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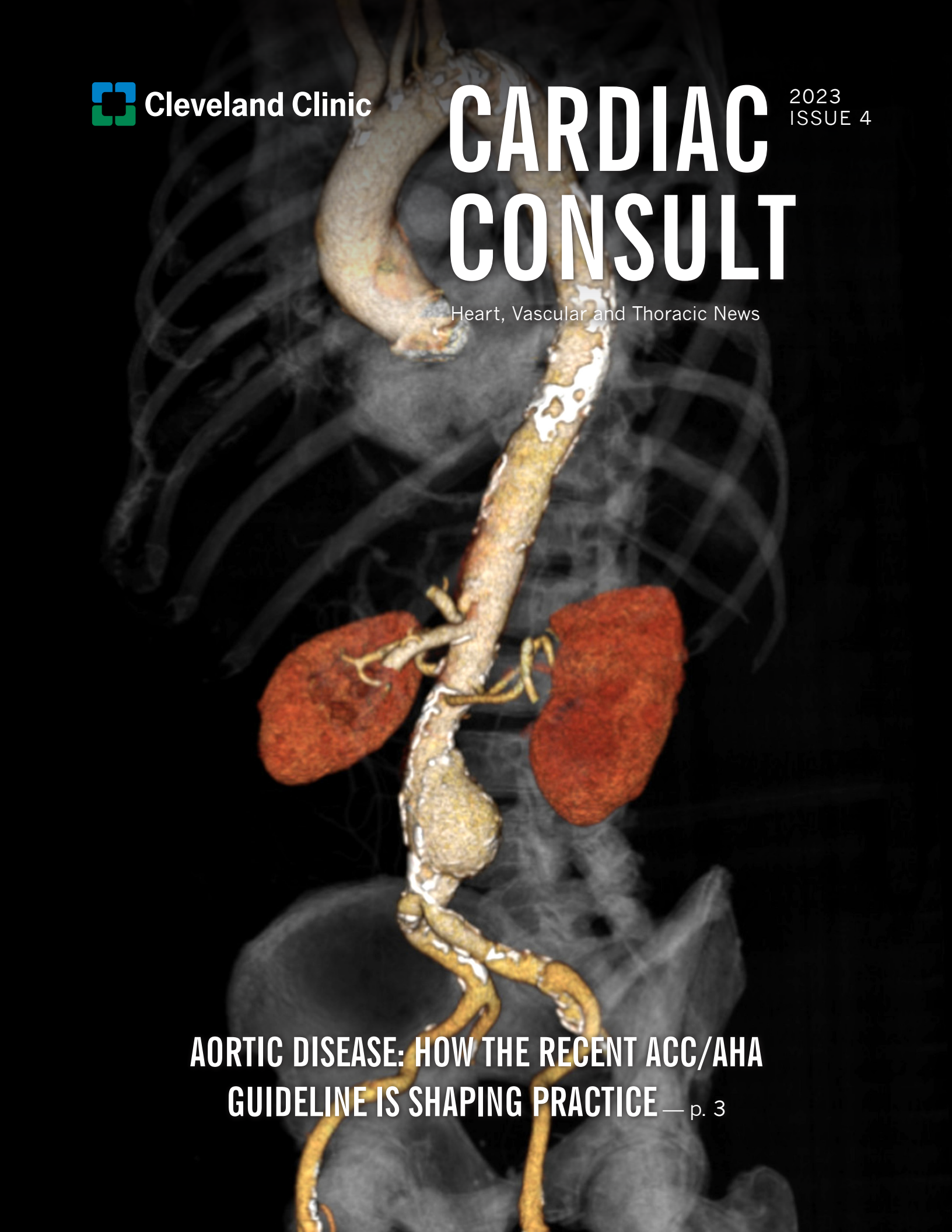


AORTIC DISEASE: HOW THE RECENT ACC/AHA GUIDELINE IS SHAPING PRACTICE

— p. 3

DEAR COLLEAGUES,

For some time now, the cardiovascular and thoracic specialties have recognized the value of a heart team approach in specific areas of care, such as when counseling patients about options for aortic valve replacement. At Cleveland Clinic, we see the value of a similar approach in an increasing number of care realms. A prime example is the management of aortic disease, where cardiologists, cardiac surgeons, vascular surgeons, genetic counselors and others are all needed to provide truly comprehensive care.

