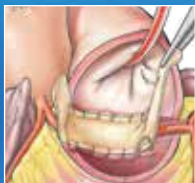




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Dear Colleagues,

"To provide better care of the sick, investigation into their problems, and further education of those who serve." That's the nearly century-old mission statement of Cleveland Clinic, and the cover feature of this issue illustrates how its middle component — *investigation into their problems* — is being pursued as robustly as ever.

In this feature we spotlight 10 studies from 2018 that staff from our Miller Family Heart & Vascular Institute either led or contributed to in important ways and that we believe may prove especially impactful. They're not strictly our "top 10" studies of the year but rather 10 that showcase both the breadth of our research efforts and the diverse types of influence these efforts have.

That impact can be in the form of establishing the efficacy and safety of devices and drugs, as in the multicenter COAPT, MOMENTUM 3 and ATTR-ACT trials. Or it can be in the form of investigations where we've tapped our voluminous cardiovascular registries and databases to gain fresh insights into disease nuances or to propose new data-driven treatment approaches.

Whatever the specific impact, these studies all focus on the lead component of our mission: *providing better care of the sick*. And in sharing them with you, our colleagues across the nation, we aim to complete our mission by *furthering education of those who serve*. We welcome your feedback and collaboration.

Respectfully,

Lars G. Svensson, MD, PhD

CHAIRMAN | Sydell and Arnold Miller Family Heart & Vascular Institute



Cardiac Consult is produced by Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute.

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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 urology care.

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10 of 2018's

Most Notable Cardiovascular Studies

777. That's the number of articles published in the peer-reviewed literature in 2017 by Cleveland Clinic Miller Family Heart & Vascular Institute staff, and the total for 2018 looks like it will end up being comparable.

Leaders of the Heart & Vascular Institute looked back on their team's hundreds of publications from 2018 to identify a handful that promise to be among the most noteworthy cardiovascular studies of the year. *Cardiac Consult* profiles 10 of those investigations here — and why they matter.

1

COAPT study of transcatheter mitral valve repair for secondary MR

› (*N Engl J Med.* 2018;379:2307-2318)

The multicenter COAPT trial found that transcatheter mitral valve repair with the MitraClip® device significantly reduced all-cause mortality and hospitalization compared with medical therapy in symptomatic patients with heart failure and secondary mitral regurgitation (MR). Benefits were consistent across multiple subgroups and were independent of MR grade and baseline left ventricular volume and function. The results are expected to lead to FDA approval of MitraClip for a new indication — treatment of secondary MR.

"This is the first large trial to show that treating functional MR not only makes patients feel better and prevents further worsening of the regurgitation, but also prevents death," says Cleveland Clinic's Samir Kapadia, MD, one of COAPT's lead investigators and steering committee

members. "It's likely to change management of this high-risk patient population with symptomatic MR secondary to heart failure."

"We have an important new option for patients with heart failure and severe functional MR," adds Cleveland Clinic Cardiothoracic Surgery Chair A. Marc Gillinov, MD, who served on advisory and central eligibility committees for the trial. "Most of these patients are not good surgical candidates, but they can now receive a mitral procedure that improves their prognosis."

Especially notable are the number-needed-to-treat results, Dr. Kapadia says: "We found that we need to treat just three patients to prevent one hospitalization and treat six patients to save a life. This is one of the most beneficial treatment effects we've ever observed in a clinical trial." ■

2

MOMENTUM 3 trial of the HeartMate 3 LVAD

› (*N Engl J Med.* 2018;378:1386-1395)

This 69-center study showed that, among patients with advanced heart failure, the HeartMate 3™ fully magnetically levitated centrifugal flow pump was superior to the HeartMate II mechanical-bearing axial-flow pump in two-year survival free of disabling stroke or reoperation to replace/remove a malfunctioning device. Moreover, the HeartMate 3 was associated with a lower risk of stroke while averting device malfunction related to pump thrombosis.

“Two-year survival with the HeartMate 3 approaches that of heart transplantation,” observes Cleveland Clinic Heart

Failure Section Head Jerry Estep, MD, who served as a leading MOMENTUM 3 co-investigator and co-chair of its flow optimization subcommittee. “This study was a tremendous opportunity to better understand hemocompatibility and the interaction between pump speed adjustments and medical management to optimize hemodynamics to improve patient outcome.” He adds that HeartMate 3 represents only the beginning of a budding evolution in left ventricular assist device (LVAD) design, which he says will include a pump with speed auto-regulation to enhance functional capacity and quality of life. ■

› “[MOMENTUM 3] was a tremendous opportunity to better understand hemocompatibility and the interaction between pump speed adjustments and medical management to optimize hemodynamics to improve patient outcome.” – Jerry Estep, MD

3

CRISP CT study: Noninvasive detection of coronary inflammation

› (*Lancet.* 2018;392:929-939)

A novel imaging biomarker that quantifies perivascular fat can predict all-cause and cardiac mortality above and beyond clinical risk factors and current coronary CT interpretation methods. So found this cross-continental collaboration between U.K. researchers and colleagues in Germany and at Cleveland Clinic. High values of the biomarker — known as the perivascular fat attenuation index — around the right coronary artery effectively identified individuals at risk of death in two large, independent and substantially different patient cohorts: a derivation cohort in Erlangen, Germany (N = 1,872), and a validation cohort at Cleveland Clinic (N = 2,040).

“The perivascular fat attenuation index is the first noninvasive biomarker of coronary inflammation measured by traditional coronary CT angiography,” says co-first author Milind Desai, MD, a Cleveland Clinic cardiologist. “Our study validates the prognostic role of this index over and above the presence of coronary stenosis or calcification. We now have, for the first time, a biomarker derived from a fairly routine imaging study that measures residual cardiovascular risk with independent and incremental value over modern risk scores and other noninvasive tests. This could have transformative effects on primary and secondary prevention.” ■



4

No ceiling to survival benefits of aerobic fitness

› (*JAMA Netw Open*. 2018;1:e183605)

Cardiorespiratory fitness is associated with long-term mortality benefits in a dose-response manner that shows no upper limit, according to the largest-ever cohort study of long-term mortality among patients undergoing exercise treadmill testing. “Extremely high aerobic fitness was associated with the greatest survival, and this benefit extended to individuals aged 70 or older,” says co-author and Cleveland Clinic cardiologist Wael Jaber, MD.

