissue and atherosclerotic plaque. When the researchers assessed the 3D-printed model on ultrasound, they demonstrated that lumen geometry of the SFA model was similar to the geometry of the actual artery. Ultrasound was able to discern between the 3D-printed materials and visualize regions with stenosis, as shown in the images above.

Imaging replication was not perfect, however: Ultrasound measures of echogenicity and wave velocity were noted to differ between the model and biological tissue.

"Although the 3D-printed model didn't demonstrate fully accurate ultrasound characteristics, it provided realistic imaging on our first attempt to create an ultrasound phantom using only commercially available equipment and materials," says Bishop, Director of Cleveland Clinic's Vascular Core Laboratory. "Visualization of the SFA model wall was enabled much as would be the case with an in vivo SFA despite differences in ultrasound properties from actual tissue."

While noting that further research is needed to refine 3D printing materials to better replicate biological tissue, Bishop and his colleagues say their model may be useful in cost-sensitive applications in which exact ultrasound accuracy is not necessary. Indeed, they estimate their total 3D printing material cost for the model to be under $20.

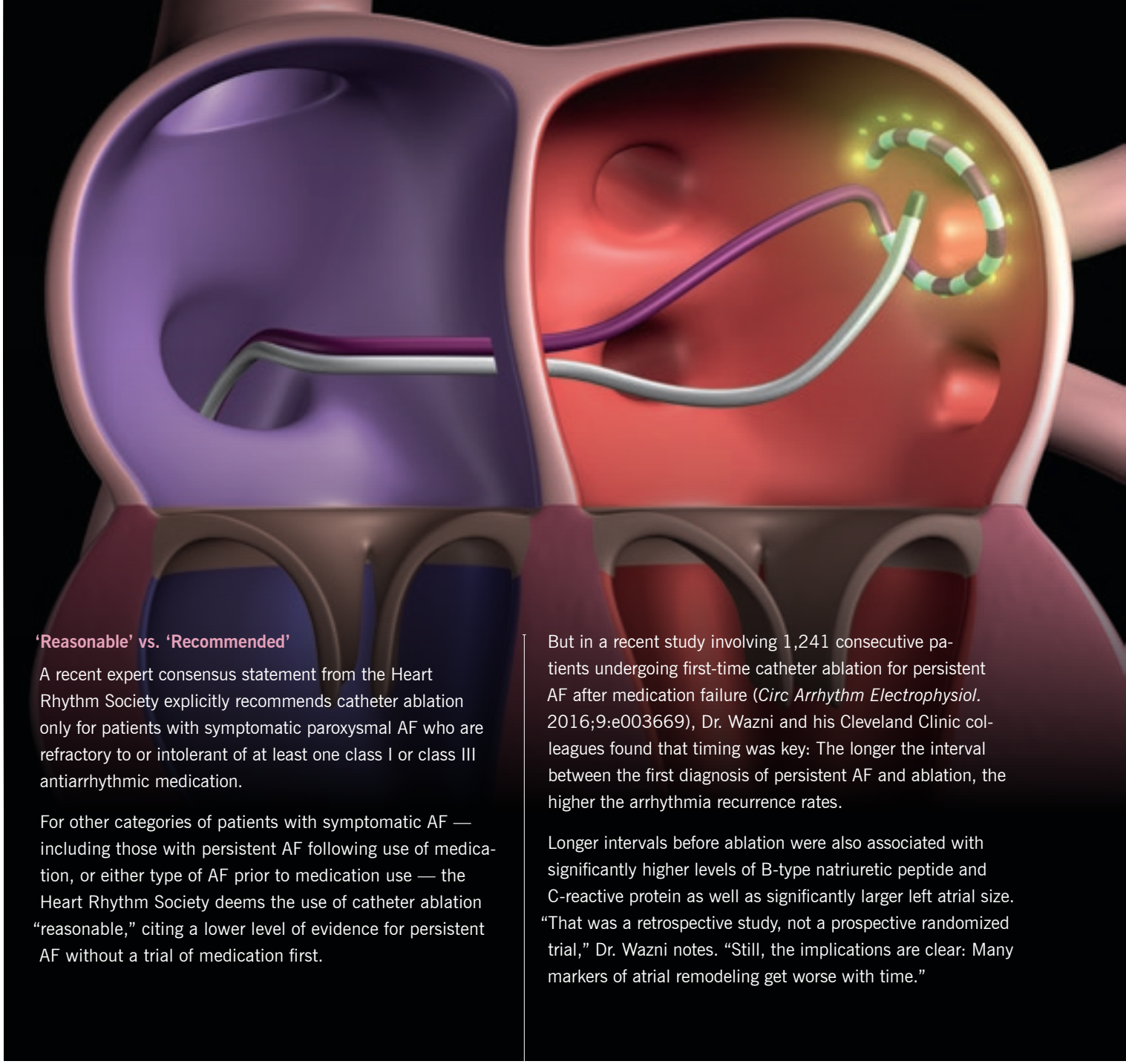
Their study was awarded the D.E. Strandness, MD, Scientific Award for Excellence in Scientific Research from the Society for Vascular Ultrasound in 2017 and has been submitted for publication. ■

Contact Bishop at bishopp@ccf.org.

Ablation First for Atrial Fibrillation?

Studies underway look to confirm suspected benefits of early ablation.

Cleveland Clinic cardiologist Oussama Wazni, MD, and his team are on a mission: They want more patients with atrial fibrillation (AF) to benefit from early catheter ablation. "Increasing research suggests that the longer we wait to treat, the worse the outcomes," says Dr. Wazni, Section Head of Cardiac Electrophysiology and Pacing. "The sooner we intervene with atrial fibrillation, whether paroxysmal or persistent, the better it appears to be for the patient."



'Reasonable' vs. 'Recommended'

A recent expert consensus statement from the Heart Rhythm Society explicitly recommends catheter ablation only for patients with symptomatic paroxysmal AF who are refractory to or intolerant of at least one class I or class III antiarrhythmic medication.

For other categories of patients with symptomatic AF — including those with persistent AF following use of medication, or either type of AF prior to medication use — the Heart Rhythm Society deems the use of catheter ablation "reasonable," citing a lower level of evidence for persistent AF without a trial of medication first.

But in a recent study involving 1,241 consecutive patients undergoing first-time catheter ablation for persistent AF after medication failure (*Circ Arrhythm Electrophysiol.* 2016;9:e003669), Dr. Wazni and his Cleveland Clinic colleagues found that timing was key: The longer the interval between the first diagnosis of persistent AF and ablation, the higher the arrhythmia recurrence rates.

Longer intervals before ablation were also associated with significantly higher levels of B-type natriuretic peptide and C-reactive protein as well as significantly larger left atrial size. "That was a retrospective study, not a prospective randomized trial," Dr. Wazni notes. "Still, the implications are clear: Many markers of atrial remodeling get worse with time."

Two New Studies to Fill the Data Gap

Now Dr. Wazni is serving as a principal investigator of two separate randomized trials to fill the evidence gap on the safety and efficacy of going straight to ablation without first trying medication in AF patients.

One study, STOP AF First: Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation (NCT03118518), is evaluating the safety and effectiveness of pulmonary vein isolation using Medtronic's Arctic Front Advance™ Cardiac Cryoablation Catheter compared with medical treatment in 210 patients with paroxysmal AF not previously treated with antiarrhythmic drugs. The multicenter trial began in June 2017 and is set to end in January 2020.

The second study, Catheter Ablation vs. Medical Therapy in Congested Hearts With AF (CATCH-AF) (NCT02686749), is a multicenter, randomized, nonblinded trial comparing catheter-based AF ablation with standard-of-care medical treatment in approximately 220 patients who have heart failure as well as either paroxysmal or persistent symptomatic AF diagnosed within the prior 12 months. CATCH-AF began in June 2016 and should be completed by December 2019.

Patients with coexisting AF and heart failure have an especially poor prognosis. However, the CASTLE-AF trial, published earlier this year in the *New England Journal of Medicine*, showed a mortality benefit with ablation in this population, which Dr. Wazni sees as lending support to further exploration in CATCH-AF.

"Overall, we're hoping to be able to change the position on this from 'reasonable' to 'recommended' by showing that patients do much better if you ablate sooner rather than later," he says. "But we're not there yet, which is why we're doing the studies."