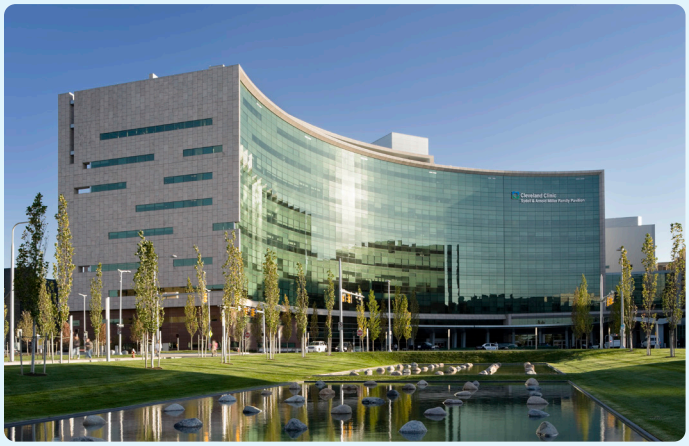
The cover story of this issue of *Cardiac Consult* profiles the impact of a recent multisociety guideline on the care of patients with aortic disease. As it notes, a key emphasis of the guideline is the importance of a multidisciplinary heart team approach for patients with aortic disease. Endorsement of this approach in a major practice guideline is welcome and may have contributed to the warm reception the guideline has received to date, as described in our story.

A heart team approach also can yield particular value in managing isolated severe tricuspid regurgitation, as reflected in the Cleveland Clinic study profiled on pages 14-15. The study concluded that surgery should be considered in this setting before overt symptoms develop. As our story illustrates, involvement of a care team offering diverse expertise — in cardiac surgery, cardiovascular imaging, interventional cardiology and more — is key to success in what is traditionally a very high-risk patient population.

If you choose to entrust a patient to our care through referral, please know that we will offer a heart team approach whenever they may stand to benefit from one.

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 — A 3D CT angiogram of the aorta showing an abdominal aortic aneurysm, one of the conditions addressed in the recent practice guideline on management of aortic disease from the American College of Cardiology and the American Heart Association. The cover story on page 3 shares key takeaways from the guideline from multidisciplinary perspectives.

HOW THE NEW ACC/AHA GUIDELINE ON AORTIC DISEASE IS STARTING TO SHAPE PRACTICE

Impacts include major emphases on multidisciplinary teams, shared decision-making

In the months since the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease was issued late last year (*J Am Coll Cardiol.* 2022;80[24]:e223-e393), the document has been welcomed by clinicians and patients alike.

"Reception has been positive," says Cleveland Clinic cardiologist Vidyasagar Kalahasti, MD, a member of the guideline writing committee. "My colleagues and other peers in the cardiovascular care community say the new guideline is pragmatic and its recommendations closely align with most of their practical experience."

The guideline was developed to be more comprehensive and detailed than several previous American College of Cardiology (ACC)/American Heart Association (AHA) guidelines that it updated. Dr. Kalahasti, who serves as Director of the Cardiovascular Marfan Syndrome & Vascular Connective Tissue Disorders Clinic in Cleveland Clinic's Aorta Center, has found it particularly helpful for instilling confidence in patients who face surgery for a genetically conferred aortic condition.

"When it comes to recommendations for operating at a certain aorta size in response to their particular mutation, we show patients what the experts who worked on this guideline advise," he explains. "They can see that it's not just my opinion, but also that of my peers."

One-stop resource

The guideline was designed as a single, comprehensive resource that fills needs previously met by ACC/AHA guidelines on thoracic aortic disease, peripheral arterial disease and bicuspid aortic valve disease dating as far back as 2010. It is expressly intended to be used with the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease.

An extensive body of research published since 2010 provided fertile ground for updating recommendations on all major aspects of aortic disease care: diagnosis, genetic evaluation and family screening, medical therapy, endovascular and surgical treatment, and long-term patient surveillance.

Advances in assessment

One area that received a major upgrade was discussion of the role of imaging in the assessment of aortic disease. Optimal imaging modalities and techniques for determining the presence and progression of aortic disease are explained in detail.