The retrospective cohort study included consecutive adults referred for symptom-limited exercise treadmill testing at Cleveland Clinic from 1991 through 2014. Median follow-up was 8.4 years. Based on their treadmill tests, patients were stratified by age- and sex-matched cardiorespiratory fitness levels into five performance groups: low (< 25th percentile), below average (25th-49th percentile), above average (50th-74th percentile), high (75th-97.6th percentile) and elite (\geq 97.7th percentile).

Risk-adjusted all-cause mortality was found to be inversely proportional to cardiorespiratory fitness, with statistically significant differences between each increment in fitness level. Elite fitness was associated with an 80 percent reduction in mortality risk relative to low fitness. The mortality increase associated with each reduction in fitness level was comparable to or greater than that of traditional clinical risk factors.

“Despite some recent evidence suggesting adverse cardiovascular effects of habitual vigorous exercise, our findings show no sign of a plateau effect with elite fitness,” Dr. Jaber notes. “These results underscore the importance of aerobic fitness to overall health, which rivals that of traditional clinical risk factors.” ■

› “Despite some recent evidence suggesting adverse cardiovascular effects of habitual vigorous exercise, our findings show no sign of a plateau effect with elite fitness.” – Wael Jaber, MD

5

ATTR-ACT study of tafamidis for amyloid cardiomyopathy

› (*N Engl J Med*. 2018;379:1007-1016)

When the multicenter phase 3 ATTR-ACT study was published a few months ago, it provided the first-ever evidence of therapeutic benefit against the ATTR form of cardiac amyloidosis outside of heart transplantation. Among 441 patients with the condition, the small-molecule compound tafamidis was associated with significantly lower rates of all-cause mortality at 30 months relative to placebo (30 percent vs. 43 percent) as well as significantly fewer cardiovascular-related hospitalizations. Adverse events in the tafamidis and placebo arms were comparable.

“The degree of survival benefit from tafamidis was impressive,” says Cleveland Clinic cardiologist Mazen Hanna, MD, lead investigator of the ATTR-ACT trial at Cleveland Clinic and a co-author of the published study. “It will change the landscape of this disease and offers long-awaited hope to our patients with wild-type TTR cardiac amyloidosis in addition to those with the hereditary variant.”

FDA approval of tafamidis is expected in 2019. ■

6

‘Drugging’ the microbiome to inhibit thrombosis

› (*Nat Med.* 2018;24:1407-1417)

A new drug class promises a novel approach to reducing platelet hyper-responsiveness and thrombosis potential without increased bleeding risk by nonlethally targeting the gut microbial pathway that produces the atherogenic metabolite TMAO. The drug class — known as halo-methylcholines, or mechanism-based inhibitors — was developed by Cleveland Clinic researchers and tested in a mouse model of arterial injury. “Outside of antibiotics, which cannot be used chronically without generating resistance, this is the most potent therapy to date for ‘drugging’ the microbiome to alter a disease process,” says lead researcher Stanley Hazen, MD, PhD.

A single oral dose of a halomethylcholine significantly reduced plasma TMAO levels in the mouse model for up to three days and reversed enhanced platelet responsiveness

and thrombus formation following arterial injury — without taking platelet function below normal. The agents were minimally absorbed into the body and remained in the gut, where they selectively accumulated in gut microbes. Because these compounds were designed not to kill bacteria, they are not expected to induce antibiotic resistance.

“We showed that gut bacteria were altered but not killed by these therapies, with no observable toxic side effects,” Dr. Hazen says. “This approach could potentially be used to target other gut microbial pathways while minimizing systemic drug exposure and antibiotic resistance. We’ve identified a new potential target for treating individuals at risk for thrombotic complications and cardiovascular disease.” ■

7

Refining estimation of heart transplant waitlist mortality

› (*J Am Coll Cardiol.* 2018;72:650-659)

Patients’ baseline risk factors for mortality at the time of listing for heart transplantation quickly become nonsignificant once subsequent events and changes in lab values reflecting organ failure are incorporated into a dynamic model that continuously updates mortality risk. So found a unique study of 414 patients listed for heart transplant at Cleveland Clinic from 2008 to 2013. The study sought to develop a decision aid to aggregate adverse events and metrics of end-organ function into a continuously updated estimate of waitlist mortality.

Of the 414 patients, 77 died while on the waitlist, yielding one- and four-year survival rates of 85 and 57 percent, respectively. The pre-listing patient factors used in existing heart failure survival models were not predictive of survival when time-varying factors were

taken into account while patients were on the waitlist. Neurological events, new requirement for dialysis, respiratory complications and increased serum bilirubin and creatinine were the time-varying factors most predictive of waitlist mortality.

The Cleveland Clinic researchers are now building on these insights in an NIH-funded collaboration with four other U.S. centers to develop the first tool to dynamically update heart transplant waitlist mortality risk using variables not included in existing models as well as serial clinical assessments. “A continuously updated mortality estimate, combined with clinical evaluation, may inform patient status changes that could reduce mortality on the heart transplant waitlist,” concludes lead researcher Eugene Blackstone, MD. ■



8

PARTNER 2A substudy probes role of prior cardiac surgery

› (*JACC Cardiovasc Interv.* 2018;11:2207-2216)

The randomized PARTNER 2A trial comparing surgical (SAVR) with transcatheter (TAVR) aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk keeps yielding useful insights through its many subanalyses. This latest one took on a previously unexplored question: Whether prior cardiac surgery confers increased risk for adverse clinical outcomes in intermediate-risk patients undergoing TAVR as it has been shown to do in those undergoing SAVR.

Of the 2,032 patients in PARTNER 2A, 509 (25 percent) had prior cardiac surgery, mostly coronary artery bypass grafting. When patients were stratified by whether or not they had prior cardiac surgery, short- and long-term clinical outcomes (all-cause death and disabling stroke) over two years were statistically comparable between the TAVR and

SAVR groups regardless of whether patients did or did not have prior cardiac surgery. However, major vascular complications and life-threatening bleeds at 30 days were disproportionately more common among patients with prior cardiac surgery who underwent SAVR.

“This subanalysis supports the long-term efficacy of both TAVR and SAVR in intermediate-risk patients who have had prior cardiac surgery, although there may be a possible early safety advantage with TAVR in this group,” says PARTNER 2A co-investigator Lars Svensson, MD, PhD, Chair of Cleveland Clinic’s Heart & Vascular Institute. “These findings underscore the importance of caring for this subpopulation with a comprehensive heart valve team approach that can adjust for nuances in patient preferences and vascular characteristics.” ■

9

Sussing out sex differences in surgical mitral valve disease

› (*Circulation.* 2018;138:1749-1751)

Women with mitral valve disease undergo mitral valve replacement at higher rates than their male counterparts do, and this has been linked to persistently poorer mitral valve surgery outcomes in women. Despite this linkage, studies to date have generally not accounted for sex differences in the etiology of surgical mitral valve disease or any changes in etiology over time. To fill that gap, Cleveland Clinic researchers analyzed 23,806 consecutive patients who underwent primary mitral valve replacement or repair at the institution from 1993 to 2016.