So far there are no prospective trials evaluating ablation specifically for persistent AF, but some are in the planning stages, he notes.

For Now, Follow Guidelines and Favor Experience

While results of further trials are pending, Dr. Wazni advises clinicians to "follow the guidelines as much as is reasonable. But it seems increasingly clear that ablation confers a mortality benefit. Particularly in the subset of patients with concomitant heart failure, ablation appears to be better than medication."

Also important, he says, is to make sure patients are referred to experienced centers. "Find out the center's complication rate, as well as the center's or operator's success rate," he counsels. "Most cities have centers with good outcomes."

Indeed, Dr. Wazni adds, patients certainly need to be told that ablation carries some risks, including perforation, injury to the esophagus, stroke during the procedure or vascular complications from the access point. "But those risks are lower in more experienced hands," he notes. "Centers that track their outcomes should be able to give patients a realistic estimate of the risks and benefits." ■

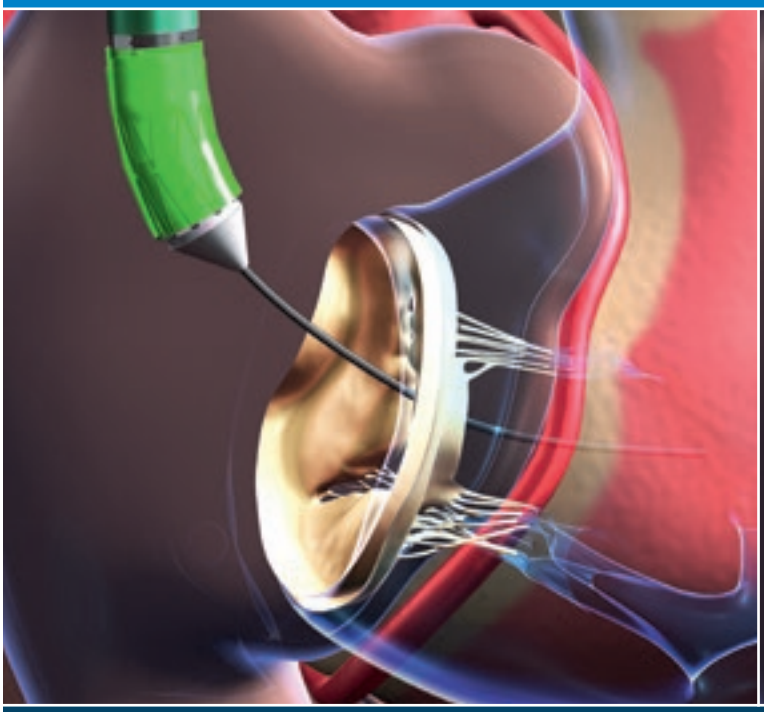
Contact Dr. Wazni at waznio@ccf.org.

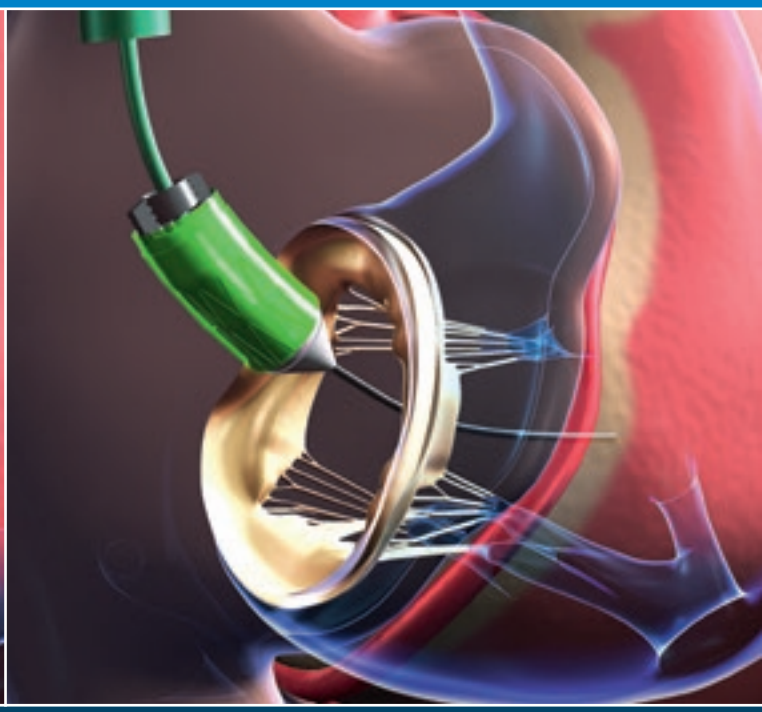
"We're hoping to be able to change the position on this from 'reasonable' to 'recommended' by showing that patients do much better if you ablate sooner rather than later. But we're not there yet, which is why we're doing the studies."

– Oussama Wazni, MD

Transcatheter Valved Stent Tames Tricuspid Regurgitation in High-Risk Patients

Insights from Cleveland Clinic Specialists Pioneering Its Implantation





Until November 2016, there were no reports of transcatheter valve implantation at the native tricuspid annulus level in humans. That's when Cleveland Clinic specialists performed the landmark first percutaneous implantation of a novel tricuspid valved stent directly to the tricuspid annulus in a 64-year-old woman with severe tricuspid regurgitation. They have since performed transcatheter placement of the self-expanding valved stent in a total of four patients through May 2018, published satisfactory results from long-term preclinical models (*JACC Basic Transl Sci*. 2018;3:67-79) and published successful results from the first two cases of human implantation of the stent (*Circ Cardiovasc Interv*. 2017;10:e005840).

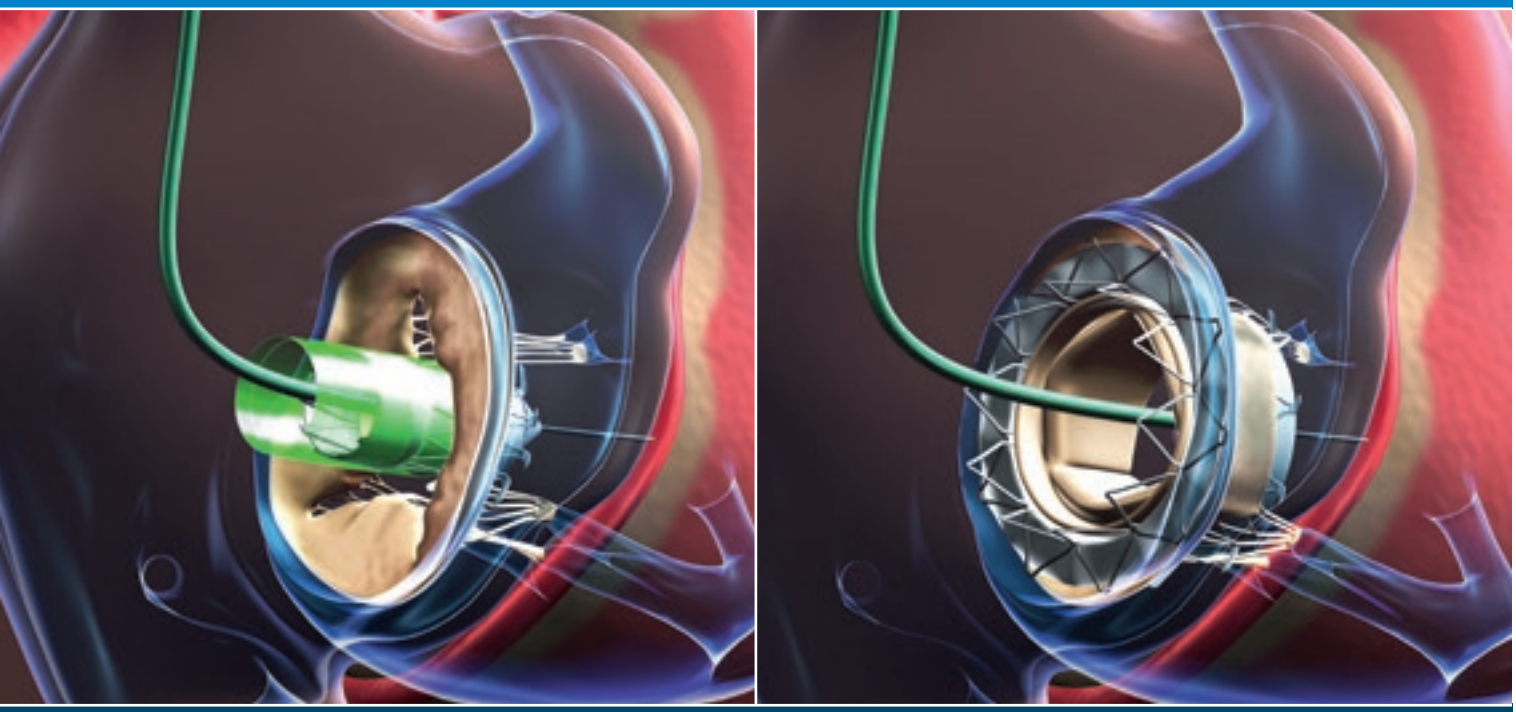
"We are satisfied with the results of this procedure in all the cases we have done to date," says the principal author of the above papers, Jose Navia, MD, Vice Chair for Innovation in Cleveland Clinic's Department of Thoracic and Cardiovascular Surgery. "There is every indication that this technique can be successfully used to replace faulty tricuspid valves in patients at high surgical risk."