In assessing the need for surgery, the threshold for intervention was lowered. Additionally, for patients who are shorter or taller than average, the standard method of indexing the aortic root or ascending aorta diameter to the patient's body surface area was replaced by a recommendation to index a cross-sectional area of the aorta to the patient's height. The newly recommended formula, pioneered by Cleveland Clinic cardiothoracic surgeon Lars Svensson, MD, PhD, was enthusiastically embraced by the writing committee.

"Body surface area changes if a patient gains or loses weight, but an adult's height is fairly stable," Dr. Kalahasti explains. "Indexing the patient's aorta diameter to their height provides a better discriminator for the timing of intervention in patients with and without heritable conditions. As a result, some patients will need surgery earlier."

"As a cardiac surgeon who subspecializes in the treatment of aortic disease, I have found the ACC/AHA guideline useful when counseling patients on timing for surgical intervention," notes Patrick Vargo, MD, staff in Cleveland Clinic's Department of Thoracic and Cardiovascular Surgery.

"One thing that's especially helpful about this guideline is that it reflects our improving understanding of nuances in the pathophysiology of dissections throughout the aortic anatomy, from

"We tried to reflect nuances and not be absolutists. It is a great advance that we have given patients permission to discuss options with their physician and then decide on a course of action." — VIDYASAGAR KALAHASTI, MD

"Aortic indications now represent more than one in every five cardiovascular operations we perform at Cleveland Clinic." — ERIC ROSELLI, MD

the ascending arch to the thoracic aorta," adds Francis Caputo, MD, Vascular Surgery Director of Cleveland Clinic's Aorta Center.

Aorta care takes a village

The guideline is likewise notable for its emphasis on new recommendations for comprehensive care that stress the role of shared decision-making and the importance of an experienced multidisciplinary care team. The latter emphasis reflects an approach long validated at Cleveland Clinic.

"Other institutions are recognizing the need for a multidisciplinary evaluation of these patients, and patients themselves increasingly realize that this is a team sport," Dr. Kalahasti says. "No single physician can manage the medical, genetic and surgical sides of aortic disease."

Dr. Caputo notes that the guideline is endorsed by major societies in a host of disciplines — thoracic surgery, vascular surgery, vascular medicine, radiology, interventional radiology, interventional cardiology and cardiovascular anesthesiology — in addition to the ACC and AHA, representing the broadest support for such recommendations to date.

Emphasis on shared decision-making

The guideline promotes substantial flexibility in treatment decisions through shared decision-making. The process requires active dialogue between patients and members of their care team.

Dr. Kalahasti cites the example of a patient with a bicuspid valve and an aorta 5.2 cm in diameter, but no other risk factors, who does not want to wait until the aorta reaches 5.5 cm to have surgery. According to the guideline, it is not unreasonable to do elective surgery now, so long as the patient understands the pros and cons of surgery versus continued surveillance.

"We tried to reflect nuances and not be absolutists," Dr. Kalahasti says. "We have given patients permission to discuss options with their physician and then decide on a course of action."

"For any individual patient or family, this guideline, despite its many strengths, is only that — a guideline," adds Eric Roselli, MD, Cardiac Surgery Director of Cleveland Clinic's Aorta Center. "An individual faced with an aortic diagnosis is best advised to work with an aorta specialist to create a precise treatment plan tailored to that individual, based on their condition and other medical and life considerations, as well as the expertise of their care team."

Dr. Caputo says the guideline recognizes this reality through its emphasis on the increasing need and ability to tailor care to the individual patient's sex, body habitus and other specific characteristics. "For example," he says, "we are now better able to counsel patients on the timing of aorta repair versus surveillance in specific situations such as pregnancy, with a whole section of the guideline devoted to pregnancy in patients with aortopathy."

Reflecting advances in genetic understanding

The wealth of information published in the past decade or so on specific genetic mutations and their genotype and phenotype differences contributed to a robust set of recommendations for patients with these mutations and the clinicians who treat them.

"For patients with Loeys-Dietz syndrome, for example, we now know that certain mutations may not confer the same high degree of risk as other genetic mutations," Dr. Kalahasti notes.

