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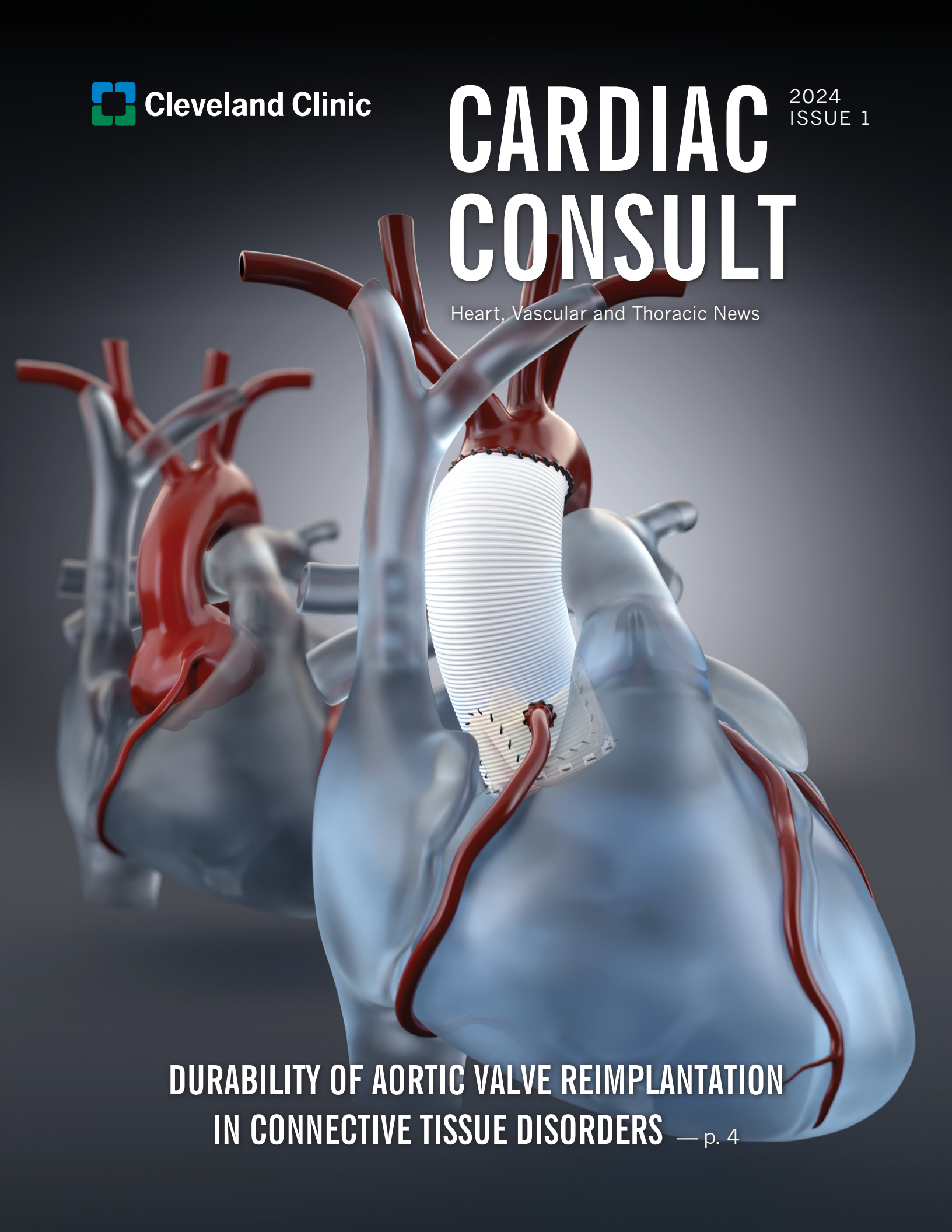


DURABILITY OF AORTIC VALVE REIMPLANTATION IN CONNECTIVE TISSUE DISORDERS — p. 4

DEAR COLLEAGUES,

This issue of *Cardiac Consult* features insights from surgical series involving fairly uncommon procedures — mitral valve re-repair (page 3) and aortic valve reimplantation in patients with connective tissue disorders (pages 4-5).

Our clinical teams amass the volumes and experience necessary to yield insights in these specialized areas because of Cleveland Clinic's long-standing approach to attracting and developing cardiothoracic surgeons with super-specialization in sub-areas of cardiac and thoracic surgery. That approach is captured in the feature story on pages 8-9, which introduces four dynamic surgeons who recently joined our Department of Thoracic and Cardiovascular Surgery.

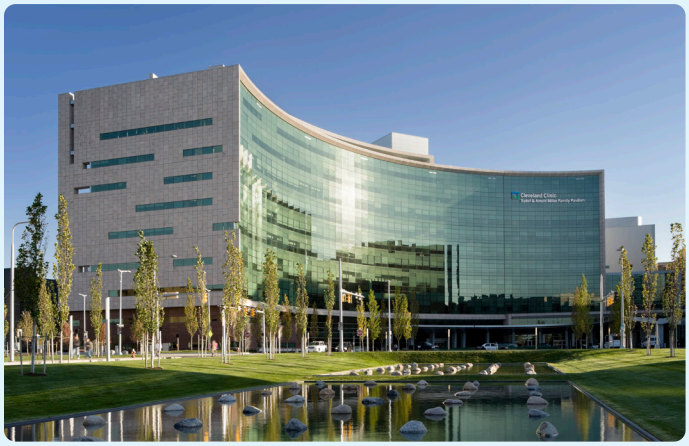
As the story notes, for decades the department has intentionally sought surgeons who can do all types of cardiothoracic operations while also bringing specialty skill sets and interests that collectively meet the full spectrum of complex patient needs.

Our latest hires take this approach to a new level, as they give our surgical team bench strength and diversity unsurpassed in our history. As Department Chair Dr. Marc Gillinov notes, this ensures an intergenerational continuity of expertise that should sustain Cleveland Clinic as a resource for the most challenging cardiothoracic cases for many years to come.

We invite you to consider Cleveland Clinic as a resource for your patients' referral needs. Our newest surgeons are allowing us to extend our culture of cardiothoracic excellence to more patients than ever before.

Respectfully,

Lars G. Svensson, MD, PhD
Chief, Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute



Cleveland Clinic's Miller Family Heart, Vascular & Thoracic Institute is nationally and internationally renowned as a leader in cardiovascular care. Its teams are dedicated to continuously improving upon their standard-setting clinical outcomes, unsurpassed volumes and experience, and rich legacy of innovation and research leadership.

ON THE COVER — Illustration of a typical Marfanoid aortic root before (background) and after (foreground) replacement with aortic valve-sparing reimplantation. The cover story starting on page 4 shares results and insights from a large cohort study showing that valve reimplantation in patients with Marfan syndrome and other connective tissue disorders can provide excellent event-free survival and aortic valve function.

MITRAL VALVE RE-REPAIR FOR RECURRENT POSTERIOR LEAFLET PROLAPSE

Cleveland Clinic series shows re-repair is feasible with excellent midterm results

An uncommon failure of initially successful mitral valve (MV) posterior leaflet repair with creation of artificial chordae involves the development of posterior leaflet prolapse and apparent elongation of the chordae, caused by normalization of left ventricular morphology.

In such cases, re-repair is likely to be safe, effective and durable whether it's accomplished with creation of new, shorter artificial chordae or with posterior leaflet resection. So found a Cleveland Clinic series of 10 patients who underwent MV re-repair for this unusual complication, as recently described in *JTCVS Techniques*.

"When a patient who had posterior leaflet repair develops recurrent mitral regurgitation with pseudo-elongation of the artificial chordae due to left ventricular reverse remodeling, the problem can often be fixed in a straightforward manner with re-repair of the mitral valve," says study co-author A. Marc Gillinov, MD, Chair of Thoracic and Cardiovascular Surgery at Cleveland Clinic. "When it is anatomically possible, we prefer this approach to valve replacement."

Mitral regurgitation due to degenerative posterior leaflet prolapse can be addressed by two equally effective repair strategies: leaflet resection or creation of artificial chordae. In rare cases, the latter approach leads to failure as the left ventricle undergoes reverse remodeling, causing prolapse of the posterior leaflet and pseudo-elongation of the artificial chordae (Figure).

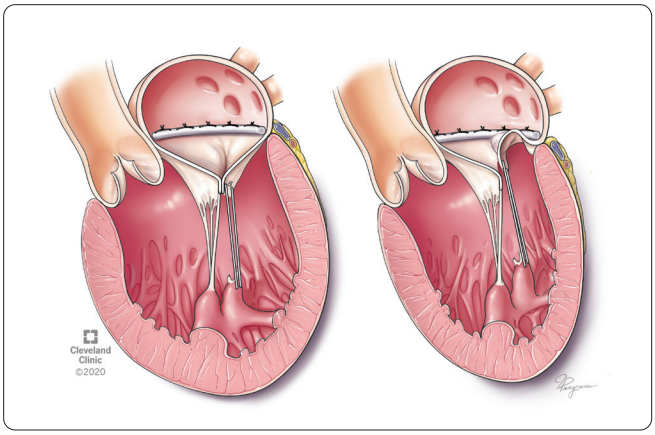


FIGURE — Recurrent mitral regurgitation due to chordal pseudo-elongation. *Left:* A seemingly perfect mitral valve repair using artificial chordae in a markedly enlarged left ventricle. *Right:* As the ventricle shrinks, the artificial chordae appear too long (chordal pseudo-elongation) for the remodeled left ventricle, leading to recurrent posterior leaflet prolapse. Reprinted from Bernabei et al., *JTCVS Techniques* (S2666-2507[23]00397-8), ©2023, with permission from Elsevier.