One of the patients to receive the stent from the Cleveland Clinic team reports: "I could not walk from one end of my house to the other before the valve was implanted. Now it feels great to go everywhere."

A Historically Neglected Need

The novel prosthesis — known as the GATE™ tricuspid valved stent, from NaviGate Cardiac Structures — addresses the need for a less-invasive treatment for tricuspid regurgitation (TR), a condition suffered by an estimated 7 million people in the U.S. and Europe. Without treatment, TR inevitably leads to right-sided heart failure and death.

Historically, TR has been ignored, and not without reason. TR is usually secondary to mitral valve dysfunction. It often presents with pulmonary hypertension, atrial fibrillation and other



serious comorbidities. Mortality for surgical repair or replacement of the tricuspid valve can be as high as 35 percent.

At one time, it was believed that TR secondary to mitral valve dysfunction would correct itself after mitral valve replacement or repair. This has been proven false.

TR is a self-exacerbating condition, with mild or residual TR eventually progressing to the torrential and fatal stage.

"Functional tricuspid regurgitation enlarges the annulus, causing a reverse flow of venous blood from the right heart — blood that should be going to the lungs," says Samir Kapadia, MD, Section Head of Interventional Cardiology at Cleveland Clinic and a co-author of the papers cited above. "It's not possible to completely eliminate torrential tricuspid regurgitation with current treatments."

It is in this context that the GATE stent system was developed, with the incorporation of Cleveland Clinic intellectual property. (Dr. Navia is the inventor of patents related to the device, and both he and Dr. Kapadia are on NaviGate Cardiac Structures' scientific advisory board and own stock in the company.)

Essentials of the Valved Stent

The GATE device is a biological valved stent with a lining designed to support the pericardial membrane wall to protect its integrity and prevent paravalvular leakage. The stent comes in five sizes (36, 40, 44, 48 and 52 mm) to meet various anatomical contingencies. It is shaped somewhat like a truncated cone, to address the fact that in most patients with TR, the ventricular annulus is more dilated than the atrial side.

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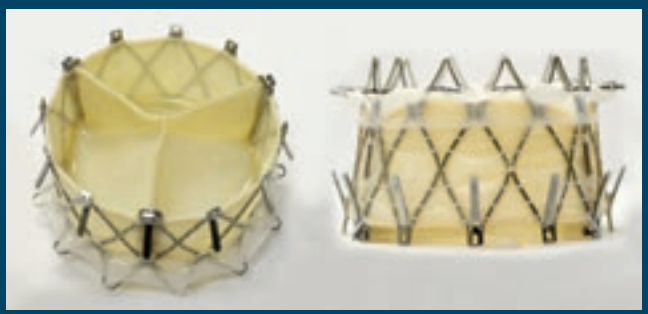


Photos of the GATE valved stent showing the outflow (left ventricle) view and side view. Reprinted from Navia et al., *JACC Basic Transl Sci.* 2018;3:67-79.

Drs. Navia (center) and Kapadia (left) during the first human implantation of the GATE tricuspid valved stent.

When assembled, the bioprosthesis undergoes a proprietary dehydration process in which all glutaraldehyde and most of its water are removed, after which the dehydrated valve is sterilized by ethylene oxide exposure. This process, which originated from Cleveland Clinic research, is intended to extend the longevity of the valvular mechanism during storage.

Two Delivery Methods — Performed on the Beating Heart

The bioprosthesis is crimped and packed into the end of an L-shaped delivery device. It is transluminally delivered to the tricuspid annulus under the guidance of fluoroscopy and intracardiac echocardiography in a hybrid operating room. Delivery can be via transatrial access (through a mini-thoracotomy) or transjugular access.

Positioned coaxially in the annulus, the valve self-expands and is held in place by barbed graspers at one end and radial pressure at the other. The valve has been designed to minimize interference with adjacent chambers, but precise placement along the plane of the annulus is critical.

Expansion and placement of the bioprosthesis takes only seconds and is performed on the beating heart without rapid ventricular pacing.

Patient Profiles

All four cases performed by the Cleveland Clinic team have been done under a compassionate-use protocol.

The first patient — the 64-year-old woman mentioned at the start of this story — had a severely dilated tricuspid valve, multiple hospitalizations for refractory right heart failure, severe pulmonary hypertension and many additional comorbidities, along with prior chest radiation for breast cancer. She underwent implantation of the valved stent via transatrial access. At five-month follow-up, she demonstrated functional improvement and her severe TR had been reduced to mild to moderate.

"There is every indication that this technique can be successfully used to replace faulty tricuspid valves in patients at high surgical risk."

– Jose Navia, MD

The second patient was a 78-year-old man with a history of three coronary artery bypass surgeries, a mitral valve repair and two tricuspid valve repairs. He also had diabetes mellitus, atrial fibrillation, obstructive lung disease and chronic kidney disease. His prosthesis was delivered via the transjugular vein and anchored in the tricuspid annuloplasty ring from one of his prior surgeries. He was faring well at one-year follow-up, with excellent valve function.

A third patient demonstrated that the bioprosthesis can be used in patients with pacemaker leads traversing the tricuspid valve. This 79-year-old woman received her implant through a transatrial approach and was discharged with a well-functioning valve. She was able to return for clinical assessment from her distant home state approximately a month after intervention.

Transatrial delivery was again used in the fourth patient, a 77-year-old woman who has had her torrential TR reduced to a mild backflow and showed excellent valvular function at one-month follow-up.

Drs. Navia and Kapadia say the Cleveland Clinic heart team applies the following criteria to identify candidates for the GATE stent:

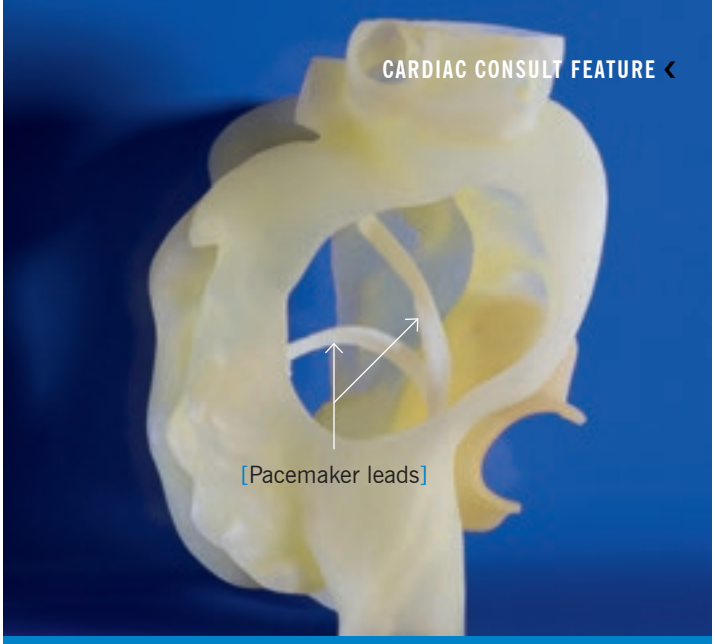
- Severe symptomatic TR
- Prohibitive surgical risk (particularly multiple comorbidities, complex reoperations or severe right ventricular dysfunction)
- Pulmonary artery pressure ≤ 90 mm Hg
- Appropriate tricuspid annulus or ring size as assessed on 4D CT

On the Horizon: Refinements and a Feasibility Trial

"The procedure still poses some technical challenges in achieving a complete seal, especially in patients with severe annular dilation," notes Dr. Navia. "Work is underway to further optimize the delivery system at the point of distal angulation."