The analysis revealed highly significant between-sex differences in prevalence of the three main types of mitral valve disease — degenerative, ischemic and rheumatic — in the cohort, with much higher rates of rheumatic disease in women and much higher rates of degenerative

disease in men. Despite changes in the prevalence of each etiology over the study period (degenerative disease became more common, and rheumatic and ischemic disease grew less common), the between-sex differences in each disease type remained consistently significant throughout the study. (For more detail on the findings, see “Image of the Issue” on page 19 of this issue.)

“Our analysis clarifies that, despite a temporal shift in etiology of surgically treated mitral valve disease overall, differences between the sexes persist into the modern era of cardiac surgery,” notes primary author Leslie Cho, MD, Director of Cleveland Clinic’s Women’s Cardiovascular Center. “We’ve identified another potential explanation for sex differences in procedure selection and outcomes.” ■



› “Our study suggests that relieving the obstruction in HOCM ... can potentially have an impact in reducing sudden death. I think we’re entering an era with surgical myectomy where we’re talking not just about symptom relief but also about modulating longer-term risk of dying.” – Milind Desai, MD

10

Predicting sudden-death risk in HOCM

› (*J Thorac Cardiovasc Surg.* 2018;156:750-759)

Risk stratification for sudden cardiac death (SCD) in patients with hypertrophic obstructive cardiomyopathy (HOCM) needs some refining, especially for patients who undergo myectomy. So concluded a retrospective observational study of 1,809 consecutive patients with HOCM evaluated at Cleveland Clinic. The study found little correlation between actual rates of SCD and the rates predicted by SCD risk models in recent guidelines from the European Society of Cardiology (ESC) or the American College of Cardiology/American Heart Association (ACC/AHA). “For example, in the highest SCD risk group, the actual five-year event rate was only about half the expected rate based on ESC risk score,” observes co-author Nicholas Smedira, MD, a Cleveland Clinic cardiac surgeon.

A full 64 percent of patients underwent surgical myectomy to relieve their HOCM. Multivariable analysis showed that myectomy — and, separately, atrial fibrillation during follow-up — was associated with significantly reduced risk of longer-term SCD, whereas ESC and ACC/AHA risk scores were not. The researchers concluded that adding myectomy and atrial fibrillation to the ESC and ACC/AHA risk scores for SCD significantly reclassified risk and provided incremental prognostic utility.

“Our study suggests that relieving the obstruction in HOCM, debulking the thick myocardium, can potentially have an impact in reducing sudden death,” says Cleveland Clinic cardiologist and lead author Milind Desai, MD. “I think we’re entering an era with surgical myectomy where we’re talking not just about symptom relief but also about modulating longer-term risk of dying.” ■

Cleveland Clinic Heart Care Model Goes to London

Cleveland Clinic London is set to open in 2021, and cardiovascular care will be a core offering.



Cleveland Clinic is preparing to bring its distinctive group practice model to a new setting — the heart of London — and cardiovascular care will be one of the flagship clinical offerings.

The U.S.-based health system will partner with specialist physicians and general practitioners in the U.K. to care for patients in state-of-the-art private facilities using Cleveland Clinic's team-based, physician-led care philosophy and infrastructure. The facilities — to be called Cleveland Clinic London — include an outpatient medical building to open in 2020 and a 21st-century inpatient hospital to open in early 2021. The 200-bed hospital is being converted from an existing building near Buckingham Palace, with its entire six-floor interior being reconstructed and reimagined for patient care in the decades to come.

Broad cardiovascular offerings

Cleveland Clinic London's cardiovascular-specific care offerings will include (1) cardiac and thoracic surgery, (2) interventional and diagnostic cardiology, (3) electrophysiology, (4) cardiac imaging and (5) vascular surgery.

The hospital will house a dedicated cardiac surgery operating theater, a hybrid theater, a biplane catheterization lab and a single-plane catheterization/electrophysiology lab, among other features.

"An interdisciplinary heart team approach — including general practitioners, when they're involved in a case — will be brought to bear for all appropriate cardiovascular patients,

especially in cases where percutaneous intervention is an option," says Cleveland Clinic Heart & Vascular Institute Chairman Lars Svensson, MD, PhD, who co-authored an article detailing the Cleveland Clinic London initiative in a recent issue of the *European Heart Journal* (2018;39:3161-3163).

The article notes that expected benefits from the initiative include swifter access to specialist care for patients in the U.K. and for existing Cleveland Clinic patients throughout Europe, greater two-way sharing of technology and best practices, and opportunities for educational collaboration between the U.S. and U.K.

Putting a premium on local expertise

Local surgeons and other specialists will be engaged to learn the Cleveland Clinic culture and work with the Cleveland Clinic London team to provide patient-centered, collaborative care in the new facilities. "We'll rely significantly on the local medical and surgical community, especially in view of the U.K.'s rich tradition of pioneering cardiovascular care," Dr. Svensson notes.

To that end, Olaf Wendler, MD, PhD, FRCS, Professor of Cardiac Surgery at King's College London, has been enlisted to lead Cleveland Clinic London's Heart & Vascular Institute. Dr. Wendler has been a consultant in cardiothoracic surgery for more than 20 years, building an international reputation for innovative minimally invasive heart surgery. Since 2013, he has been lead cardiac surgeon in the Clinical Advisory Group of the NHS London Cardiovascular Strategic Clinical Network. ■

For more, visit clevelandcliniclondon.uk.



For Success in Congenital Heart Surgery, Start Planning Early and Be Ready to Innovate

BY HANI NAJM, MD

Success in surgery for congenital heart disease is inseparable from two things: the way an institution's program is organized, and the program's readiness to innovate at any turn. At Cleveland Clinic, we optimize congenital heart surgery outcomes by starting before the infant with a congenital defect is born and carefully detailing every step in advance to expedite the newborn's first surgery and subsequent procedures.

A new approach to a rare defect

Our experience also allows us to innovate. At the recent Society of Thoracic Surgeons annual meeting in San Diego, we presented a novel approach to a rare congenital heart defect: anomalous aortic origin of left main coronary artery (LMCA) arising from right coronary sinus with posterior extension of the right ventricular outflow tract.