In two recent articles, Cleveland Clinic surgeons discuss the techniques of MV re-repair and its advantages over valve replacement (*Oper Tech Thorac Cardiovasc Surg.* 2021:26:42-65, and *J Thorac Cardiovasc Surg.* 2022:S0022-5223[22]01023-6). Their newest study was designed to assess outcomes of MV re-repair specifically for repair failure accompanied by posterior leaflet prolapse with pseudo-elongation of the artificial chordae.

Patient characteristics and outcomes

During a recent 15-year period, 11 patients presented to Cleveland Clinic with moderately severe or severe mitral regurgitation due to recurrent prolapse after initially successful posterior leaflet repair with artificial chordae and annuloplasty. Six of the 11 patients were male, mean age was 58 years, median time between initial operation and reoperation was 14 months, and left ventricular diameters were reduced across the cohort.

Reoperation consisted of valve replacement in one patient, with the other 10 undergoing re-repair: half had creation of new, shorter artificial chordae and half had posterior leaflet resection. Eight patients had a new annuloplasty ring implanted. No deaths or major complications occurred. Last echocardiographic follow-up (median of 20 months) showed no more than mild mitral regurgitation.

Lessons from the series

The series demonstrated that re-repair for failure of initial MV repair in this setting of posterior leaflet prolapse due to ventricular remodeling is feasible and effective with excellent midterm outcomes. Re-repair was equally durable whether accomplished with leaflet resection or placement of shorter artificial chordae.

Careful selection of the initial repair technique can help avoid recurrent regurgitation due to posterior leaflet prolapse as ventricular morphology normalizes, notes Cleveland Clinic cardiac surgeon Tarek Malas, MD. "In patients with an enlarged left ventricle, one must be mindful of potential remodeling and, if placing artificial chords, make appropriate length adjustments to avoid recurrent leaflet prolapse if reverse remodeling ensues," he says.

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Contact Dr. Gillinov at 216.445.8841 and Dr. Malas at 216.445.1652.

AORTIC VALVE REIMPLANTATION SHOWS LONG-TERM DURABILITY IN PATIENTS WITH CONNECTIVE TISSUE DISORDERS

Many young patients can avoid lifelong anticoagulation with a valve-sparing approach

Patients with Marfan syndrome or other connective tissue disorders (CTDs) often require prophylactic aortic root replacement at a relatively young age, yet there has been uncertainty about how durable reimplanted myxomatous aortic valves are in these individuals. Now a new study from Cleveland Clinic offers reassurance about the long-term durability of valve-sparing approaches in this complex patient population.

"Treatment decisions in these patients — whether to replace the aortic valve or attempt repair with a valve-sparing approach — carry lifelong ramifications," says the study's lead author, Lars Svensson, MD, PhD, Chief, Cleveland Clinic Heart, Vascular & Thoracic Institute, and Surgical Director of the Cardiovascular Marfan and Connective Tissue Disorder Clinic. "Our data show that valve reimplantation in this setting is associated with excellent event-free survival and valve function through at least 10 years while freeing patients of the established risks of anticoagulation that come with mechanical composite valve grafts."

Study backdrop and design

The current study (*J Thorac Cardiovasc Surg.* 2023;166:1617-1626) extends and expands upon an earlier series reported by Dr. Svensson and colleagues involving 178 Cleveland Clinic patients with CTDs. That analysis (*Ann Thorac Surg.* 2013;95:555-562) showed that prophylactic root and valve preservation using David reimplantation was safe and provided excellent midterm effectiveness with a low risk of late events.

In the updated series, the investigators retrospectively analyzed patients who underwent elective aortic valve reimplantation surgery at Cleveland Clinic up to 2020. Of these, 214 had a CTD and 645 did not. The CTD cohort consisted of 164 patients (77%) with Marfan syndrome, 23 (11%) with Loeys-Dietz syndrome, seven (3%) with Ehlers-Danlos syndrome and 20 (9%) with other CTDs.

Patients with CTDs were significantly younger than those without CTDs (mean age of 39 vs. 53 years) and were more likely to be women, less likely to have aortic regurgitation, and more likely to have mitral valve regurgitation, left ventricular dysfunction and chronic obstructive pulmonary disease.

To adjust for differences between the two groups, 96 CTD patients were matched to 96 non-CTD patients using propensity scores. Outcomes were compared over follow-up that continued beyond 15 years in some patients and for more than nine years in 25% of the cohort.

Key findings

Results in the overall CTD cohort. Among the overall cohort of 214 patients with a CTD, initial results were excellent, with no operative deaths, one stroke (0.47%) and one early valve reoperation (0.47%). Over longer follow-up, 97% of patients remained free from valve reoperation at five years and 95% at 12 years. All reoperations (n = 5) were among patients with Marfan syndrome. Survival was 96% at five years and 92% at 12 years. At 10-year echocardiographic follow-up, 86% of patients had no aortic regurgitation, 11% had mild regurgitation and 3% had moderate regurgitation.

"These findings all compare favorably to those in the general reimplantation population," Dr. Svensson notes.

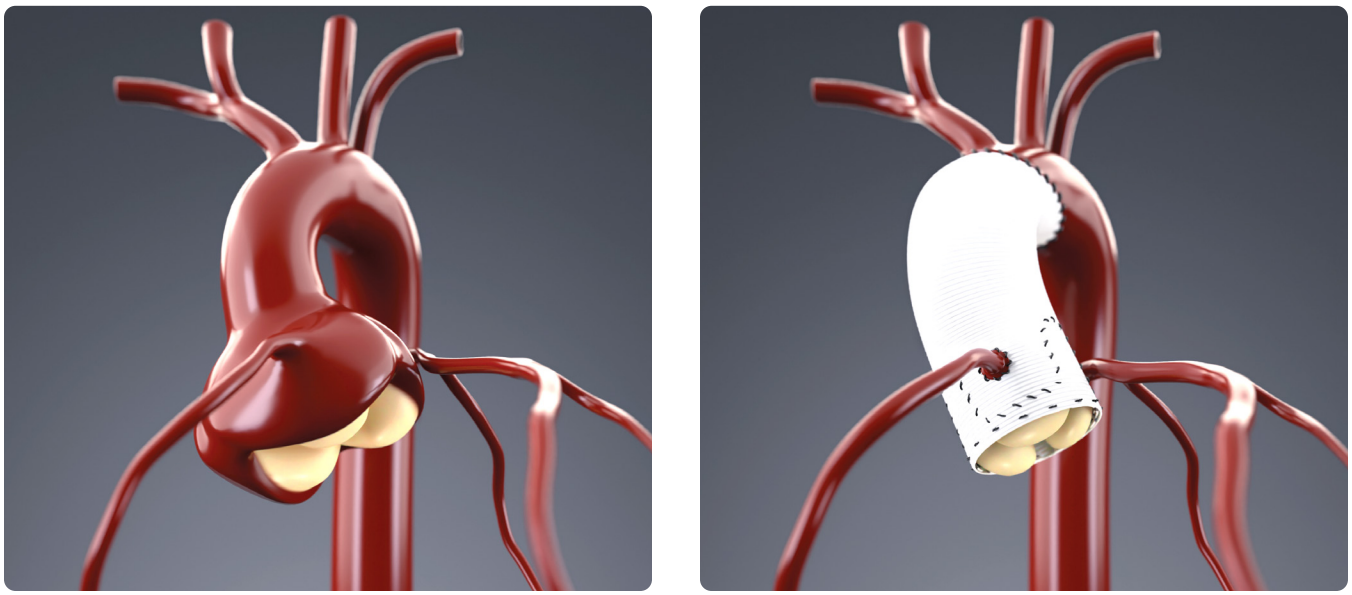
Comparative results from the propensity-matched cohorts. In the propensity-matched cohorts, there were no significant differences between the groups with and without CTDs in terms of in-hospital outcomes, longitudinal aortic regurgitation and mean gradient, risk of aortic valve reoperation, or risk of late death. Notably, the share of patients with 10-year freedom from aortic valve reoperation was nonsignificantly higher in the CTD group than in the non-CTD group (98% vs. 93%; $P = .3$).

Implications for practice and advising patients

"These long-term results help validate aortic valve reimplantation as a durable option with low rates of valve deterioration in patients with connective tissue disorders," says Dr. Svensson. "Freedom from reoperation compared favorably even to published outcomes with mechanical valve grafts."

The authors attribute the excellent durability to proper patient selection aimed at avoiding use of valves with large fenestrations.

BELOW — Illustration of a typical Marfanoid aortic root before replacement (left) and after replacement with aortic valve-sparing reimplantation (right).



They note that intraoperative assessment of leaflet pathology and fenestrations is critical in selecting appropriate candidates. Downsizing annular dimensions to normal by use of a Hegar dilator also likely optimized cusp coaptation.

"After weighing the need for lifelong anticoagulation and risk of bleeding with mechanical valves, many patients with connective tissue disorders should consider an attempt at valve repair when undergoing root replacement if acceptable valve tissue is present," Dr. Svensson observes.