Despite those challenges, he and his counterparts at the handful of other U.S. and European centers that have implanted the GATE bioprosthesis under compassionate-use protocols remain bullish on the technology. The company developing the device is now gathering data to enable the launch of an early feasibility clinical trial. ■

Contact Dr. Navia at naviaj@ccf.org, Dr. Kapadia at kapadis@ccf.org and Dr. Harb (see sidebar at right) at harbs@ccf.org.



3D-Printed Models Prove Invaluable for Planning

Cleveland Clinic's pioneering implantations of the GATE tricuspid valved stent were planned using patient-specific 3D-printed models.

The models are created based on information from CT and MRI studies. They allow the specialists who will be performing the procedures to study each patient's unique anatomy from all angles. Most critically, the models provide an opportunity to insert and deploy the stent in a perfect model of the patient's tricuspid valve annulus.

Contrast-enhanced 4D CT is the preferred modality for building models for 3D printing, but sometimes it must be supplemented with other imaging methods, such as 3D transthoracic echo, due to imaging challenges posed by patients' comorbidities. In patients with renal failure that prohibits contrast administration, models can be created from a combination of cardiac MRI and noncontrast CT imaging.

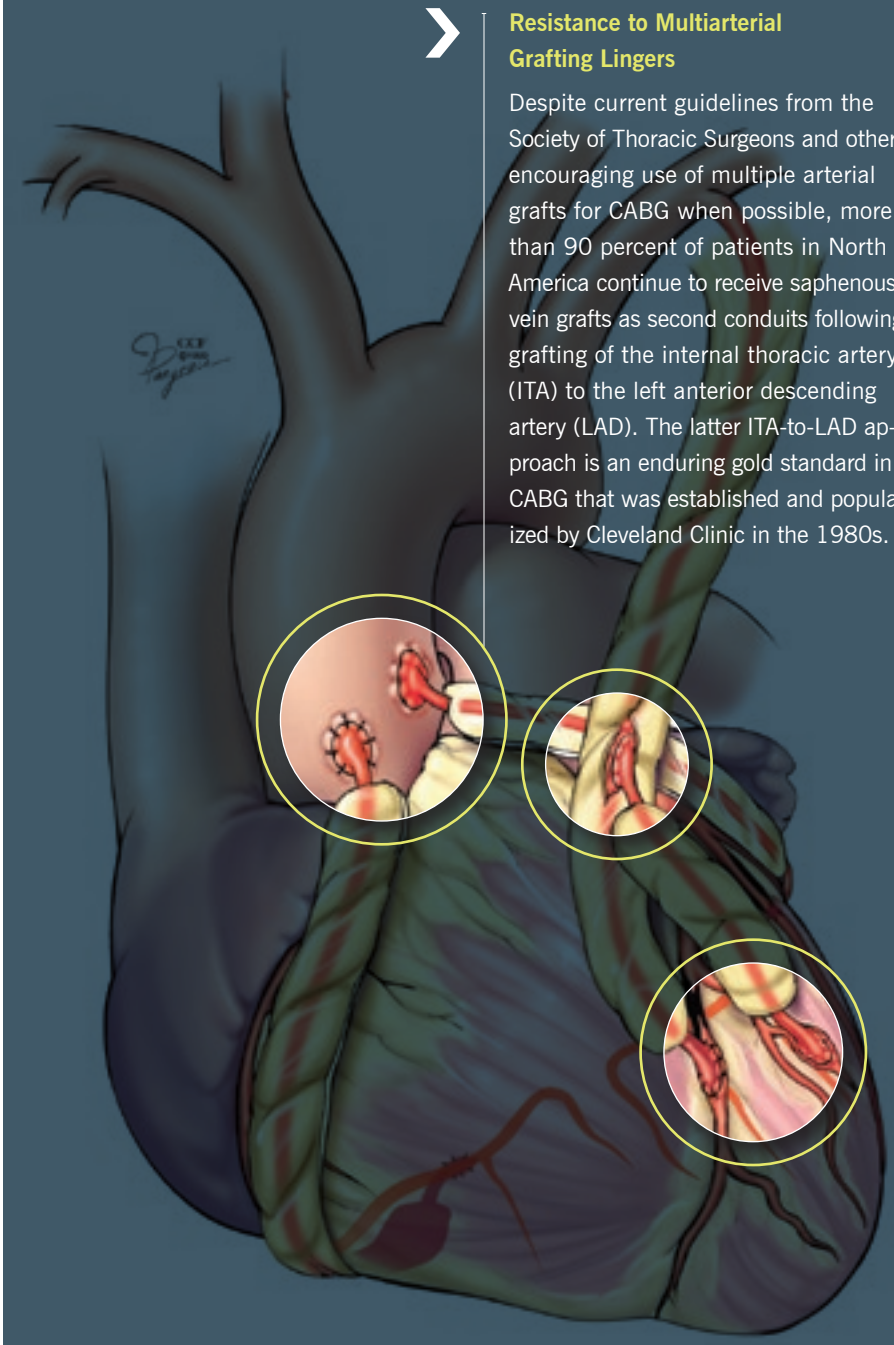
The 3D-printed models include annulus rings or other artifacts from prior surgeries — even pacemaker leads that run through the tricuspid valve, as in the model shown above.

For more on this, see the "Imaging Vignette" published by Cleveland Clinic cardiovascular imaging specialist Serge Harb, MD — along with Drs. Navia, Kapadia and other Cleveland Clinic colleagues — in *JACC Cardiovascular Imaging* (2018 Jun 9 [Epub ahead of print]).

Vessels of Truth

The quest continues for definitive data on the merits of multiarterial CABG.

Growing evidence points to the superiority of using radial or internal thoracic artery grafts rather than saphenous vein grafts as second conduits in coronary artery bypass graft surgery (CABG), as multiarterial grafting can be associated with enhanced longevity in appropriately selected patients. Cardiothoracic surgeons at Cleveland Clinic, where CABG was pioneered, are now involved in two trials expected to greatly inform surgical practice on this question.



Resistance to Multiarterial Grafting Lingers

Despite current guidelines from the Society of Thoracic Surgeons and others encouraging use of multiple arterial grafts for CABG when possible, more than 90 percent of patients in North America continue to receive saphenous vein grafts as second conduits following grafting of the internal thoracic artery (ITA) to the left anterior descending artery (LAD). The latter ITA-to-LAD approach is an enduring gold standard in CABG that was established and popularized by Cleveland Clinic in the 1980s.

A lack of robust randomized trial data regarding clinical benefit has fueled surgeons' reluctance to embrace multiple arterial grafts, says Cleveland Clinic cardiothoracic surgeon Faisal Bakaeen, MD. He notes that additional factors behind the reluctance include greater technical difficulty, a potential increase in sternal wound complications when harvesting bilateral ITAs, longer operating time with no additional reimbursement, and increasing focus on short- versus long-term outcomes.

"There's no incentive for surgeons to use multiple arterial grafts," Dr. Bakaeen explains. "They want to do an expeditious and safe operation and get their patients out of the hospital because that's what determines how they are ranked and reimbursed. No one tracks the long-term outcomes, but an early sternal wound infection is a definite penalty."

What's more, he notes, studies of multiarterial grafting have lacked funding, since there is no commercial interest in the use of radial arteries or a second ITA graft.

Meta-Analysis Underscores Benefit of the Radial Artery

In an attempt to overcome the problem of underpowering in recent trials, the multicenter Radial Artery Database International Alliance (RADIAL) conducted a patient-level meta-analysis of six published randomized trials with at

"The bottom line is that in a population that conforms to the requirements of a randomized trial, using the radial artery is beneficial, and it's perhaps more beneficial in certain subgroups." – Faisal Bakaeen, MD

least two years of follow-up comparing radial artery grafts with saphenous vein grafts as second conduits in CABG. The analysis was published earlier this year in the *New England Journal of Medicine* (2018;378:2069-2077).

After a mean follow-up of 60 months, the incidence of adverse cardiac events was significantly lower (hazard ratio = 0.67; 95% CI, 0.49-0.90; *P* = .01) in the group that received radial artery grafts to supplement left ITA grafting (n = 534) compared with those given saphenous vein grafts (n = 502).