Rather than performing a bypass, we have used trans-conal unroofing to produce successful outcomes in five patients. All were adults, but our experience with surgical approaches to congenital malformations directly informed our development of the new surgical approach.

In all five surgeries, we used a trans-conal approach for extensive unroofing of the intraseptal LMCA, followed by patch augmentation of the posterior wall of the right ventricular outflow tract (Figure). The trans-conal approach gives direct exposure of the full length of the LMCA for effective mobilization of the proximal kinked segment and full muscular unroofing of the body of the artery. Posterior extension of the right ventricular outflow tract helps avoid arterial compression during exercise.

For the best surgical outcomes in congenital heart disease, it's important to make the diagnosis during pregnancy whenever possible.

All five patients — who ranged in age from 35 to 60 years — have undergone their operations within the past year, and all are doing well. All had ischemia preoperatively, but none do now. We continue to follow them.

Innovation can bolster outcomes

New approaches such as this have contributed to improved outcomes. In 2018, Cleveland Clinic's 30-day mortality rate was zero across more than 400 congenital heart disease surgeries, with one late mortality. This compares well with the typical 3 percent rate across the nation (according to the Society of Thoracic Surgeons Congenital Heart Surgery Database). This means that outcomes are more than 10 times better than the national average and that an extra 12 patients left Cleveland Clinic's congenital heart disease program alive and well than would have been the case had they been operated on at another center.

We attribute this success not to fancy machines or devices but to the ability to diagnose early, do proper surgery and care for our patients appropriately after surgery. That's why patient survival is higher than at other centers.

Preparing from the very start

For the best surgical outcomes in congenital heart disease, it's important to make the diagnosis during pregnancy whenever possible, usually by fetal echocardiography between 18 and 25 weeks' gestation. Our heart surgery team makes the diagnosis and counsels the parents about the nature of the lesion, the anticipated surgery and its timing, and the expected outcome.

Sometimes surgery is necessary within hours of birth. An example would be an in utero diagnosis — confirmed via fetal echo — of univentricular or biventricular obstructed total anomalous pulmonary venous drainage. Once the obstruction occurs, any delay in management compounds the damage.

We handle such cases in Cleveland Clinic's Special Delivery Unit (SDU). A mother comes in for a planned cesarean section,

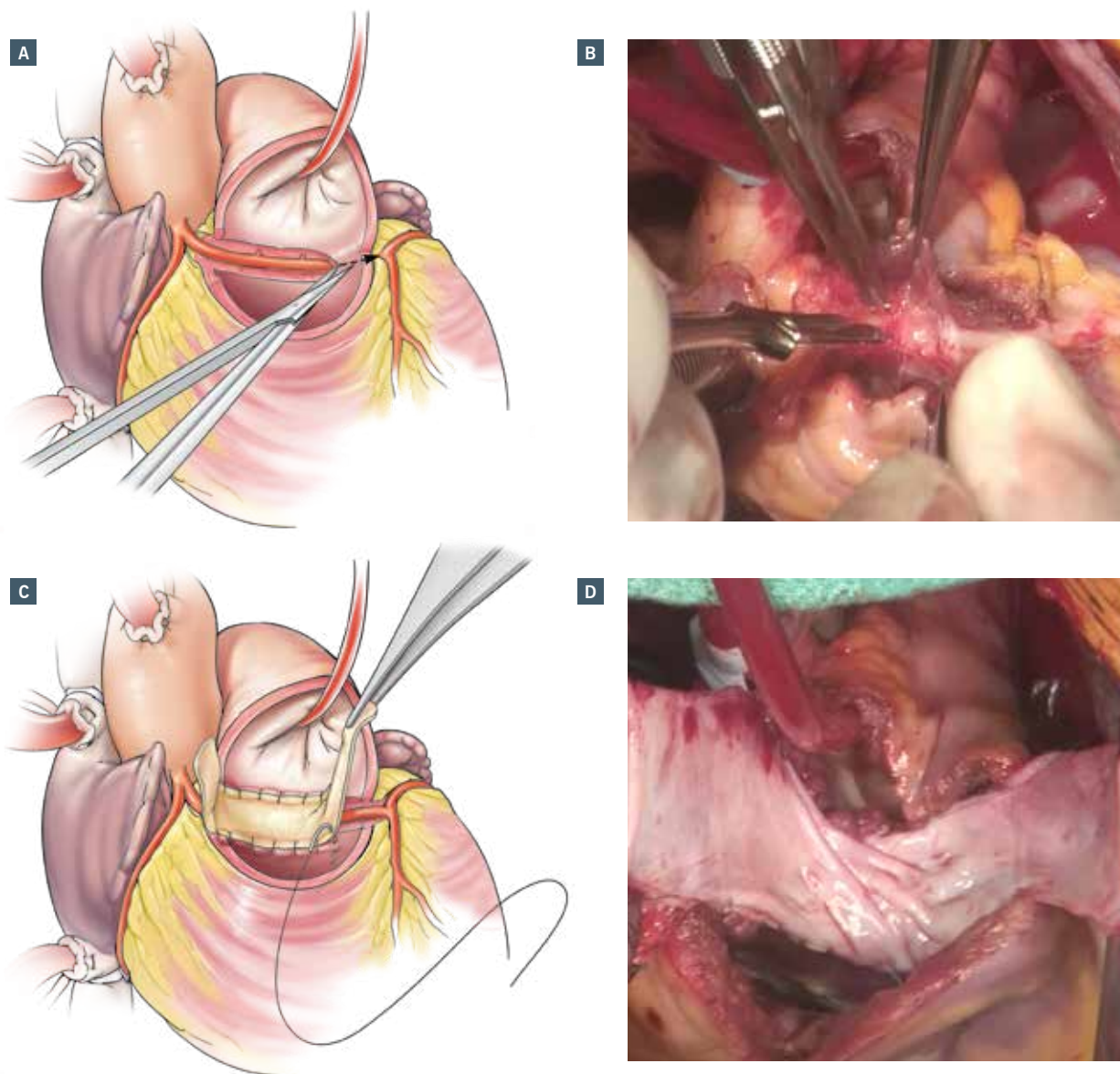


Figure. Key steps in our novel trans-conal procedure. (A) Schematic illustration of the division of the right ventricular outflow tract (RVOT). (B) Photo of the unroofed left main coronary artery behind the RVOT. (C and D) Illustration and surgical photo of the autologous pericardial patch extension of the RVOT.

which is performed at 7:30 a.m. Within hours of the delivery, the baby is in the OR receiving open-heart surgery. We're able to do this because the SDU is across the corridor from the catheterization lab and right next to the OR. There is no wasted time or transport.