The authors note that a randomized trial comparing reimplantation with composite valve grafts would be ideal for determining the best approach for patients with CTDs, although the likelihood of such a study is highly uncertain. And they caution that the results they report may differ at lower-volume centers without Cleveland Clinic's extensive experience with aortic valve reimplantation, given the complexity of the operation, particularly in the setting of tissue fragility often seen with CTDs.

"Regardless of the surgical approach taken, close lifelong echocardiographic monitoring is required in this high-risk patient population," adds co-author Vidyasagar Kalahasti, MD, a cardiologist who serves as Medical Director of Cleveland Clinic's Cardiovascular Marfan and Connective Tissue Disorder Clinic. "Even so, valve-sparing aortic root replacement is a game changer for patients with connective tissue disorders, as it allows aortic valve preservation without the patient needing to take anticoagulation or suffer early bioprosthetic valve degeneration."

"These real-world data provide reassurance that we can achieve lasting outcomes when reimplanting valves in suitable patients with connective tissue disorders," Dr. Svensson concludes. "While lifelong imaging follow-up is still needed, we can tell appropriate patients that bioprosthetic and mechanical valve options may not offer advantages over preserving their native aortic valve."

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Contact Dr. Svensson at 216.445.4813 and Dr. Kalahasti at 216.445.7259.

Our data show that valve reimplantation in this setting is associated with excellent event-free survival and valve function through at least 10 years while freeing patients of the established risks of anticoagulation that come with mechanical composite valve grafts. — LARS SVENSSON, MD, PHD

RESEARCH ROUNDUP FROM RECENT CARDIOVASCULAR MEETINGS

Takeaways from major trials with key Cleveland Clinic involvement

PARTNER 3: Similar 5-Year Outcomes for TAVR and SAVR in Low-Risk Patients

Extended follow-up from the PARTNER 3 trial comparing transcatheter and surgical aortic valve replacement (TAVR and SAVR) in patients at low surgical risk showed statistically comparable rates of a composite of death, stroke and rehospitalization — and of the individual component events — at five years. The results, presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2023 conference and published in the *New England Journal of Medicine* (2023;389:1949-1960), represent an attenuation of the differences seen at one year, which had favored TAVR.

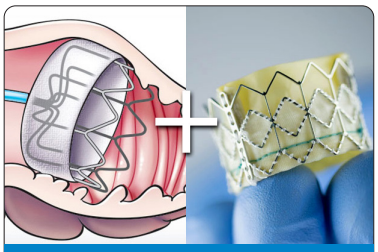
"Prior randomized trials have shown similar five-year outcomes for TAVR and SAVR in high- and intermediate-risk patients, but comparative outcomes beyond two years in low-risk patients hadn't been reported," says study co-author Samir Kapadia, MD, Chair of Cardiovascular Medicine at Cleveland Clinic. "Because low-risk patients tend to be younger than patients at higher risk, longer-term outcomes are especially important to decision-making in this group."

At five-year follow-up among the trial's 1,000 patients, Kaplan-Meier event rates for the composite primary endpoint of death, stroke and rehospitalization were 22.8% in the TAVR arm and 27.2% in the SAVR arm ($P = .07$). This statistically similar result was maintained across all major patient subgroups. Additionally, rates of bioprosthetic valve failure were highly comparable between the two treatment arms. The only endpoint that differed significantly between the arms was valve thrombosis, which occurred more often with TAVR than SAVR (incidence of 2.5% vs. 0.2%).

Follow-up will continue for 10 years. "In SAVR studies, valve degradation is usually not expected until eight to 10 years after surgery, so the 10-year data from this trial will be of great interest, not only for survival, but also to see if there are any consequences of the elevated valve thrombosis with TAVR," notes Cleveland Clinic cardiothoracic surgeon Lars Svensson, MD, PhD.

WATCH-TAVR Supports Concurrent TAVR and Watchman Placement

In patients with severe aortic stenosis and atrial fibrillation (AF) undergoing TAVR, a strategy of concurrent TAVR and left atrial appendage occlusion (LAAO) with the Watchman™ 2.5 device is noninferior to TAVR plus medical therapy with anticoagulation. So concluded the randomized controlled WATCH-TAVR trial, presented by Cleveland Clinic's Samir Kapadia, MD, at the TCT 2023 conference and published in *Circulation* (Epub 24 Oct 2023).



WATCH-TAVR trial of TAVR + LAAO

A strategy of concomitant TAVR and LAAO with Watchman was found noninferior to TAVR plus anticoagulation therapy in a randomized trial.

The Cleveland Clinic-led multicenter trial was prompted by the 15% to 40% prevalence of AF among TAVR patients and by evidence that AF raises the risk of death, stroke and rehospitalization among patients undergoing TAVR.

The study was conducted as a prospective, open-label investigation among 349 patients with planned TAVR and documented AF. Patients were randomized 1:1 to TAVR plus concurrent LAAO with the Watchman 2.5 device (this was before FDA approval of the Watchman FLX) or to TAVR plus medical therapy (i.e., anticoagulation with or without antiplatelet therapy). A noninferiority design was used, with the primary endpoint being first occurrence of a composite of all-cause mortality, stroke and major bleeding at two years after TAVR.

Rates of the primary endpoint were 22.7 events/100 patient-years in the TAVR+LAAO arm versus 27.3 in the TAVR+medical therapy arm, which met the predefined criteria for noninferiority but did not demonstrate statistical superiority of TAVR+LAAO.

"Observational studies have suggested that concomitant TAVR and LAAO is feasible and safe," says Dr. Kapadia, the study's first author. "Now, for the first time, a prospective randomized trial has confirmed that these procedures can be performed concurrently without increased risk of complications. These data support LAAO at the time of TAVR as an alternative to chronic oral anticoagulation for the many TAVR patients with a history of AF. This combined procedural approach offers potential benefits in terms of patient convenience, enhanced safety through avoidance of multiple procedures and potential overall cost efficiencies."

CLASP IID: M-TEER Systems Are Comparable at 1 Year

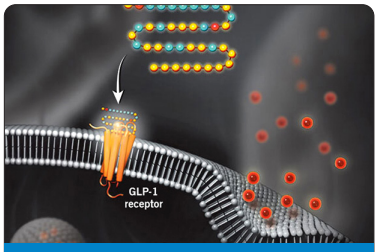
After one year, intervention with the PASCAL transcatheter valve repair system demonstrated noninferiority to intervention with the more established MitraClip™ system for mitral valve transcatheter edge-to-edge repair (M-TEER) in the CLASP IID randomized trial comparing the two M-TEER systems. The results, from 300 patients with severe degenerative mitral regurgitation (MR) at prohibitive risk for mitral valve surgery, updated previously reported 30-day results from CLASP IID that supported FDA approval of the PASCAL system. The new one-year data were presented at the TCT 2023 conference and published in *JACC: Cardiovascular Interventions* (2023;16:2803-2816).

Noninferiority of PASCAL for the primary endpoints — safety (30-day composite major adverse events [MAEs]) and efficacy (six-month MR ≤ 2+) — persisted across the full study cohort. Between-group differences in survival, freedom from heart failure hospitalization and MAE rates were nonsignificant at one year, and both groups sustained significant improvements from baseline in functional classification and quality of life.

"These one-year outcomes are reassuring, considering this very frail population who are not surgical candidates," says study co-author Samir Kapadia, MD, principal investigator at CLASP IID's Cleveland Clinic site. "They support PASCAL as a good therapy option for high-risk patients." Follow-up continues through five years.

SELECT: CV Prevention Benefit Achieved in Patients With Obesity but No Diabetes

For the first time, a pharmacotherapy for overweight and obesity has been shown to reduce cardiovascular events in patients with established cardiovascular disease (CVD) in the absence of type 2 diabetes. The finding, achieved with the GLP-1 receptor agonist semaglutide in the multicenter SELECT trial, establishes overweight/obesity as a modifiable risk factor for CVD, according to lead investigator A. Michael Lincoff, MD, of Cleveland Clinic, who presented the study at the American Heart Association (AHA) Scientific Sessions 2023. Results were simultaneously published in the *New England Journal of Medicine* (2023;389:2221-2232).



SELECT trial of semaglutide

The GLP-1 receptor agonist was found to reduce cardiovascular events in patients with overweight or obesity without diabetes.

The study's 17,604 participants had a body mass index of 27 or greater and preexisting CVD without diabetes. They were randomized 1:1 to receive semaglutide 2.4 mg once weekly or placebo on top of standard-of-care CVD therapy. Over mean follow-up of 40 months, the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke occurred 20% less often with semaglutide versus placebo ($P < .001$). The protective effect was seen regardless of sex, ethnicity, age and baseline body weight.

"This is the first pharmacologic intervention for overweight or obesity that's been shown in a rigorous fashion to reduce the risk of cardiovascular events," Dr. Lincoff notes.

Novel siRNA Reduces Lp(a) by Over 90% for 48 Weeks

A novel short interfering RNA (siRNA) therapy known as lepodisiran reduced levels of lipoprotein(a), or Lp(a), below the lowest limit of quantitation for nearly nine months in a first-in-human phase 1 trial. Results of the study, presented by Cleveland Clinic's Steven Nissen, MD, at the AHA Scientific Sessions 2023 and published in *JAMA* (2023;330:2075-2083), represent the most potent and durable Lp(a)-lowering effect with any therapy to date.