Use of radial artery grafts was also associated with significantly lower risks of occlusion, myocardial infarction and repeat revascularization, although there was no between-group difference in all-cause mortality.

In subgroup analyses, greater benefit for radial artery grafts with regard to major adverse cardiovascular events was found in several patient groups: women, patients younger than 75 years and patients without renal insufficiency.

How Generalizable Are the Findings?

"I think it's an important study," notes Dr. Bakaeen, who wasn't involved in the analysis. "It adds further evidence that the use of more arterial grafting, such as with the radial artery, can have long-term advantages in patients who are suitable candidates for those kinds of conduits."

He adds some caveats, however. First, the data from randomized trials aren't generalizable to all patients. "For example, if it's an emergency, or if the patient doesn't have a suitable target for the radial artery or has a disease that precludes taking the radial artery, they would've been excluded from the studies," Dr. Bakaeen observes.

Moreover, he says, all the centers participating in the trials had considerable expertise in radial artery harvesting and use.

"The bottom line," he concludes, "is that in a population that conforms to the requirements of a randomized trial, using the radial artery is beneficial, and it's perhaps more beneficial in certain subgroups."

Cleveland Clinic's Approach, and Trials in Progress

At Cleveland Clinic, where multiarterial CABG is the default procedure unless contraindicated, about 20 percent of all CABG patients, and the majority of lower-risk patients undergoing elective CABG, receive multiple arterial grafts.

Those proportions are far above national and international averages despite the fact that Cleveland Clinic receives many of the highest-risk patients from around the country and the world, some of whom have already had one or more prior operations and may not be suitable candidates for multiarterial bypass, Dr. Bakaeen notes.

Cleveland Clinic surgeons are now involved in two randomized clinical trials aimed at providing the data that will be needed if routine surgical practice is to change.

The largest randomized trial to date comparing the radial artery with the saphenous vein as a second conduit involves 757 veterans who underwent first-time elective CABG at 11 Veterans Affairs medical centers nationwide.

At one year, there were no significant differences in the primary end point of angiographic graft patency, nor in secondary end points. Those findings were published in *JAMA* in 2011, with Dr. Bakaeen — who practiced at a VA medical center at the time — as a co-author. Now he's working with his collaborators to prepare the 10-year results for publication.

The other study, Randomization of Single vs. Multiple Arterial Grafts (ROMA), just began in early 2018. It's a prospective, nonblinded trial enrolling at least 4,300 patients in 25 international centers, including Cleveland Clinic. The trial is comparing either the radial artery or a second ITA with the saphenous vein as a second conduit for all non-LAD target vessels.

The primary outcome is a composite of death from any cause, stroke, post-discharge myocardial infarction and/or repeat revascularization. The estimated completion date is March 2028.

"In modern-day practice, surgeons should have an open mind about using more arterial grafting," observes Dr. Bakaeen. "To get definitive answers, these ongoing studies will help us reach that point." ■

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New Grants Fund Exploration of Afib Prevention and Survival Before/After Heart Transplant

$3.7M from AHA to Probe Atrial Fibrillation Prevention

The American Heart Association (AHA) has awarded Cleveland Clinic $3.7 million to fund three related research projects aimed at improving patient outcomes through prevention of atrial fibrillation (AF) development and progression.

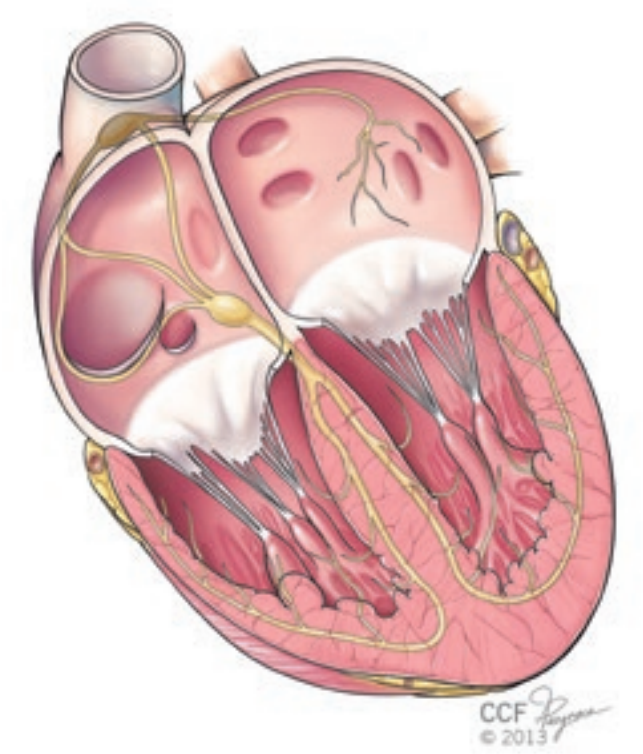
The four-year competitive award will support basic, clinical and translational research by a multidisciplinary team led by electrophysiologist Mina Chung, MD, Director of Cleveland Clinic's Center of Excellence for Cardiovascular Translational Functional Genomics.

Cleveland Clinic is one of six U.S. institutions selected for funding from the AHA's new $28 million Atrial Fibrillation Strategically Focused Research Network. The Cleveland Clinic site will be named the Sarah Ross Soter Center for Atrial Fibrillation Research.

"Once AF starts, it typically worsens over time, with episodes becoming longer and less likely to cease on their own," says Dr. Chung. "Despite intense effort, there are few effective and safe therapies. With this AHA support, we are focusing on developing novel therapies for preventing AF development and progression. Our new center will use molecular data to find, choose and personalize targets for preventive therapies."

The award will help continue the work of a Cleveland Clinic team that has collaborated for nearly 20 years, publishing more than 40 major papers together and making significant contributions to the understanding of AF mechanisms and cardiac genomics. The following three research projects will be funded:

- **Gene-Aging-Metabolism Interaction in AF Pathogenesis**, led by Jonathan Smith, PhD, Department of Cellular and Molecular Medicine. This project builds on the team's previous AF genomics research to identify new molecular pathways that can be targeted with medications. It will explore how aging and metabolism, along with certain identified genes, may work together to cause AF.



- **Targeting Risk Interventions and Metformin for AF**, led by Dr. Chung. This involves a new clinical trial to test the effectiveness of two therapeutic strategies to reduce AF progression. The team will enroll 270 participants with pacemakers and implantable cardioverter-defibrillators to study lifestyle modifications and use of a repurposed diabetes medication, metformin, in reducing AF burden. The research builds on studies suggesting that weight loss and exercise, as well as metformin, are associated with reduced AF risk.
- **Multi-omic Analyses of Atrial Metabolism, Electrophysiology and AF Progression**, a translational population health project led by David Van Wagoner, PhD, Department of Molecular Cardiology, with key collaborator John Barnard, PhD, Department of Quantitative Health Sciences. In an effort to develop personalized treatments, they will characterize AF subtypes and identify biological signatures of disease progression to better understand patient-specific therapy responses. ■

Contact Dr. Chung at chungm@ccf.org.

Two Cleveland Clinic cardiologists will be leading ambitious research initiatives into atrial fibrillation and heart failure survival thanks to major new multiyear grants, as detailed below.

$2.8M from NIH to Help Predict Pre-/Post-Heart Transplant Survival

The National Institutes of Health has awarded a team led by cardiologist Eileen Hsich, MD, $2.8 million to examine disparities in survival among heart failure patients before and after heart transplantation. The four-year grant also supports development of new data tools, including machine learning methods, to optimize outcomes in this population.

"Survival disparities exist among patients during their time on the waiting list and also after heart transplant," says Dr. Hsich, Associate Medical Director of Cleveland Clinic's Cardiac Transplant Program and co-principal investigator on the grant. "This award will help us identify factors contributing to these population differences, with the aim of improving survival and minimizing organ wastage."

The goal is to lay the groundwork for ultimate development of "a dynamic and improved way to allocate donor hearts in the future," she notes.