Planning the patient's future care

About 70 percent of infants with congenital heart disease will have simple defects that can be repaired in one procedure, although they all require lifelong monitoring. Some patients, such as those with tetralogy of Fallot, will require a pulmonary valve implant at some point in their adult lives, sometimes decades later.

But infants born with univentricular hearts will require a series of staged operations. Typically this involves a Norwood procedure, a shunt or band at or near birth, a bidirectional Glenn anastomosis at age 4 to 6 months, and a Fontan procedure at age 2 to 4 years.

Patients will usually remain cyanotic until they receive the Fontan procedure, after which they should turn a healthy pink. At this point, those without comorbid developmental problems can lead relatively normal lives with just a single pumping chamber, although they must always avoid competitive sports. ■

Dr. Najm (216.444.5819) is Chair of Pediatric and Congenital Heart Surgery at Cleveland Clinic.



Operational Efficiency in the Cardiac Cath Lab: The Time for Metrics Is at Hand

More than a few guideline and consensus statements have been developed to define quality of care in the cardiac catheterization laboratory, but the same is not true for operational efficiency of the cath lab. A new review paper by Cleveland Clinic interventional cardiologists and a Harvard Business School professor aims to change that by laying out the first proposed standardized metrics of cath lab efficiency.



“Many institutions are desperate for guidance on how to efficiently provide high-quality cardiac cath lab care,” says Samir Kapadia, MD, Director of the Sones Cardiac Catheterization Laboratories in Cleveland Clinic’s Miller Family Heart & Vascular Institute and senior author of the review, which was published in the *Journal of the American College of Cardiology* (2018;72:2507-2517). “We developed this paper to demonstrate the importance of operational efficiency to cath labs’ sustainability by approaching the topic from a business perspective and proposing standardized metrics of efficiency that could be used in future public reporting around the value of cath lab care.”

Introducing congruence modeling

The paper focuses on *operational efficiency*, or the ability to deliver a service in a cost-effective manner while maintaining high quality standards. “With continuing shifts in reimbursement away from fee-for-service models toward quality-based models, it is paramount for hospitals and health systems to control costs,” notes Dr. Kapadia. “Those organizations that embrace operational efficiency in the cath lab will benefit in this environment.”

To make the case for such action, Dr. Kapadia and his Cleveland Clinic colleague Grant Reed, MD, partnered with Michael L. Tushman, PhD, of Harvard Business School on the paper, which provides a framework for improving efficiency based on the Nadler-Tushman congruence model, a commonly used tool for designing and aligning organizational management.



“Pinpointing opportunity gaps can be an important growth strategy for a cath lab that’s already functioning well.”

– Samir Kapadia, MD

A congruence model helps assess the performance and efficiency of an organization by examining several interconnected elements: executive leadership, strategy, critical tasks, formal organization, people and culture. “The greater the alignment, or congruence, among these elements, the better a cath lab’s performance and efficiency will be,” observes co-author Dr. Reed.

Well-functioning cath labs can benefit too

The authors note that congruence modeling can help cath labs address *performance gaps* — i.e., inefficiency-related differences between actual and optimal performance — as well as *opportunity gaps* — i.e., areas of potential growth if the lab were to embrace novel procedures, technologies or innovations. “Pinpointing opportunity gaps can be an important growth strategy for a cath lab that’s already functioning well,” Dr. Kapadia says.

The paper reviews how each of the elements examined within the congruence model figures into cath lab operational efficiency, with an emphasis on the particular importance of effective leadership by the physician cath lab director, whom the authors dub the “cath lab chief executive officer.”

The authors then share a detailed example of how Cleveland Clinic used a congruence model to address a performance gap — i.e., how to increase the cath lab’s ability to perform elective cardiac catheterizations for inpatients within 24 hours of a request. The steps taken led to a rise in the number of completed same-day or next-day cases from 71.1 percent to 80.9 percent, which resulted in more same-day discharges and related cost efficiencies.

Nine proposed efficiency metrics

The paper’s centerpiece is the authors’ proposal for standardized metrics of cath lab efficiency, which are laid out and defined as follows:

- **Case volume:** Number of cases in a specified time period
- **Room utilization:** Ratio of the hours each cath lab room is staffed to the hours the room is utilized
- **Percentage of days at full capacity:** Proportion of days the whole lab is at full operating capacity

- **Percentage of on-time starts:** Proportion of times the patient and physician arrive on time for the first case of the day in a given lab room
- **Turnaround time:** Time between exit of the prior patient and arrival of the next patient in a lab room
- **Percentage of sheath pulls in room:** Proportion of nonradial cases in which the vascular access sheath is pulled in the lab room
- **Productivity per FTE:** Ratio of case volume per nonphysician full-time employee (FTE)
- **Percentage of after-hours cases:** Proportion of scheduled cases that occur after normal operating hours
- **Percentage of overtime hours:** Proportion of hours paid to FTEs that are classified as overtime

The authors note that they longitudinally assessed these metrics in a recent study of a cath lab quality improvement (QI) initiative that Drs. Kapadia and Reed published (with other Cleveland Clinic colleagues) in *JACC Cardiovascular Interventions* (2018;11:329-338). Their latest paper also shares goals for each efficiency metric from that QI study, noting that they obtained improvements in virtually all the metrics by addressing performance gaps identified from a congruence model they ran for the initiative.

The net result was a gain of 5.1 to 5.6 hours per day of additional cath lab time, which arose from improved utilization and reduced room turnaround times, the authors note. This was achieved without negative effects on case volume and with improvements in employee satisfaction and productivity, as detailed in a recent issue of *Cardiac Consult*.

“A systematic approach to operational efficiency using a congruence model can be a valuable tool for improving cath lab management,” Dr. Kapadia concludes. “We encourage cath labs to report results from their QI initiatives using metrics similar to those we’ve defined in this review paper.” ■

Contact Dr. Kapadia at 216.444.6735 and Dr. Reed at 216.445.7396.