The study randomized 48 adults with Lp(a) ≥ 75 nmol/L but no known cardiovascular disease to placebo or one of six doses of lepodisiran, each given as a single subcutaneous injection. Lepodisiran disappeared from patients' plasma within 48 hours of administration in all dose groups and showed good tolerability, with no serious treatment-related adverse events. Meanwhile, the highest doses of lepodisiran yielded long-lasting reductions in Lp(a), with the highest dose lowering Lp(a) to a level undetectable by the standard assay from day 29 to day 281 following administration, and to a level 94% below baseline at the end of the 48-week study.

"This is an unprecedented degree and duration of Lp(a) reduction, which suggests lepodisiran could potentially be given once or twice a year, like a vaccine," says Dr. Nissen. "Elevated Lp(a) is currently an untreatable risk factor for CVD, so the implications of these effects could be significant." Lepodisiran is now in phase 2 testing, with a phase 3 trial being planned.

Contact Dr. Kapadia at 216.444.6735, Dr. Svensson at 216.445.4813, Dr. Lincoff at 216.444.2367 and Dr. Nissen at 216.445.3224.

INTRODUCING OUR NEWEST CARDIOTHORACIC SURGEONS

Four recent hires add bench strength and diversity to meet complex patient needs

Cleveland Clinic's Department of Thoracic and Cardiovascular Surgery has long been one of the largest in the nation, but it recently surpassed a growth marker never before achieved in its distinguished history: the hiring of four new staff surgeons within a 12-month period.

The new surgeons — who are individually profiled below — have given the department an unprecedented degree of diversity while also enhancing its bench strength. "We have been busier than ever before and are performing more complex operations," says A. Marc Gillinov, MD, who chairs the department. "We therefore needed to grow and expand our expertise, and we have very intentionally brought in surgeons who can do all types of cardiothoracic operations while also bringing specialized skill sets to specifically address targeted areas of patient need."

He adds that the staff additions align with a principle that's guided the department since it was chaired by Floyd (Fred) Loop, MD, and Delos (Toby) Cosgrove, MD, from the mid-1970s to the mid-2000s: Find and hire the best people you can for each position. "Why did we hire all four at this time?" he says. "Because they were the best people in the country, if not the world, for their positions."

It also helped that all four new surgeons spent at least a year of their training at Cleveland Clinic, which ensured a good fit with the department's culture.

The hires are also part of a growth strategy for the department to make sure that all key areas of specialty interest have an appropriate age distribution of surgeons. "If you look at our array of surgeons in each area — aortic surgery, robotic surgery, reoperative surgery, heart failure and others — we have surgeons in the first third of their career, surgeons in the middle third of their career and surgeons in the last third of their career," Dr. Gillinov explains. "This ensures a continuity of expertise that gets passed from one generation to the next."

The result, he adds, is an opportunity to bring more expertise to bear for patients, especially those requiring very complicated operations or minimally invasive operations. "We increasingly face complex problems that require our surgeons to work together, which demands a large enough cadre of surgeons to take care of the patients," Dr. Gillinov concludes.

Donna Kimmaliardjuk, MD

Specialty interests: Off-pump CABG; multi-arterial and total arterial bypass grafting; single-vessel small thoracotomy bypass grafting (MIDCAB)

A bit about her training: "I completed a fellowship in advanced cardiac surgery at Cleveland Clinic, which gave me exposure to a breadth of cardiac operations, including high-risk cases and very sick patients."

Research interests: "I continue to be curious about coronary arteries and revascularization, and I would love to understand better how we can optimize conduit selection for targets, such as through consideration of the functional severity of blockages. I also plan to continue doing research looking at cardiovascular health and outcomes of minority populations — namely, women and Indigenous and Black populations."

What's something that excites you about practice today? "The opportunity to address the historical underrepresentation of women in cardiovascular research and the underdiagnosis and undertreatment of heart disease in women. As a female cardiac surgeon, I feel a responsibility to help improve outcomes for women undergoing cardiac surgery. We also know that having a diverse and representative group of health professionals improves patients' access to care, perceptions of care, and care outcomes. As an Inuit woman, I think it's important for women wanting to pursue medicine to see themselves reflected in these positions and know that it's possible to be a female cardiac surgeon."

"[Our strategy] ensures a continuity of expertise that gets passed from one generation to the next."

— A. MARC GILLINOV, MD

Xiaoying Lou, MD

Specialty interests: Aortic aneurysms, dissections and stenosis; connective tissue disorders; heart valve disease

A bit about her training: "During my integrated cardiothoracic surgery training at Emory University, I also obtained an MS in clinical research as part of an NIH TL1 postdoctoral research training award. I then completed an aortic surgery fellowship at Cleveland Clinic before starting as staff."

Research interests: "I'm interested in open and endovascular aortic surgery as well as valvular surgery outcomes, at both an institutional database level and a national trial level. I also plan to help integrate advanced imaging modalities, such as 4D MRI, into our growing database of aortic tissue histology and biomechanics to better understand the risk of aortic catastrophes and optimize surgical outcomes in this complicated patient population."

What's something that excites you about practice today? "Opportunities for mentorship, which is what led me to cardiac surgery. I've been lucky to have amazing mentors throughout my training, and I am passionate about passing on the wisdom and experience I have gained from them. I have tremendous interest in mentoring anyone who is considering the field of cardiothoracic surgery, but particularly women and minorities who traditionally may not have had many mentors who looked like them. Mentorship is critical to the growth and success of our specialty."

Tarek Malas, MD

Specialty interests: Minimally invasive surgery; robotic surgery; percutaneous structural interventions; complex valvular disease; CABG; atrial fibrillation surgery

A bit about his training: "I have been fortunate to train at some of the largest and best centers in North America for minimally invasive and complex disease, including training in robotic and minimally invasive cardiac surgery under Dr. Marc Gillinov here at Cleveland Clinic."

Research interests: "A background in both engineering and medicine has given me an excellent basis for innovative research. I have particular interest in mitral and aortic valve disease, with an emphasis on minimally invasive approaches. I also enjoy research on tackling challenges in our healthcare system at a population level, which stems from my background in public health."

What's something that excites you about practice today? "One of the most exciting developments in cardiac surgery is the collaboration between cardiac surgery and cardiology to perform procedures using a minimally invasive or hybrid approach. This can significantly improve recovery times and help patients return to their daily lives more quickly with the same overall excellent outcomes that are achievable with a more invasive open-heart surgery."

Anthony Zaki, MD

Specialty interests: Heart transplantation; ventricular assist devices; arterial coronary revascularization; pericardiectomy; aortic surgery

A bit about his training: "I was fortunate to complete my cardiothoracic residency training at Cleveland Clinic with advanced training in heart and lung transplantation and mechanical circulatory support, including ventricular assist devices."

Research interests: "My research interests are focused on optimizing surgical management of advanced heart failure, whether with heart transplantation or mechanical support. I'm also interested in the ways mechanical support can be used to assist conventional cardiac surgery and prevent cardiovascular deterioration in high-risk patients."

What's something that excites you about practice today? "Modern cardiac surgery is less than a century old, yet it's constantly evolving and innovating, especially in the past decade. It is an exhilarating time to practice heart surgery at Cleveland Clinic and to be able to offer patients and their families the full breadth of cardiovascular care in a less invasive and more reliable manner."

Contact Dr. Gillinov at 216.445.8841, Dr. Kimmaliardjuk at 216.445.7208, Dr. Lou at 216.445.7808, Dr. Malas at 216.445.1652 and Dr. Zaki at 216.444.5613.

LIPOPROTEIN(a): PROMISING PROGRESS ON ONE OF THE LAST UNTREATABLE FRONTIERS OF CARDIOVASCULAR RISK

It's time to increase testing for this major cardiovascular risk factor in advance of new therapies

Once a week, Steven Nissen, MD, has a clinic in which almost every patient has elevated levels of lipoprotein(a), or Lp(a). Patients come to this clinic from around the world, yet their profiles are highly similar: Most have had multiple family members suffer a myocardial infarction (MI) or stroke — and/or undergo bypass surgery or coronary stent placement — by their 40s or 50s.

"These patients typically tell us, 'I just had my Lp(a) checked and it's really high; I'm scared to death,'" relates Dr. Nissen, Chief Academic Officer for Cleveland Clinic's Heart, Vascular & Thoracic Institute. He adds that while there are currently no FDA-approved therapies for lowering Lp(a) levels, there are now four promising investigational therapies in clinical trials, and Cleveland Clinic is leading several of those trials.

"We are a focal point for much of the research into treating Lp(a)-related cardiovascular risk," Dr. Nissen says, "and we are advocates for patients getting their Lp(a) levels checked. In addition to raising awareness of Lp(a) as an important risk factor, this identifies individuals at elevated risk of cardiovascular events so we can treat all their other risk factors super aggressively and consider enrollment in a clinical trial of an investigational therapy if appropriate."

Genetically determined supercharger of risk

Dr. Nissen and his Cleveland Clinic colleagues are increasingly focused on Lp(a) because of the emergence of the investigational therapies and because the clinical impacts of Lp(a) elevation, although once underappreciated, have grown increasingly apparent in recent years.