The grant supports three research projects focused on:

- Applying machine learning statistical methods to the national Scientific Registry of Transplant Recipients (SRTR) to identify major risk factors and quantify how their interactions affect differences in survival before and after transplant. Among the factors to be assessed are sex, race, type of heart disease, socioeconomic status, presence/absence of mechanical circulatory support and U.S. region.
- Using data from Cleveland Clinic and four other centers to develop the first method to dynamically update risk of death on the national heart transplant waiting list so that clinicians are alerted to patients' changing conditions. The researchers will use variables not now collected by the SRTR — such as tests of sodium, albumin and natriuretic peptides — as well as serial clinical assessments reflecting changes in condition. The four other participating centers are Northwestern University, University of Pennsylvania, University of Pittsburgh and Duke University Medical Center.
- Using data from the first two projects to develop statistical models that simultaneously estimate risk of waiting list mortality, time to transplantation and risk of post-transplant death. The models will base risk estimates on patient characteristics and health while patients are on the waiting list. The aim is to improve estimates of optimal timing for transplant as a patient's condition evolves, along the lines of risk prediction models used in lung, liver and kidney transplantation.

"The existing heart allocation system is based on tiers that prioritize patients by risk of death mainly based on need for mechanical circulatory support or certain medications, but it doesn't account for how their condition changes, their likelihood of getting transplanted or their risk of death after transplant," explains Dr. Hsich. "Our approach is innovative because it uses new mathematical approaches and seeks to shift heart failure research and practice paradigms by accounting for population differences rather than basing decisions solely on ejection fraction, presence of coronary artery disease, and disease stages." ■

Contact Dr. Hsich at hsiche@ccf.org.

When Atrial Ablation Leads to Atrio-Esophageal Fistula: How to Save the Day

Case study underscores the need for prompt recognition and repair.

› BY SIVA RAJA, MD, PHD; DEAN SCHRAUFNAGEL, MD; ERIC ROSELLI, MD; AND OUSSAMA WAZNI, MD

Case Background

A 54-year-old man underwent repeat ablation for paroxysmal atrial fibrillation at an outside hospital. He was otherwise in good health. About 10 days after the repeat procedure, he was admitted to the same hospital with vague complaints of chest pain. He was diagnosed with pericarditis and discharged home the next day.

Five days later, he was readmitted with chest pain, abdominal bloating, fever, chills, right hemiparesis, aphasia and new onset of seizures. Workup with CT and echocardiography showed pneumocephalus, pneumomediastinum and pneumopericardium.

The team, which included a gastroenterologist and a cardiac surgeon, diagnosed an atrio-esophageal fistula and attempted to repair it. They first performed an endoscopy, which revealed a mid-esophagus perforation 10 mm long by 4 mm wide with pulsation detected at the base of the tear. The surgeon covered the perforation with a 10 mm x 100 mm esophageal stent.

They next conducted a median sternotomy and started full cardiopulmonary bypass. The pericardium was opened, and purulent fluid was found and drained. A 1.5-cm hole in the floor of the left atrium with exposed esophageal tissue was located; it was excluded from the inside with a bovine pericardial patch. The patient was rewarmed and closed.

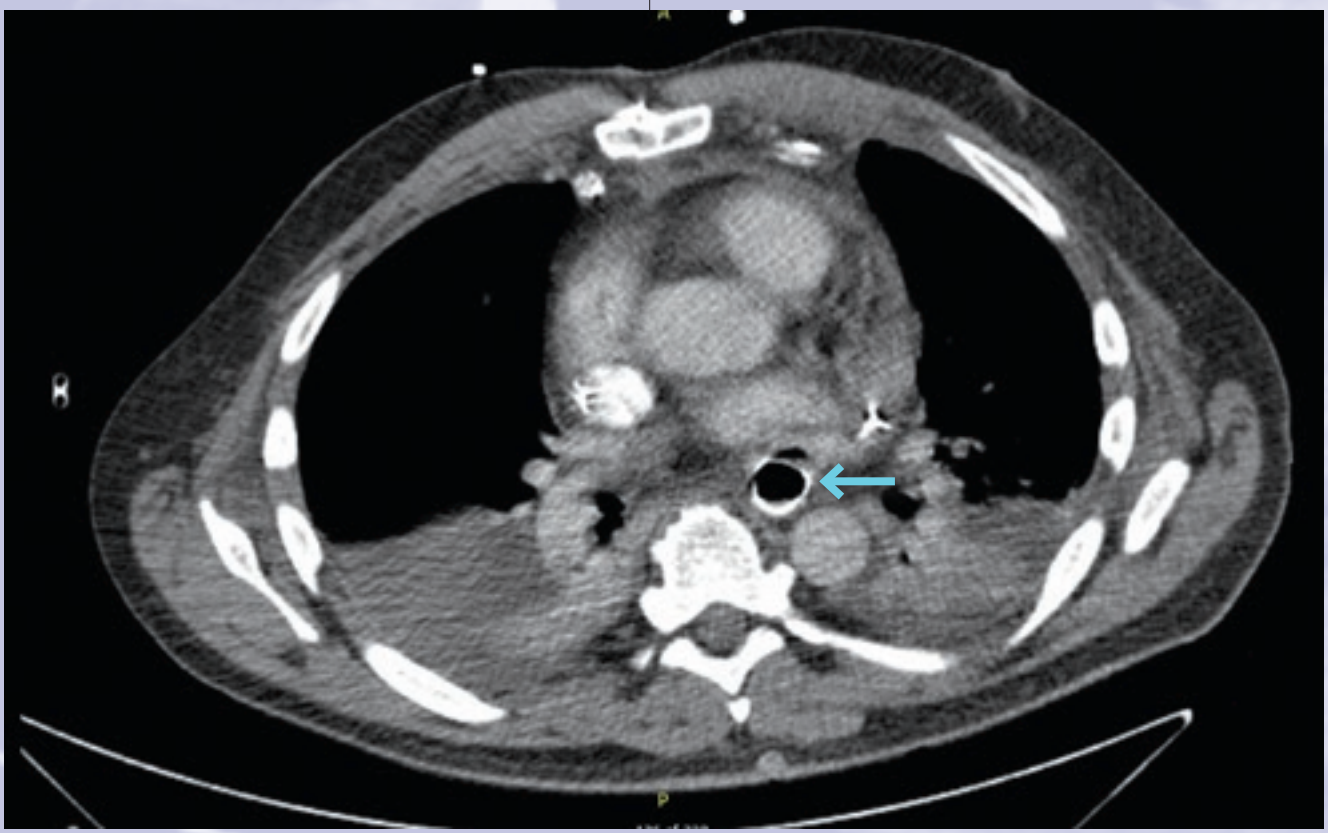


Figure 1. Contrast CT upon presentation at Cleveland Clinic showing the esophageal stent abutting the left atrium, with a rim of air visible outside the stent (arrow).

Two days later, the patient was extubated and appeared to be recovering. However, his neurological symptoms recurred when he restarted oral intake, at which point he was transferred to Cleveland Clinic for further management.

Second Repair Needed

On arrival to our institution, the patient was immediately evaluated with IV contrast CT (Figure 1), which showed the esophageal stent abutting the left atrium and a rim of air outside the stent.

A right thoracotomy was performed, based on the reasoning that it would provide better access to the esophageal fistula (although more challenging access to the left atrium). An intercostal muscle flap was taken in order to buttress the repair of the fistula and to create separation between the repair of the esophagus and the atrium. Empyema was incidentally found, requiring lung decortication.

The area of the fistula was identified, and the esophagus was controlled above and below. After separating the esophagus from the atrium, an endoscopy was performed to remove the stent to allow better visualization of the esophagus and the left atrial defect. Active bleeding from around the side of the atrial patch was seen, and the decision was made to put the patient on cardiopulmonary bypass.

The right common femoral artery and right atrium were cannulated, and cardiopulmonary bypass was started. Sufficient blood volume was maintained in the left atrium to avoid air embolization. The left atrial defect was more widely exposed, and large sutures were placed through the atrial wall surrounding it. The internal patch was left in place, and a new piece of bovine pericardium was parachuted down over the defect from the outside and tied into position.

Next, a two-layer repair was performed in the esophagus by closing the submucosa as well as the muscle, soft tissue and adventitia above it. Endoscopy was performed to confirm the seal. The intercostal muscle flap was sutured onto the esophagus between the esophageal and left atrial defects. The three panels of Figure 2 show various stages of the repair.