Role of the Robot in Evolving Thoracic Surgery Practice

How robotic technology is continually shaping our approaches and outcomes

BY SUDISH MURTHY, MD, PHD

Over the past few decades, the use of robotic assistance has swept through almost every surgical specialty, from bariatric and cardiovascular to gynecologic and urologic. Today's sophisticated robotic systems, with mechanical "wristed" arms holding surgical instruments — controlled by the surgeon with the aid of high-definition, magnified 3D optics — allow for greater flexibility, finer control and better precision than can be achieved using conventional surgical methods.

At Cleveland Clinic, we have wholeheartedly adopted robotic technology into thoracic surgery practice and are advancing its use for increasingly sophisticated procedures.

Taking advantage of this technology is critical to our goal of treating disease with as little collateral injury as possible. Only very small incisions are needed for robotically assisted surgeries, and deep tissues can gently be pushed out of the way with the robotic arms instead of cut, causing less internal damage as well. This results in less blood loss and reduced postoperative pain. Scarring is also minimized compared with traditional open operations, and this is a big advantage if additional surgery is needed. Moreover, patient recovery times are shorter, with fewer days spent in hospital and a more rapid return to work and daily activities.

The value of volume

As a tertiary care center, Cleveland Clinic enjoys the advantage of a high volume of thoracic surgery cases: We perform over 2,000 thoracic operations annually, including a large number of complex cases.

Following our successful experiences with robotic assistance for cardiovascular surgery, we were among the first adopters of robotic technology for general thoracic surgery. Our applications quickly expanded: We now use video-assisted thoracic surgery (VATS) or robotic assistance for most of our lobectomies for lung cancer, including for almost 90 percent of patients with stage I disease.



We also perform thymectomies and treat mediastinal masses robotically. Procedures for benign esophageal diseases — including achalasia, reflux, para-esophageal hernias and giant gastric hernias — are now often done robotically as well.

We are also increasingly using the robotic system for esophagectomies for cancer. This complex operation often entails combined robot-assisted and conventional surgery. Patient outcomes are improved, and recovery is noticeably expedited.

Cleveland Clinic is proud to be the only institution in the country to earn three-star composite quality ratings from the Society of Thoracic Surgeons for both lobectomy for lung cancer and esophagectomy for the three-year period ending in December 2017. These ratings, based on mortality and major complications, are the highest possible and distinguish Cleveland Clinic as a statistical outlier in terms of superior quality. We believe our judicious use of minimally invasive VATS and robot-assisted techniques is an important contributing factor to these high marks.

Clinical judgment always at the fore

The adoption of robotics has allowed us to increase treatment options for our patients. But as with any new technology, it is critical to know when — and when not — to use it and to customize its use for each patient as appropriate. The fanciest tools are no substitute for judgment and experience. Minimally invasive operations can quickly be converted to conventional surgery, and we employ that option whenever the situation warrants it.

Factors to consider that may favor an open surgical approach include prior open chest surgery, radiation to the chest, pulmonary infections or coronary artery bypass graft surgery.

Staying current is important

At Cleveland Clinic, we use the da Vinci® Xi, the fourth-generation and latest robotic surgical system. It is smaller and lighter than the previous version, and the arms have a better reach inside the body. Optics have improved with higher magnification, enabling more precise surgery. Despite more sophisticated functionality, we find it easier to use, with a more intuitive interface.

Is it critical to update to each new system as it comes on the market? We believe so. Although it is an expensive proposition for any institution and requires a certain amount of retraining in addition to the capital costs, our experience has been that each successive version has offered significant improvements (such as those outlined in the previous paragraph), allowing us to provide the best care available to our patients.



Looking to the future

The trend of applying robotic assistance to increasingly complex surgeries will continue, which means it's likely that the days of most large-incision operations are numbered.

The role of high-volume centers such as Cleveland Clinic is to keep pushing the envelope so that patients can reap the benefits of outcomes equivalent to those with open surgery even as treatment-related morbidity continues to diminish as robotic technology is refined.

An additional role is to teach and share innovations, and Cleveland Clinic's cardiothoracic surgical teams are happy to accommodate surgeons and technicians from other institutions who wish to observe advanced robotic techniques. ■

Dr. Murthy (216.444.5640) is Section Head of Thoracic Surgery at Cleveland Clinic.



Teasing Out the Role of Red Meat and TMAO in Cardiovascular Risk

Two new studies add insights and home in on therapeutic targets.

Two new human studies from a Cleveland Clinic research team led by Stanley Hazen, MD, PhD, have yielded further insights into why and how regular consumption of red meat can increase the risk of cardiovascular disease (CVD) and the role gut bacteria play in the process.

The studies — published online in December by the *European Heart Journal* and the *Journal of Clinical Investigation* — build on previous work by Dr. Hazen's team and others showing that the metabolite TMAO (trimethylamine *N*-oxide) — a gut bacteria byproduct generated during digestion — is mechanistically linked to the pathogenesis of atherosclerotic heart disease. TMAO is produced when gut bacteria digest choline, carnitine and lecithin — nutrients that are abundant in animal products, particularly red meat.

"These studies bring us closer to therapeutic interventions to reduce CVD risk in humans by reducing TMAO levels through diet manipulation or novel therapies targeted at specific steps in TMAO's metaorganismal pathway," says Dr. Hazen, Chair of the Department of Cellular and Molecular Medicine and Co-Section Head of Preventive Cardiology.

A firmer take on TMAO metabolism

The research in the *European Heart Journal* was a dietary intervention study assessing the impact of chronic dietary patterns on TMAO levels, metabolism and renal excretion. One hundred thirteen healthy adult volunteers were sequentially given four-week isocaloric meal plans prepared using either red meat, white meat or non-meat (mostly vegetarian) protein sources as 25 percent of daily calories. All participants also received a washout diet for at least two weeks between each of the monthly meal plans.



Results showed that chronic ingestion of red meat increased plasma levels of TMAO approximately threefold compared with consumption of white meat or non-meat protein ($P < .0001$), with some participants demonstrating increases of more than tenfold. Similar significant increases in urine levels of TMAO were observed during the red meat diet ($P < .0001$).

After discontinuation of the red meat diet, plasma TMAO levels subsided within four weeks.

Red meat consumption also significantly decreased fractional renal excretion of TMAO but significantly *increased* fractional renal excretion of carnitine and two other gut microbiota-produced metabolites of carnitine: gamma-butyrobetaine and crotonobetaine. "This is the first study we know of to show that the kidneys can change how effectively they excrete different compounds — other than salts and water — depending on the diet consumed," observes Dr. Hazen.

In a subgroup of participants given oral isotope tracers, isotope challenge showed that red meat and white meat — but not non-meat protein — significantly increased gut microbiota production of TMAO and its precursor TMA from carnitine but not from choline.