Those impacts manifest as a heightened risk — and often an accelerated course — of cardiovascular disease, particularly premature MI, venous thromboembolism and calcific aortic stenosis. "Elevated Lp(a) can nearly double the risk of atherosclerotic cardiovascular disease and aortic stenosis," Dr. Nissen says, "and it tends to lead to disease at a younger age."

Elevated Lp(a) is a genetically determined risk factor, and there is no evidence that Lp(a) level changes over the course of a lifetime. Normal Lp(a) levels are less than 25 mg/dL. Significant risk of atherothrombotic events begins at levels between 50 and 70 mg/dL and rises thereafter. And that risk is quite prevalent: 64 million U.S. residents have an Lp(a) level of 60 mg/dL or higher. More than 3 million have levels of 180 mg/dL or greater, which confer extremely high risk.

"Lp(a) is an important cause of early and aggressive coronary disease, particularly in individuals without other traditional cardiovascular risk factors," says Luke Laffin, MD, a staff cardiologist in Cleveland Clinic's Section of Preventive Cardiology. "We have no FDA-approved therapies to reduce Lp(a) and its related cardiac risk, so this has been a substantial challenge we've been unable to treat."

Indeed, Lp(a) levels are unaffected by available lipid-lowering therapies or by lifestyle interventions. "Elevated lipoprotein(a) is one of the last untreatable frontiers of cardiovascular risk," Dr. Nissen notes.

A booming therapeutic landscape

That may soon change, however, in view of the development of several investigational therapies known collectively as nucleic acid therapeutics.

To best understand these therapies, it's helpful to review a few Lp(a) essentials. Lp(a) is a variant of low-density lipoprotein (LDL) that contains an atherogenic component, apolipoprotein B100, and a prothrombotic component, apolipoprotein(a). Elevated blood Lp(a) levels are mostly due to genetic variations in the *LPA* gene that encodes apolipoprotein(a). Nucleic acid therapeutics are designed to silence the *LPA* gene to reduce elevated Lp(a) levels and their harmful effects.

There are two classes of nucleic acid therapeutics — antisense oligonucleotides and short interfering RNAs (siRNAs) — that both act by degrading the messenger RNA that codes for apolipoprotein(a). Both conjugate with *N*-acetyl-galactosamine (GalNAc), a sugar that binds to receptors in hepatocytes. This concentrates the therapeutic in the liver, where it blocks the synthesis of apolipoprotein(a) required for Lp(a) formation while minimizing its presence in the circulation.

Four nucleic acid therapeutics — all administered subcutaneously — are now in clinical testing, as follows:

- *Pelacarsen.* This antisense oligonucleotide, given once monthly, is being studied in the phase 3 Lp(a) HORIZON outcomes trial (NCT04023552) in a collaboration between the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and Novartis. Results may be available in 2025.
- *Olpasiran.* This siRNA, given every 12 weeks, is being assessed in the phase 3 OCEAN(a) outcomes trial (NCT05581303). Results are expected in 2027.
- *Zerlasiran.* This siRNA (dose frequency still to be determined) is being studied in a phase 2 trial coordinated by C5Research and Silence Therapeutics.
- *Lepodisiran*. This siRNA, which can likely be given once or twice a year, is being evaluated in a phase 2 trial (NCT05565742) in a collaboration between C5Research and Eli Lilly. A phase 3 trial is also being planned.

Lepodisiran is particularly intriguing, says Dr. Nissen, who presented results of a phase 1 trial of the agent at the American Heart Association Scientific Sessions 2023 (also published in *JAMA.* 2023;330:2075-2083). "A single dose of lepodisiran lowered Lp(a) to a level undetectable by the standard assay from day 29 to day 281 following administration, and to a level 94% below baseline at the end of the 48-week study," he says. "This is an unprecedented degree and duration of Lp(a) reduction, which suggests lepodisiran could potentially be given once or twice a year, like a vaccine."

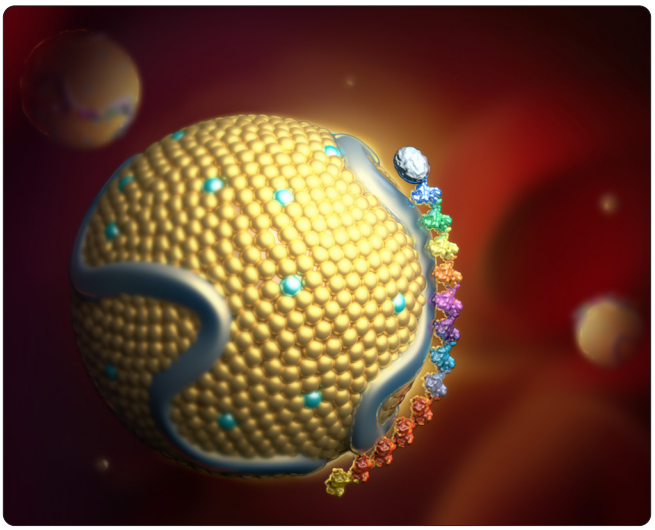
Because the Lp(a) HORIZON and OCEAN(a) studies are both outcome trials, they should help determine whether significant Lp(a) lowering reduces major adverse cardiovascular events in individuals with Lp(a) elevation, as well as the magnitude of Lp(a) reduction needed to yield event reduction.

An imperative for broader Lp(a) testing

Since no large trials have previously assessed the effects of Lp(a) reduction, this new wave of studies — some of which are international — will also likely yield insights into potential differential effects in different patient subpopulations.

In fact, insights are still emerging on how Lp(a) levels themselves may differ among various groups prior to any treatment. Cleveland Clinic investigators recently bolstered these insights by publishing findings from Lp(a) HERITAGE (*Open Heart.* 2022;9:e002060), the first large study to report Lp(a) and LDL cholesterol levels in patients with atherosclerotic cardiovascular disease (ASCVD) from an ethnically and regionally diverse global population.

This 48,000-patient, six-continent epidemiological study found that median Lp(a) levels were highest in patients who were Black, female or younger than 65. It also revealed important public health findings that applied across the entire cohort:



ABOVE — Illustration of a lipoprotein(a) particle. Elevated blood levels of lipoprotein(a) confer cardiovascular risk independent of other lipid levels and traditional risk factors.

- Only 13.9% of these patients with ASCVD had a known Lp(a) level prior to the study.
- More than 25% of patients had Lp(a) levels above the established threshold for increased cardiovascular risk (50 mg/dL or 124 nmol/L), and 10% had a level of 100 mg/dL or higher.

"The vast majority of patients with ASCVD worldwide are being managed without knowledge of their Lp(a) levels even though over a quarter are at heightened risk because of their Lp(a)," observes Leslie Cho, MD, Co-Section Head of Preventive Cardiology at Cleveland Clinic and a study co-author. "These findings underscore the need for major global educational efforts to promote Lp(a) measurement in routine clinical practice. The emerging therapeutics for Lp(a) reduction can only improve outcomes if physicians are aware of their patients' Lp(a) levels."

"We want clinicians to start assessing Lp(a) now so that when Lp(a)-targeted therapies become available, we'll be ready to treat the patients who need them," Dr. Nissen concludes.

Contact Dr. Nissen at 216.445.3224, Dr. Laffin at 216.444.3666 and Dr. Cho at 216.445.6320.

PERICARDIAL CO_2 INSUFFLATION VIA INTENTIONAL CORONARY VEIN PERFORATION FACILITATES EPICARDIAL ACCESS

Procedure allows for safer epicardial ventricular tachycardia mapping and ablation

Pericardial access for epicardial mapping and ablation for ventricular tachycardia (VT) is sometimes necessary to target areas that cannot be accessed from the endocardium.

The standard procedure involving subxiphoid entry to gain access, first described by Sosa and colleagues in 1996, continues to be challenging. Because the pericardial cavity is normally a virtual space, risks of inadvertent right ventricle puncture and coronary artery injury remain substantial, limiting the procedure to highly experienced operators at specialized centers.

"Being able to access the epicardium has changed the way we do electrophysiology," says Pasquale Santangeli, MD, PhD, Medical Director of Cleveland Clinic's Ventricular Arrhythmia Center. "But it's a procedure in need of innovation to make it safer and more accessible to operators in nonspecialty centers."

Carbon dioxide (CO_2) insufflation of the pericardial cavity via intentional coronary venous perforation from the coronary sinus is emerging as an important method to create safer conditions, as it creates a large and visible target space for subxiphoid puncture. Dr. Santangeli was the first to bring the procedure to the U.S. and is one of a small number of users of the technique in the nation. He recently co-authored a step-by-step description of how it is performed (*J Interv Card Electrophysiol.* 2023;66:109-116), and he reported on the method at Cleveland Clinic's Global EP Summit 2023. Key points of his talk are summarized below.

The need for safer pericardial access

Since pericardial access techniques were introduced nearly 30 years ago, the current standard approach — accessing the virtual space of the pericardial cavity via a subxiphoid approach with a Tuohy or micropuncture needle — has not changed substantially. The technique is associated with a rate of complications up to 10%, highlighting the need for a safer strategy.

During this time, indications for epicardial access have expanded dramatically. Access to the pericardium is also needed to treat some cases of supraventricular arrhythmias and Brugada syndrome, as well as for left atrial appendage ligation with percutaneous epicardial devices. It could also be useful for annuloplasty and to treat patients with preexisting adhesions or localized effusions.