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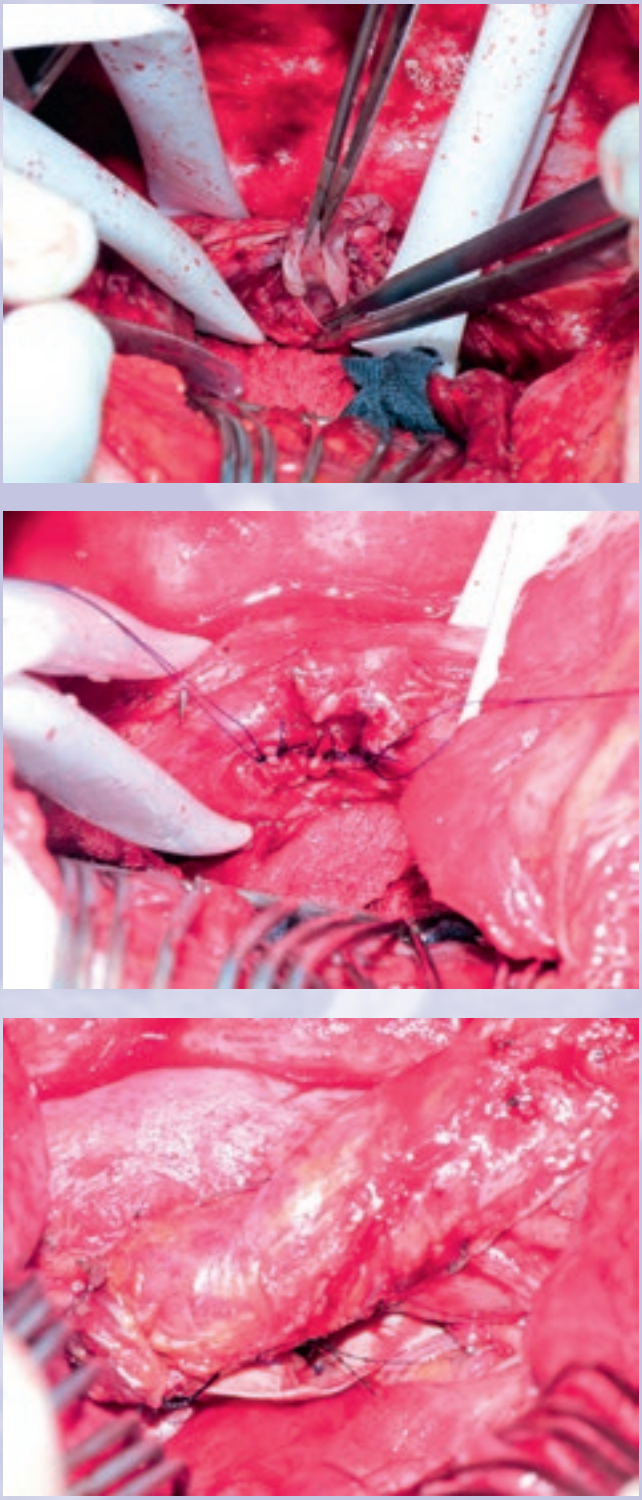

Figure 2. Top image shows the full-thickness esophageal defect. Middle image shows primary repair of the esophageal defect. Bottom image shows the intercostal muscle flap.

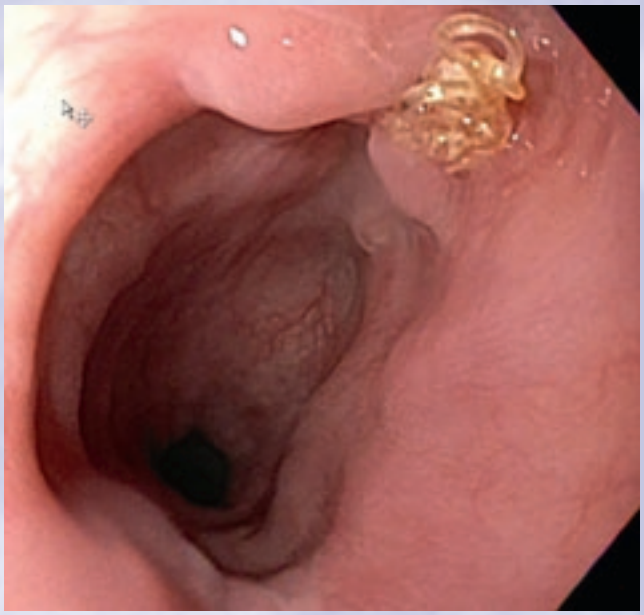

Figure 3. Endoscopy image taken three months postoperatively showing excellent healing with one suture visible.

Follow-up

Three months later, endoscopy showed excellent healing (Figure 3) and the patient was back to work and eating a regular diet. He felt completely recovered except for mild residual weakness in one hand.

Lessons from the Case

Prompt fistula recognition is critical. Fistula formation is a very rare but recognized complication of atrial ablation, occurring in about 1 in 2,000 cases. As was the case for this patient, sepsis and neurological symptoms usually manifest in about two weeks, although they can arise as late as six weeks after ablation. Rapid recognition and repair are critical: Without correction, mortality is 100 percent, usually within 24 hours of symptom onset.

Within a week or two after atrial ablation, patients commonly present with chest pain, especially associated with breathing and sometimes swallowing. Usually an echocardiogram is done, pericarditis is diagnosed and pain relief is provided. A fistula is not usually considered (and an echo would not help detect it) unless the pain persists or other signs develop.

Endoscopy with atrio-esophageal fistula is contraindicated. The fact that the patient did not present with hematemesis indicated that blood from the atrium was not entering the esophagus but rather that contents from the esophagus were entering the atrium. The direction of flow makes the danger of causing an air embolus during insufflation extremely high. If absolutely necessary, endoscopy can be performed using hyperbaric oxygen or CO_2.

Surgical drainage and repair are essential. Esophageal stenting will not result in a healed fistula.

Avoiding this complication is not easy. No technique to keep the esophagus out of harm's way during atrial ablation is surefire. If the esophagus is right next to the posterior wall of the atrium, it may be best to avoid ablating there. But the esophagus is mobile and stretchy, so even doing a CT scan or barium swallow ahead of the ablation may not reveal its location during the procedure.

Monitoring the temperature in the esophagus using a thermistor throughout the ablation may help. This is routinely performed at Cleveland Clinic. The tip of the transesophageal probe can be guided with the help of fluoroscopy to the area where the ablation is occurring. But again, not knowing the exact position of the esophagus significantly limits the effectiveness of this technique. Cooling the esophagus with cold water during ablation is also under investigation, but this complication is so rare that proving benefit for any of these methods may ultimately be impractical.

Ablation is usually safe. According to the literature, the risk of death from ablation for atrial fibrillation is about 1 in 1,000 and is mostly due to tamponade. Institutions with small volumes can have much higher rates, whereas Cleveland Clinic, with our large caseload, has 1 death in about 11,000 ablations. ■

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Research Roundup **Quick Takes on Recent Cardiovascular Studies of Note**

Sudden Death Risk in Obstructive HCM: Time to Refine Criteria?

Risk stratification for sudden cardiac death (SCD) in patients with obstructive hypertrophic cardiomyopathy (HCM) needs some refining, especially for patients who undergo myectomy. So suggests a retrospective observational study of 1,809 patients with obstructive HCM evaluated at Cleveland Clinic. Patients were assigned to low-, medium- and high-risk groups for SCD based on European Society of Cardiology (ESC) five-year risk score. Their risk score-based expected rates of SCD or appropriate ICD discharge (composite primary end point) were then compared with their actual observed rates.

At five-year follow-up, observed event rates were statistically comparable among the three risk groups (from 4.6 to 5 percent) despite a wide range of expected event rates (2.5 to 9 percent) based on patients' five-year risk scores. Multivariate analysis showed that undergoing myectomy was highly associated with reduced risk, whereas a lower ESC risk score wasn't. "There was little correlation between actual SCD rates and those predicted by risk models," says Milind Desai, MD, lead author of the study, published in the *Journal of Thoracic and Cardiovascular Surgery*. "Adding myectomy to the risk score significantly reclassified risk and provided incremental prognostic utility." More at **consultqd.clevelandclinic.org/scd**.

PARTNER 2A Substudy: Watch the Right Ventricle

New data from a Cleveland Clinic-led research team highlight the importance of right ventricular (RV) function in intermediate-risk patients undergoing transcatheter aortic valve replacement (TAVR) and could help point toward a more personalized therapeutic approach.