Dietary levels of saturated fat (low vs. high) were also examined across the study with each of the diets (red meat, white meat and non-meat protein) and were found to have no impact on TMAO or its metabolites.

"These findings add substantially to our understanding of diet and TMAO metabolism," says Dr. Hazen. "In view of the growing evidence supporting a mechanistic link between TMAO and CVD pathogenesis, interest in TMAO-reducing therapeutic interventions is mounting. This study begins to provide evidence-based results regarding dietary manipulations that can effectively lower TMAO levels."





Potential new target for CVD prevention

The other new study, published in the *Journal of Clinical Investigation*, aimed to define the contribution of one of the abovementioned metabolites of carnitine, gamma-butyrobetaine (gamma-BB), in gut microbiota-dependent L-carnitine metabolism in humans in light of evidence that L-carnitine accelerates atherosclerosis in mice via TMAO formation in the gut.

The work was propelled by findings Dr. Hazen's team published in *Nature Medicine* in August 2018 showing that a new drug class developed by Cleveland Clinic researchers reduced platelet hyperresponsiveness and thrombosis potential in a mouse model without increasing bleeding risk. The novel drug class acts by nonlethally targeting the gut microbial pathway that produces TMAO.

"Preclinical studies indicate that therapeutic targeting of microbial contributors to the TMAO pathway may hold promise for preventing or treating CVD," Dr. Hazen explains. "But improved understanding of the microbial pathways involved in TMA/TMAO formation from distinct nutrients in humans is a necessary step in developing targeted therapies to disrupt these processes."

To that end, the new *Journal of Clinical Investigation* study compared the impact of chronic daily oral carnitine supplements in omnivores versus vegans/vegetarians. At baseline, vegans/vegetarians showed virtually no ability to produce TMAO from



carnitine, whereas omnivores rapidly produced TMAO. After one month of supplementation, both groups showed an increased capacity to produce TMAO, though vegans/vegetarians still produced decreased amounts relative to omnivores.

The researchers found that carnitine is converted to TMAO in the gut through a two-step process facilitated by distinct gut bacteria. The first step — rapid generation of the atherogenic intermediate metabolite gamma-BB — is similar in omnivores and vegans/vegetarians. But the second step — gamma-BB transformation into TMA — is significantly enhanced in omnivores (i.e., by the chronic dietary exposure found in an omnivorous versus a vegetarian diet). The researchers demonstrated that a daily carnitine supplement can induce TMAO production, even in vegans and vegetarians who continue consuming their usual diets. They also isolated and identified human gut commensals from fecal samples that could support each step in the transformation of carnitine to TMA/TMAO.

"We showed that gut microbial transformation of gamma-BB into TMA and then TMAO is induced by omnivorous dietary patterns and chronic carnitine exposure," notes Dr. Hazen. "These findings provide important insights for efforts to develop therapeutic interventions to inhibit dietary conversion of carnitine into TMAO in humans." ■

Contact Dr. Hazen at 216.444.9426.





CME Preview: Find Time for These Satellites at Heart Rhythm 2019

If you're attending the Heart Rhythm Society's Heart Rhythm 2019 meeting in San Francisco in May, save spots in your schedule to take in two highly practical CME-certified satellite sessions over dinner. Both are free of charge, so register while spots remain at ccfcme.org/hrsep19 and ccfcme.org/hrsleadmgt19.

Clinical Challenges in EP Practice: Innovations and Solutions 2019 and Beyond

Tues., May 7, 2019, 6:30-9:15 p.m. (complimentary dinner program)
InterContinental San Francisco
Official educational satellite session at Heart Rhythm 2019

Management of challenging clinical scenarios is the focus of this fast-paced 2.25-hour session, which features seven short presentations and case studies from top electrophysiologists at Cleveland Clinic and elsewhere.

Practicality will be at a premium, as revealed by presentation titles such as "The PVs are isolated: Now what?" and "His bundle pacing: When and how?"

Keeping up to date is also a priority, as faculty will review the data behind new techniques and technologies for diagnosing and treating complex arrhythmia cases in presentations such as "The year in EP: Top advances and new frontiers" and "AF post-CABANA: Ablation in the real world and patient-reported outcomes."

Additional areas of focus include challenging cases of left atrial appendage closure, hemodynamic support in high-risk ventricular tachycardia ablation, and diagnostic and therapeutic approaches to ventriculo-nodal pathways.

➤ Visit ccfcme.org/hrsep19 to register and for the full agenda and faculty listing.

Lead Management 2019: What Have We Learned and What Questions Remain?

Wed., May 8, 2019, 6:30-9:15 p.m. (complimentary dinner program)
InterContinental San Francisco
Official educational satellite session at Heart Rhythm 2019

New technologies in cardiac implantable electronic devices (CIEDs) present new challenges for device and lead extraction. That's the premise of this jam-packed 2.25-hour session featuring short talks and case presentations from six expert electrophysiologists from Cleveland Clinic and other leading U.S. centers.

The focus is the fast-evolving landscape of CIED and lead management, and faculty will share the latest on best practices for minimizing infection risk and performing lead and device extractions when indicated. Special attention will be paid to specific emerging scenarios, such as extraction of leadless pacemakers.

The scope of presentations ranges from hyperpractical specificity ("When the coronary sinus lead doesn't just slide out") to big-picture thought leadership ("How can we prepare the next generation of electrophysiologists for the next wave of lead extraction?"). In between are talks devoted to lessons in CIED infection learned from the PADIT and WRAP-IT trials, tips on preoperative imaging for transvenous lead extraction, and more.

The last 45 minutes are devoted to real-world case presentations with audience participation.