Dr. Santangeli led a review of 60 manuscripts from 1996 to 2013 for complications associated with standard percutaneous epicardial access. Out of 1,591 cases in which the procedure was done for VT, 97% achieved successful access. Major complications — including hemopericardium, tamponade, right ventricle perforation and coronary artery damage — occurred in about 4% of cases, with another 4% involving minor complications.

How CO_2 insufflation is conducted

Dr. Santangeli outlined the major steps involved in CO_2 insufflation of the pericardial cavity via coronary sinus distal vein perforation. He noted that under most circumstances, perforation of the coronary sinus does not result in significant bleeding because of the low systolic and diastolic pressure within the distal coronary sinus.

First, a coronary sinus venogram is used to select the target vessel for puncture (Figure 1). Via femoral venous access, an intracardiac echocardiography catheter (to evaluate pericardial effusion after coronary vein exit) and a deflectable sheath are advanced into the mid-right atrium. Any coronary vein that offers favorable anatomy and permits apical cannulation can serve as the target vessel. About 90% of the time, a posterolateral branch of the coronary sinus is chosen.

After cannulation of the target vessel, exit is performed with a high-tip-weight coronary wire designed for chronic total occlusion interventions. Briskly advancing the wire to exit the coronary vein provides access to the pericardial cavity.

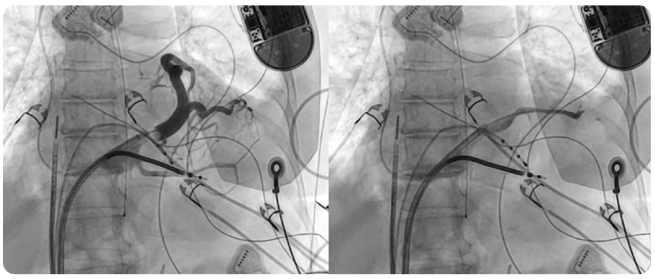


FIGURE 1 — Images depicting selection of the target distal coronary sinus branch for intentional perforation. (Reprinted, with permission, from Cerantola and Santangeli, *J Intervent Card Electrophysiol.* 2022;66:109-116.)

"After perforation of the coronary sinus, if the catheter bends and cannot be advanced into the pericardial space, it may indicate the presence of adhesions," Dr. Santangeli warns. "At that point, we cross over to surgical epicardial access."

After successful access, a CO_2 contrast tank is connected to a syringe, and CO_2 is slowly allowed to passively flow into the pericardial space until adequate separation is achieved (typically with 100-200 mL of CO_2). A slight drop in blood pressure usually results but rarely requires intervention.

Because CO_2 has a low molecular weight, it distributes anteriorly if the patient is supine, displacing pericardial fluid posteriorly (Figure 2). This is the opposite of injecting a contrast agent, which is heavier than pericardial fluid and therefore collects posteriorly.

Once separation of the pericardial space is achieved, subxiphoid epicardial access can be conducted targeting the area of largest pericardial separation as seen by fluoroscopy (Figure 3). A needle preloaded with a wire is used to prevent pericardial deflation after access.

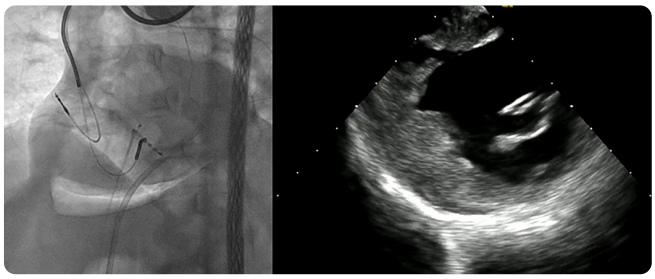


FIGURE 2 — Images showing typical findings — a drop in blood pressure but no posterior effusion, due to the fact that CO_2 is lighter than pericardial fluid and is localized to the anterior right ventricle.

Unanswered questions and future directions

Dr. Santangeli notes that the safety of coronary vein puncture in patients with advanced right ventricular failure and high right atrial pressures has yet to be established, and it is important to ascertain whether there is an excessive risk of bleeding in this situation.

In addition, safety for patients on uninterrupted oral anticoagulation is also unknown. "I suspect it's safe," Dr. Santangeli says. "But in most cases, oral anticoagulation is stopped, so it's unlikely that this issue will ever be adequately studied."

He adds that epicardial access using CO_2 insufflation requires many steps, which can cause operators to become frustrated and switch to a conventional approach.

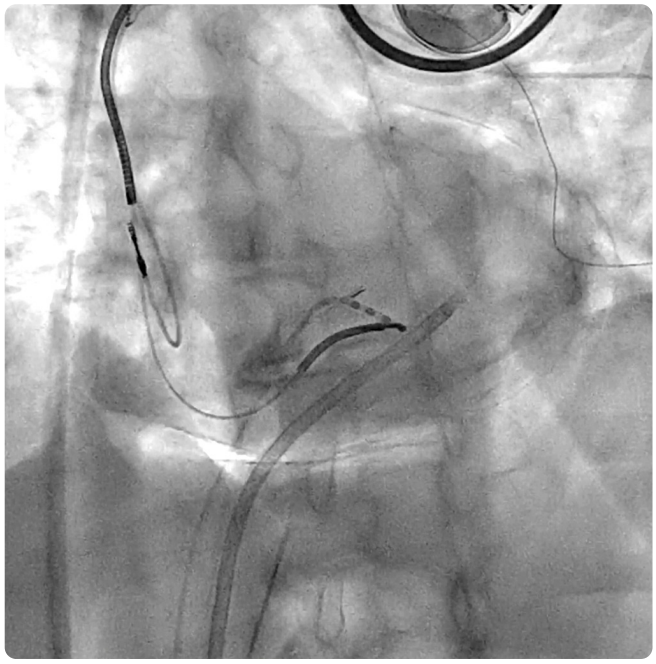


FIGURE 3 — Image showing epicardial access targeting the area of largest pericardial separation on fluoroscopy.

"We need better tools to minimize the number of required procedural steps," he concludes. "Once we simplify the procedure and gain more experience, access to this procedure can be expanded to more operators."

Ultimately, he adds, a prospective randomized trial comparing CO_2 insufflation with "dry" entry into the pericardial space should be conducted.

"Given the substantial risks, pericardial access for epicardial mapping and ablation is currently performed only by centers with deep experience in VT ablation," notes Oussama Wazni, MD, MBA, Section Head of Cardiac Electrophysiology and Pacing at Cleveland Clinic. "With the emergence of intentional perforation of cardiac structures with insufflation of CO_2 to facilitate pericardial access, there is now a path forward to potentially expand this practice to more centers so that more patients can benefit."

Contact Dr. Santangeli at 216.445.1940 and Dr. Wazni at 216.444.2131.

POOLED 2-YEAR OUTCOMES OF DETOUR TRIALS SUPPORT PERCUTANEOUS TRANSFEMORAL ARTERIAL BYPASS

Larger dataset confirms safety, efficacy and durability for superficial femoral artery lesions > 20 cm

There's more evidence that the DETOUR™ percutaneous transfemoral arterial bypass (PTAB) system — which received FDA approval in June 2023 — is a viable alternative to open surgical bypass for long-segment, complex superficial femoral artery (SFA) disease.

Ad hoc analysis of aggregated data from the two prospective, single-arm DETOUR 1 and DETOUR 2 trials, involving 273 patients with two-year follow-up, demonstrates that percutaneous transarterial bypass for complex peripheral artery disease (PAD) lesions is safe and effective, with good durability. Outcomes were presented in a late-breaking clinical trials session at the VIVA (Vascular InterVentional Advances) 2023 conference.

"Combined data from the similarly designed international DETOUR trials further support the use of this PTAB method for long, complex SFA lesions," says presenter Sean Lyden, MD, a study principal investigator and Chair of Vascular Surgery at Cleveland Clinic. "These results provide encouragement that this alternative to traditional open prosthetic bypass surgery will become a more commonly used intervention for patients who previously only had endovascular options with limited durability."

DETOUR system and DETOUR trials in brief

Open femoral-popliteal bypass surgery is the gold standard for treatment of long, complex femoropopliteal lesions. However, its use is limited due to risks of high morbidity, lengthy hospital stays and high readmission rates. Although endovascular intervention is possible for such lesions, restenosis commonly occurs, which limits durability.

The DETOUR system is designed to be a completely endovascular approach for accomplishing bypass for patients with symptomatic femoropopliteal disease involving long lesions (20-46 cm) with chronic total occlusion, in-stent restenosis or diffuse stenosis (>70%) with moderate to heavy calcification. The system involves construction of a percutaneous femoropopliteal bypass using standard endovascular techniques, the Endocross™ novel crossing device and the TORUS™ stent graft (Figure). During the procedure, the interventionalist enters the SFA origin and crosses into the femoral vein using the Endocross at least 3 cm distal to the origin of the vessel and then travels down the femoral vein and reenters the popliteal artery, landing above the tibial plateau in a nondiseased portion of popliteal artery. TORUS stent grafts are then lined from the distal end to the SFA origin.

"The Endocross device has a powerful spring-loaded needle to penetrate the artery and vein," says J. Eduardo Corso, MD, a colleague of Dr. Lyden's in Cleveland Clinic's Department of Vascular Surgery. "This is especially needed at the distal anastomosis and works well for reentry."