Findings from a substudy of the multicenter PARTNER 2A trial show that worsening RV function is significantly more common — three times as much — following surgical aortic valve replacement (SAVR) than following TAVR. This is a new finding, notes lead author Paul Cremer, MD, a Cleveland Clinic cardiologist.

But regardless of baseline status or AVR procedure type, patients with worsening RV function at 30 days post-procedure had significantly higher rates of overall mortality and cardiovascular death. "The message is that once you have worsening RV function, it really doesn't matter whether you had a TAVR or SAVR — your outcome is going to be worse," Dr. Cremer says. The substudy was published in the *European Heart Journal*. More at **consultqd.clevelandclinic.org/partnersubstudy**.

Leadless Pacing Slashes Rates of Traditional Pacemaker Complications

Acute and medium-term complications are significantly reduced with a leadless cardiac pacemaker relative to traditional transvenous pacemakers, concludes the first direct safety comparison between the device types. The study, published in *Heart Rhythm*, was a propensity score-matched analysis comparing safety data with the leadless pacemaker Nanostim from the pivotal LEADLESS II IDE trial against complication rates with transvenous pacemakers from a large U.S. insurance claims database. The leadless pacemaker cohort had significantly fewer complications in both short-term (< 1 month) and medium-term (1-18 months) follow-up. Notably, lead-related, pocket-related and infectious complications were entirely absent from the leadless pacemaker cohort.

"This suggests leadless pacemaker technology has done what it was intended to do — successfully target the most common sources of traditional pacemaker complications," says lead author Daniel Cantillon, a Cleveland Clinic cardiologist. The findings were tempered by an excess of uncommon but serious pericardial effusions in patients receiving leadless devices, but these events are likely to diminish with greater operator experience and device refinements, Dr. Cantillon notes. More at **consultqd.clevelandclinic.org/leadless**.

In FMD, Diagnosis at Late Age Suggests Milder Course

When fibromuscular dysplasia (FMD) is diagnosed at an older age, its course appears to be more benign and less symptomatic than when recognized in middle age, finds an analysis of the U.S. Registry for Fibromuscular Dysplasia published in *JAMA Cardiology*. While most cases of FMD are diagnosed in middle age, 170 (16.7 percent) of the first 1,016 patients enrolled in the registry were diagnosed at age 65 or later. Compared with their registry counterparts diagnosed before age 65, these older patients were significantly more likely to be asymptomatic at diagnosis, had significantly fewer major vascular events and had undergone significantly fewer therapeutic vascular procedures.

"This confirms that FMD is not solely a disease of younger women but a vascular disorder that can emerge across the lifespan," says senior author Heather Gornik, MD, of Cleveland Clinic. "It also suggests that patients diagnosed with FMD at an older age can be reassured that they're more likely to have a milder disease course and may fare well with medical management alone." More at **consultqd.clevelandclinic.org/fmd**.

CME Preview: Master the Mitral Valve with This Course in NYC

Mastering the Mitral Valve: A Case-Based Approach

Fri.-Sat., Nov. 30-Dec. 1, 2018

JW Marriott Essex House | New York, New York
ccfcme.org/mitralmasters

For many complex areas of practice, nothing teaches as well as a good case. That's the philosophy behind this Cleveland Clinic-sponsored live CME event in New York City.

Cases will serve as the window into mitral valve management, with two of the six sessions in the 1.5-day course devoted solely to challenging cases and with case studies figuring prominently in each of the four other sessions. All sessions consist of highly focused presentations or Q&As no longer than 15 or 20 minutes.

The case-based emphasis is a new wrinkle in this second annual offering of the course, which returns to the same hotel venue just steps from Central Park.

"We're building on last year's popular inaugural course with this increased focus on case-based learning, which will enhance its relevance to cardiologists and engage participants in discussions and debates around clinical decision-making," explains course co-director Brian Griffin, MD, Section Head of Cardiovascular Imaging at Cleveland Clinic.

"Management of mitral valve disease can be challenging and complex," adds co-director A. Marc Gillinov, MD, Cleveland Clinic's Chair of Thoracic and Cardiovascular Surgery. "Questions abound: Which imaging modality — MRI or stress echo? When to refer a patient to surgery? What type of surgery — repair or replacement? We will address each of these issues and provide answers to help attendees optimize patient care."

The program starts with a stage-setting session that provides a contemporary framework for approaching mitral valve disease by reviewing current guidelines and controversies, key recent papers and the role of the valve center in patient management.

Next comes a session devoted to imaging the mitral valve, from basic echo to advanced techniques, followed by a session on mitral valve surgery and surgical decision-making. Each uses abundant case studies to bring real-world applications to bear or to discuss strategies for managing important issues often related to degenerative mitral valves, such as tricuspid repair or atrial fibrillation ablation.

Then come two sessions consisting solely of challenging cases. Here's a sampling of the 14 scenarios to be explored:

- Severe tricuspid regurgitation after previous mitral surgery
- 45-year-old man with hypertrophic obstructive cardiomyopathy and severe mitral regurgitation
- Pregnancy in a patient with valvular heart disease
- Mitral bioprosthesis thrombus formation

The course concludes with a session on emerging transcatheter mitral and tricuspid valve technologies, again with case studies.

The faculty combines 14 Cleveland Clinic experts in cardiology, cardiothoracic surgery, interventional cardiology and cardiothoracic anesthesiology with three renowned specialists from Northwestern University and Brigham and Women's Hospital. The program is designed for cardiothoracic surgeons, cardiologists, interventional cardiologists, internists, physician assistants and nurses.

"At Cleveland Clinic we've devoted much effort to achieving the highest quality in mitral valve surgery, including with the aid of robotic surgery," notes Heart & Vascular Institute Chair Lars Svensson, MD, PhD, another course co-director. "Those efforts have yielded unequaled outcomes. In the Society of Thoracic Surgeons' Adult Cardiac Surgery Database analysis for January 2015-December 2017, Cleveland Clinic achieved the maximum three-star rating in all five categories, including the two newly reported categories of mitral valve repair/replacement surgery with or without coronary artery bypass. Only two of 1,012 database participants achieved these results. We believe it's important for Cleveland Clinic to share with the wider cardiovascular community the lessons we've learned for enhancing the care of patients with mitral valve disease."

Register at ccfcme.org/mitralmasters. Early-bird rates end Oct. 1.

This activity has been approved for *AMA PRA Category 1 credit™*.

For more live cardiovascular CME from Cleveland Clinic, see the back cover of this issue.

RESOURCES FOR PHYSICIANS

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CME Opportunities: **ccfcme.org**

50 Years of Heart Health:

View our multimedia timeline of cardiovascular advances at **cle.clinic/2fcvBg2.**

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,500 physicians and researchers represent 140 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 and Cleveland Clinic Abu Dhabi.

In 2018, Cleveland Clinic was ranked a top U.S. hospital in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 5 hospitals in 12 specialty areas, and the top hospital in heart care (for the 24th consecutive year) and urologic care.

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CARDIOLOGY & HEART SURGERY 2018-19

Cleveland Clinic

The Cleveland Clinic Foundation
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Cardiac Consult

Upcoming Live CME Events from Cleveland Clinic

State-of-the-Art Echocardiography

Fri.-Sun., Sept. 14-16, 2018
Hilton Cleveland Downtown | Cleveland, Ohio

- Comprehensive coverage of echo in contemporary care, including many special and emerging topics like multimodality imaging, diastolic dysfunction and contrast use in echo
- Up to 20.5 ABIM MOC points in addition to CME credit

Information and registration:
ccfcme.org/echocardio

3rd Annual Advances in Pediatric & Congenital Heart Summit: Atrial Isomerism — the Road to Survival

Fri.-Sat., Sept. 28-29, 2018
InterContinental Hotel & Conference Center
Cleveland, Ohio

- One of the most in-depth explorations ever of how to manage this rare congenital heart disease also known as heterotaxy syndrome
- Preceded by full-day "Updates on Congenital Heart Disease Symposium" on Thurs., Sept. 27 (separate registration fee)

Information and registration:
ccfcme.org/pediatricheart18

Mastering the Mitral Valve: A Case-Based Approach

Fri.-Sat., Nov. 30-Dec. 1, 2018
JW Marriott Essex House | New York, New York

- See page 18 for an in-depth profile of this course

Information and registration:
ccfcme.org/mitralmasters

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

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See a sampling of outcomes in the insert to this issue.