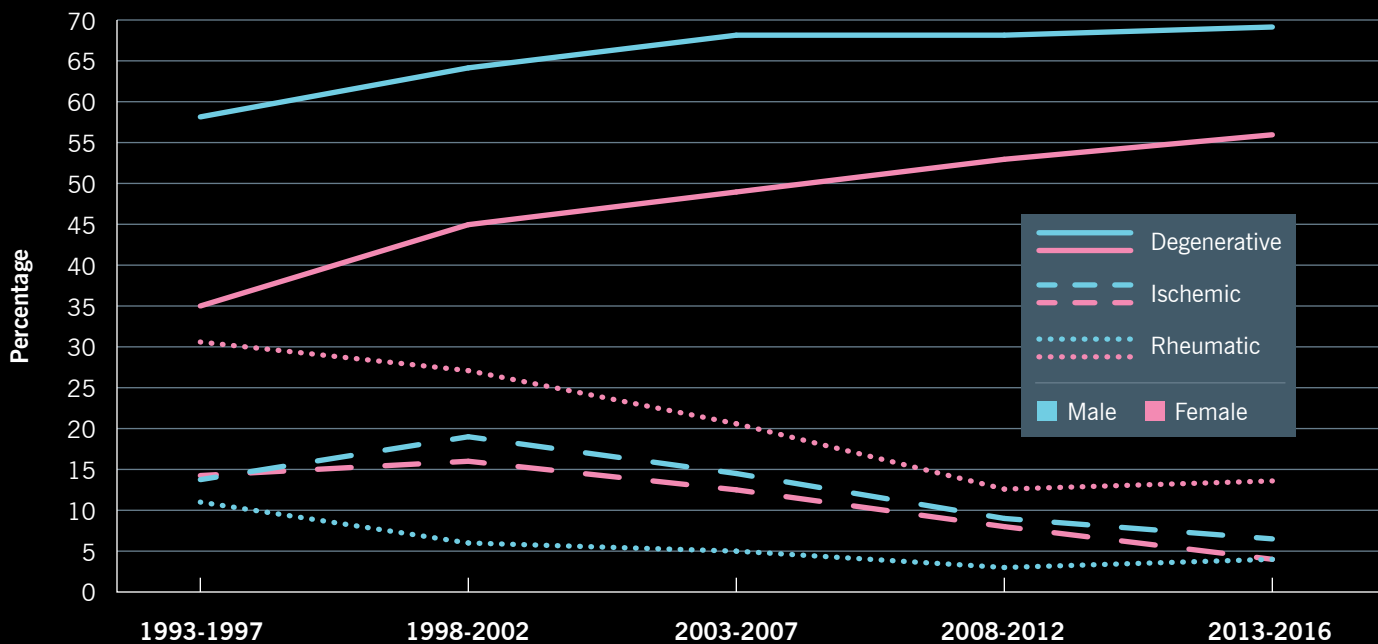
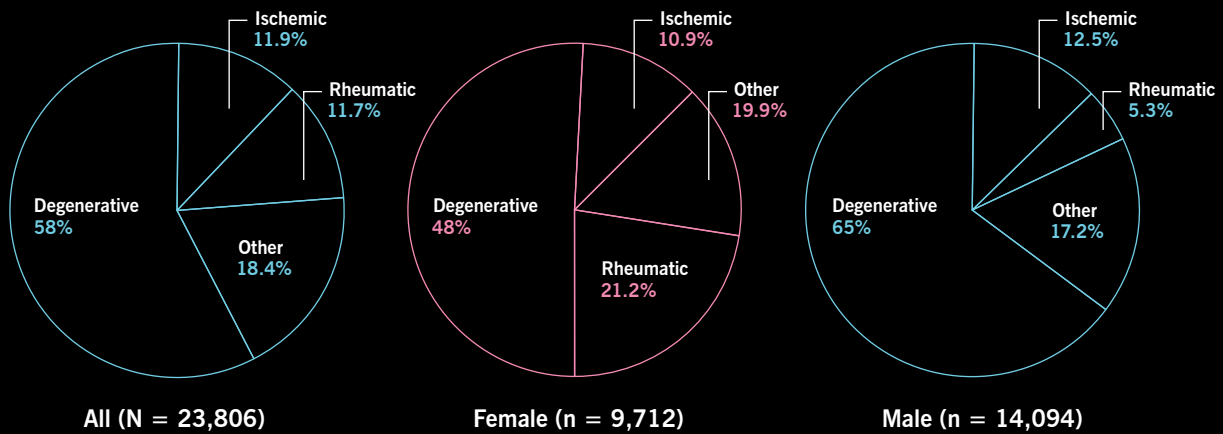
➤ Visit ccfcme.org/hrsleadmgt19 to register and for the full agenda and faculty listing.

The programs described above are not part of the Heart Rhythm 2019 Official Scientific Sessions as planned by the Heart Rhythm Society Scientific Sessions Program Committee. They are neither sponsored nor endorsed by the Heart Rhythm Society.

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



Image of the Issue



MITRAL VALVE DISEASE ETIOLOGY: EFFECTS OF SEX AND TIME

Studies generally haven't accounted for sex differences in the etiology of surgically treated mitral valve disease or changes in etiology over time. Suspecting that such differences might help explain differences in surgical procedure choice and outcomes between male and female patients, Cleveland Clinic researchers analyzed 23,806 consecutive patients who underwent primary mitral valve operations at their institution from 1993 to 2016.

As shown in the pie charts above, they found that between-sex differences in prevalence of the three main disease types — degenerative, ischemic and rheumatic — were highly

significant ($P < .001$), with much higher rates of rheumatic disease in women and much higher rates of degenerative disease in men.

As shown in the line graph above, they also found that prevalence of degenerative disease rose significantly over time, while prevalence of ischemic and rheumatic disease declined ($P < .001$ for all).

The study was published in *Circulation* (2018;138:1749-1751). For commentary on the findings from co-author Leslie Cho, MD, see the study recap on page 7. ■

Cardiac Consult



Live CME Events from Cleveland Clinic

Valve Disease, Structural Interventions and Diastolic Dysfunction

Fri.-Sun., March 8-10, 2019

Loews Portofino Hotel | Orlando, Florida

Information/registration: ccfcme.org/echo

Controversies and Consensus in the Prevention and Management of Cardiovascular Disease in 2019

Fri., March 15, 2019, 7-9:15 p.m.

(complimentary dinner symposium)

The Westin New Orleans Canal Place | New Orleans

An independent certified session at the American College of Cardiology Scientific Session (ACC.19)

Information/registration: ccfcme.org/cvprevention

Clinical Challenges in EP Practice: Innovations and Solutions 2019 and Beyond

Tues., May 7, 2019, 6:30-9:15 p.m.

(complimentary dinner program)

InterContinental San Francisco | San Francisco

An official educational satellite session at Heart Rhythm 2019

Information/registration: ccfcme.org/hrsep19

(see page 18 for more detail)

Lead Management 2019: What Have We Learned and What Questions Remain?

Wed., May 8, 2019, 6:30-9:15 p.m.

(complimentary dinner program)

InterContinental San Francisco | San Francisco

An official educational satellite session at Heart Rhythm 2019

Information/registration: ccfcme.org/hrsleadmgt19

(see page 18 for more detail)

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



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