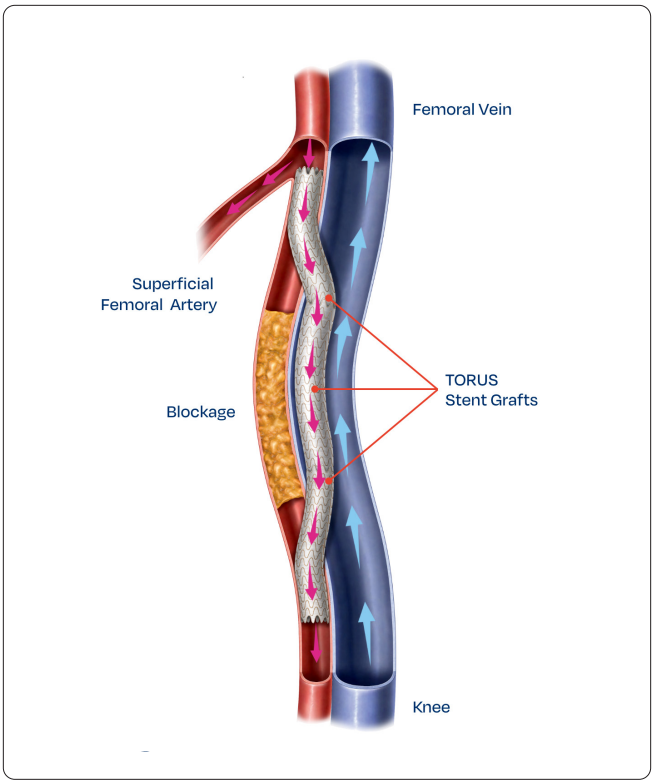


FIGURE — Illustration of the femoropopliteal bypass created with the DETOUR system. *Image provided courtesy of Endologix LLC.*

"These results provide encouragement that this alternative to traditional open prosthetic bypass surgery will become a more commonly used intervention for patients who previously only had endovascular options with limited durability." — SEAN LYDEN, MD

The system has been tested in two similar prospective, single-arm international trials:

- DETOUR 1 was conducted in Europe, South America and New Zealand. The primary safety endpoint was freedom from major adverse events at 30 days, defined as death, clinically driven target vessel revascularization and major amputation. The primary efficacy endpoint was patency at six months, defined as the absence of clinically driven target vessel revascularization or a peak systolic velocity ratio (PSVR) of more than 2.5 within the stent. Two-year results for 78 patients were published in the *Journal of Endovascular Therapy* (2021;29:1:84-95).
- DETOUR 2 was a larger study conducted at 35 sites in Europe and the U.S., including Cleveland Clinic (results not yet published). The primary safety endpoint was freedom from major adverse events at 30 days, defined as death, clinically driven target lesion revascularization, amputation, deep venous thrombosis, pulmonary embolism and major bleeding. The primary efficacy endpoint was patency at 12 months, defined as the absence of clinically driven target lesion revascularization and a PSVR of more than 2.5 within the stent.

A continued access study of DETOUR 2 (NCT04625660) is in progress, with follow-up continuing to three years.

The current aggregate analysis was conducted on variables common to both studies.

Combined cohort characteristics and outcomes

The analysis included 273 patients treated with the DETOUR system (mean age of 68 years, 76.3% male). Baseline comorbidities included coronary artery disease (87.6%), hypertension (86.5%), diabetes (44%) and renal insufficiency (9.8%). Mean lesion length was 31.6 cm, with 94% of cases involving total occlusions and 14% involving in-stent restenosis. Half the patients had a previous PAD intervention, and 16% had a previous PAD surgery.

Procedural outcomes included a mean procedure time of 166 ± 92 minutes and fluoroscopy time of 46 ± 20 minutes. Mean contrast volume was 204 ± 104 mL. Estimated blood loss was 54 ± 60 mL. Mean length of stay was 1.3 days.

DETOUR 1 and DETOUR 2 showed agreement on efficacy endpoints. Specific clinical outcomes included the following:

- Freedom from major adverse events through 30 days was 97.8%, with no pulmonary emboli occurring.
- Rate of clinical success (defined as Rutherford Clinical Classification improvement ≥1) was 92.9% at 30 days, 96.0% at one year and 95.3% at two years.
- At two years, primary patency was 69.2% and freedom from target vessel revascularization was 68.1%.
- Freedom from symptomatic deep vein thrombosis was 96.7%.

Two-year conclusion: A promising alternative to surgical bypass

"PTAB demonstrates high procedural success and two-year efficacy comparable to that of open prosthetic bypass for long, complex SFA lesions," Dr. Lyden concludes. "Unlike surgery, this intervention does not require general anesthesia and avoids long hospital stays and high risk of complications."

He adds that third-year DETOUR 2 trial results, along with real-world data from registries over time, are needed to confirm and extend these two-year findings.

Meanwhile, experience with the DETOUR system is mounting since it became commercially available last year. "The patients I have treated with this system have had good short-term results and shorter length of stay compared with surgical bypass," says Dr. Corso. "It allows some distal above-knee targets to be reached beyond what is easily accessible through a medial surgical approach. In the right patients, this allows preservation of a below-knee distal target with a good result. In the setting of prior SFA stenting with thrombosis or heavy calcification, this system provides a good alternative."

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Contact Dr. Lyden at 216.444.3581 and Dr. Corso at 440.333.8600.

LOW-DOSE DAILY ASPIRIN SLOWS ABDOMINAL AORTIC ANEURYSM PROGRESSION

Large cohort study finds significant effect in men and nonsmokers

Low-dose daily aspirin slows the growth of abdominal aortic aneurysms (AAAs), particularly in men and nonsmokers. So finds a retrospective study conducted at Cleveland Clinic (*JAMA Netw Open.* 2023;6[12]:e2347296).

The study, which involved the largest cohort at a single institution analyzed to investigate this issue, included more than 3,000 adults followed over a period of up to 10 years. Survival rates were similar in patients who did and did not take aspirin, with no increased risk of major bleeding in aspirin takers and no change in aneurysm dissection or rupture.

"Our findings indicate that daily low-dose aspirin slows the advancement of abdominal aortic aneurysms," says the study's corresponding author, Scott Cameron, MD, PhD, Section Head of Vascular Medicine at Cleveland Clinic. "No other medication has been found to have a comparable effect."

Increasing evidence of protection from antiplatelet therapy

Cleveland Clinic researchers have been active in investigating the protective role of antiplatelet therapy for AAAs. A letter in the *Journal of the American College of Cardiology* (2020;75[13]:1609-1610) detailed an analysis of nearly 1.5 million patients with AAA identified from the U.S. National Inpatient Sample that determined antiplatelet agents were associated with significantly lower incidence of AAA, along with protection from dissection and rupture in patients with an existing AAA. The use of anticoagulants did not show these trends, except for a marginal protective effect against rupture.

Dr. Cameron has also conducted preclinical research on the effects of antiplatelet agents on human tissue and murine models of AAA, as described in the *Journal of Clinical Investigation* (2022:132[9]:e152373). The research implicated olfactory receptors in regulating platelet activation and aneurysmal progression, potentially offering new targets for therapy.

Without data from large clinical trials establishing the use of aspirin in AAA management, the American College of Cardiology and American Heart Association (ACC/AHA) Joint Committee on Clinical Practice Guidelines gave low-dose aspirin (75-162 mg daily) a Class 2b indication for managing AAA — indicating a weak recommendation — in its 2022 updated guideline for AAA diagnosis and management. Cleveland Clinic staff were involved in creating the guideline, which was published in *Circulation* (2022;146[24]:e334-e482).

The current study on the effects of daily low-dose aspirin on AAAs was designed to provide evidence from real-world clinical data to inform guidelines.

Study population and outcomes

The cohort was identified from patients who underwent AAA ultrasound screening and at least one additional abdominal vascular ultrasound at Cleveland Clinic between 2010 and 2020. Adults with AAA (defined as maximal aortic diameter ≥ 3.0 cm below the renal arteries) were included; those with a history of prior aneurysm repair, dissection or rupture were excluded.

Data from 3,435 patients were analyzed, including 2,150 (63%) verified to be on aspirin therapy, with the majority taking 81 mg daily and continuing over a median duration of 10.6 years. Overall, average age was 73 years, 78% were male, 89% were white and median follow-up was 4.9 years (interquartile range, 2.5-7.5 years).

Major outcomes comparing patients taking aspirin versus those not taking aspirin were as follows:

- Slower mean annualized increase in aneurysm diameter (2.8 vs. 3.8 mm/year; $P = .001$)
- Less likelihood of rapid (> 5 mm/year) aneurysm progression (adjusted odds ratio = 0.64; 95% CI, 0.49-0.89, $P = .002$)

These effects were seen only in men and nonsmokers. "This suggests that male patients who continue to smoke will lose the protective effect of aspirin," Dr. Cameron notes.

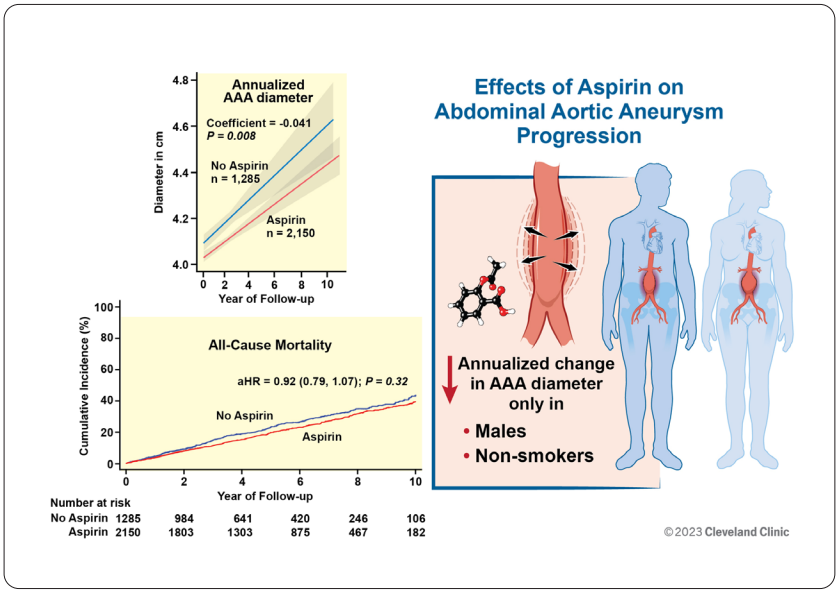
Overall, no difference between aspirin users and aspirin nonusers was detected in rates of all-cause mortality, major bleeding, or a composite of aneurysm dissection, rupture and repair at 10 years.

Supportive evidence for aspirin use

Dr. Cameron concludes that this large, long-term study provides strong evidence that aspirin can help reduce aneurysm progression.

"[Aspirin] is an inexpensive, low-risk medication that over time may potentially stave off a rupture, a dissection or the need for intervention due to aneurysm enlargement."

— SCOTT CAMERON, MD, PHD



ABOVE — A graphic summary of key outcomes from the Cleveland Clinic study.

He notes that the study raises some interesting questions:

- *Why do men benefit more than women, and nonsmokers more than smokers?* Differences, he says, might be attributable to the typically more aggressive course of AAA disease in women and smokers, masking the benefits of aspirin therapy.
- *Beyond slower aneurysm progression, why were no clinical benefits of aspirin therapy observed?* Overall, few aneurysm dissections (n = 15) and ruptures (n = 13) occurred in the entire cohort, likely due to this being a highly monitored and well-managed population. At baseline, the cohort was also relatively healthy, with only about 25% being smokers and less than a quarter having diabetes.

Dr. Cameron adds that a randomized clinical trial is warranted to better determine the role of aspirin for managing aneurysmal disease, but he speculates that this could be prohibitively difficult, given that it would likely take decades to see an effect.

In the meantime, Dr. Cameron routinely puts his AAA patients on maintenance low-dose aspirin, with the justification of the updated ACC/AHA guideline and with the understanding that the majority of patients have AAA as a consequence of atherosclerosis, which leads him to consider aspirin therapy as secondary prevention.

"It is an inexpensive, low-risk medication that over time may potentially stave off a rupture, a dissection or the need for intervention due to aneurysm enlargement," he says.

Additional perspectives

"This study was an extension of previous elegant mechanistic studies performed by Dr. Cameron's team that implicated a causal contribution of platelets to AAA development — a perfect example of going from bedside to bench and back again to the bedside," says Stanley Hazen, MD, PhD, Co-Section Head of Preventive Cardiology at Cleveland Clinic and a co-author on the manuscript.

At the same time, further investigation of this question would be welcome, notes Sean Lyden, MD, Chair of Vascular Surgery at Cleveland Clinic. "It would be ideal to confirm that aspirin still confers its effects at larger aneurysm sizes, so prospective data are needed to validate these results," he says.

Dr. Cameron acknowledges the contributions of the study's first author, Essa Hariri, MD, who served as Cleveland Clinic Chief Medical Resident when the study was conducted.

Contact Dr. Cameron at 216.444.1680, Dr. Hazen at 216.444.9426 and Dr. Lyden at 216.444.3581.

CME PREVIEW

AUGUST COURSE PROMISES EFFICIENT, ENGAGING WAY TO GET UP TO SPEED ACROSS THE RANGE OF CARDIOLOGY PRACTICE

Over 50 Cleveland Clinic faculty cover what's new and notable in all major subspecialties

State-of-the-Art Topics in the Prevention and Management of Cardiovascular Disease

Fri.-Sun., Aug. 2-4, 2024
InterContinental Cleveland, Cleveland, Ohio
Information/registration: ccfcme.org/cvd2024

Keeping up with the latest in cardiology practice can be daunting. Cleveland Clinic is looking to help by offering this comprehensive 2.5-day live CME event in Cleveland this summer.

The course is a successor to the long-standing Cleveland Clinic Intensive Review of Cardiology, which the course directors have refreshed with an enhanced focus on the latest research and practice updates along with expanded opportunities for interaction with a faculty of more than 50 expert physicians from Cleveland Clinic's Heart, Vascular & Thoracic Institute.

"Comprehensive coverage of developments in all major cardiovascular subspecialty areas is still our guiding principle for the course, which retains a focus on complex patient management and clinical decision-making," says course co-director Venu Menon, MD. "This new conception of the course simply devotes greater attention to the very latest clinical trial data and guideline recommendations."

A focus on the new

That's a particular priority on the first day, which launches with overviews of recent major cardiovascular trials presented by their lead investigators. These are followed by recaps of key changes and practical takeaways from recent multisociety treatment guidelines on coronary artery revascularization, aortic disease management and evaluation of chest pain. Next come expert assessments of implications from the top five trials of 2023-2024 in five subspecialty areas: electrophysiology, interventional cardiology, heart failure and transplantation, cardiac imaging and preventive cardiology.

The first day concludes with reviews of new developments in eight evolving specialty topics too often neglected in general cardiology CME courses: pericarditis, amyloidosis, sarcoidosis, hypertrophic obstructive cardiomyopathy, pulmonary hypertension, sports cardiology, infective endocarditis and cardiac rheumatology.

Covering all the bases — plus some interesting extras

Much of the rest of the course — all day Saturday and Sunday morning — consists of sessions devoted to timely topics in six subspecialty areas: interventional cardiology, heart failure, preventive cardiology, vascular medicine, cardiac critical care and electrophysiology.

An additional session features Cleveland Clinic cardiac surgeons exploring select surgical issues with high relevance for cardiology practitioners. Another session addresses more practice areas not adequately covered in many cardiology CME courses, including cardio-obstetrics, management of adult congenital heart disease, imaging for structural heart interventions and the role of 3D printing in current practice.

All presentations are 20 minutes long, including time for Q&A. Presentation formats range from general updates (e.g., "Up-to-Date Approach to the Prevention of Sudden Cardiac Death") to ultrapractical reviews (e.g., "Workup of a Microvascular Disease") to forward-looking discussions (e.g., "Coronary Calcium Score: Looking Into the Future"), among others.

Content relevance across the range of subspecialty areas is ensured by the breadth of the team of Cleveland Clinic course co-directors: Venu Menon, MD, Section Head of Clinical Cardiology; Leslie Cho, MD, Co-Section Head of Preventive Cardiology and Director of the Women's Cardiovascular Center; Ayman Hussein, MD, of the Section of Electrophysiology; Ran Lee, MD, of the Section of Heart Failure; Grant Reed, MD, of the Section of Interventional Cardiology; and Samir Kapadia, MD, Chair of Cardiovascular Medicine.

"This course is designed to bring cardiovascular practitioners and trainees up to speed across the spectrum of major subspecialty areas in an efficient, engaging way," says Dr. Menon. "We look forward to welcoming attendees to this event in Cleveland, where there will be ample opportunity for one-on-one networking with the faculty."

A livestream option will be available to attendees residing outside North America.

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Course and registration details are at ccfcme.org/cvd2024.

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The Present and Future of EP Practice 2024: The Cleveland Clinic Perspective
Satellite symposium at Heart Rhythm 2024
Thu., May 16, 2024
Westin Boston Seaport | Boston, Massachusetts
Information/registration: ccfcme.org/ccfep2024

State-of-the-Art Topics in the Prevention and Management of Cardiovascular Disease
Fri.-Sun., Aug. 2-4, 2024
InterContinental Cleveland | Cleveland, Ohio
Information/registration: ccfcme.org/cvd2024

Global EP 2024
Fri.-Sat., Sept. 20-21, 2024
Hilton Cleveland Downtown | Cleveland, Ohio
Information/registration: ccfcme.org/globalep24

Cardiovascular Update 2024
Thu.-Fri., Oct. 31-Nov. 1, 2024
Hilton Cleveland Downtown | Cleveland, Ohio
Information/registration: ccfcme.org/cvupdate24

Advancing Cardiovascular Care 2024
Fri., Nov. 8, 2024
Hyatt Regency Columbus | Columbus, Ohio
Information/registration: ccfcme.org/columbuscvcare24

Dimensions in Cardiac Care
Sun.-Tue., Nov. 10-12, 2024
InterContinental Cleveland | Cleveland, Ohio
Information/registration: ccfcme.org/cardiaccare24

Mastering the Management of the Mitral Valve
Fri.-Sat., Dec. 6-7, 2024
JW Marriott Essex House | New York, New York
Information/registration: ccfcme.org/mitralvalve

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

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