He adds that mounting detail on specific genetic conditions — addressed in the new guideline — has resulted in earlier referrals for surgery, which he identifies as a positive development. "In patients with genetically mediated diseases, the aorta can dissect at a small size," he says. "One way to prevent this catastrophic event is to do elective surgery."

Dr. Caputo concurs. "We often need to be a bit more aggressive in managing patients with connective tissue disorders because their aortic pathologies tend to be more aggressive," he says.

"The continued explosion of knowledge about gene mutations associated with aortic dissections and ruptures helps us tailor care to each individual patient," adds Dr. Vargo, "and the most recent data are captured in this updated guideline."

Indeed, the Marfan Foundation, the John Ritter Foundation for Aortic Health and other organizations that advocate for individuals with heritable aortic diseases are highlighting the guideline to increase awareness among patients.

Dr. Roselli notes that the guideline itself provides much-needed consciousness-raising about aortic disease more broadly. "Aortic indications now represent more than one in every five cardiovascular operations we perform at Cleveland Clinic," he says. "This document helps raise awareness of this increasingly important condition."

Data Snapshots from Cleveland Clinic's Aorta Center

The new ACC/AHA guideline aligns with most practices of Cleveland Clinic's Aorta Center, the highest-volume aorta program in the U.S. Below is a sampling of statistics that underlie Cleveland Clinic's unsurpassed experience base in aortic disease.

1,396
aorta surgeries in 2022:

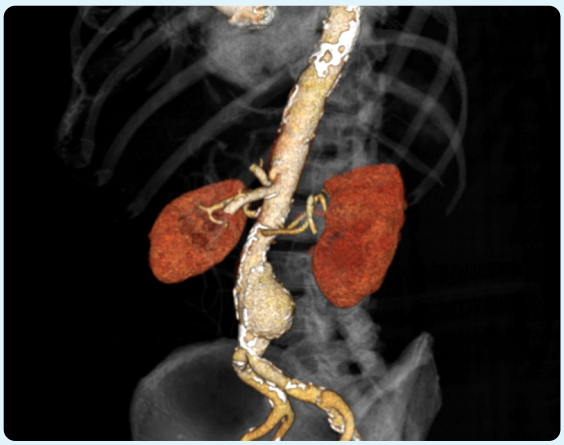
- **872** open ascending/arch repairs
- **136** open abdominal repairs
- **130** endovascular descending/thoracoabdominal repairs
- **126** frozen elephant trunk hybrid procedures
- **93** endovascular abdominal repairs
- **35** open descending/thoracoabdominal repairs
- **4** endovascular proximal aorta repairs

0.7%
in-hospital mortality for elective ascending aorta and aortic arch open surgeries in 2022 (N = 710)

6.2%
in-hospital mortality for emergency ascending aorta and aortic arch open surgeries in 2022 (N = 162)

0.0%
in-hospital mortality for elective open abdominal aortic aneurysm repairs in 2022 (N = 112)

12.5%
in-hospital mortality for emergency open abdominal aortic aneurysm repairs in 2022 (N = 24)



591 aortic root replacements in 2022:

- **392** Bentall procedures
- **112** valve-sparing root replacements
- **63** homografts
- **24** Ross procedures

0.8%
in-hospital mortality for elective root replacements in 2022

5.6%
in-hospital mortality for emergency root replacements in 2022

More frequent updates are likely

The breadth and depth of changes made to the various ACC/AHA guidelines that the new document supersedes made it clear that more frequent updates would benefit patient care. As a result, the writing committee plans to reconvene in a few years to review the literature published since this 2022 guideline and decide whether another update is warranted.

Meanwhile, Dr. Kalahasti encourages cardiologists and even primary care physicians to familiarize themselves with the 2022 guideline so they can refer appropriate patients. "A large share of my practice is based on incidental diagnoses made by primary care doctors from imaging tests ordered for other conditions," he says. "When an enlarging aorta is found early on, that's when we are best positioned to effectively manage it."

Contact Dr. Kalahasti at 216.445.7259, Dr. Vargo at 216.444.2288, Dr. Caputo at 216.445.9580 and Dr. Roselli at 216.444.0995.

UPDATES FROM CLEAR OUTCOMES AND VALOR-HCM: EXPANDED BENEFITS WITH BEMPEDOIC ACID AND MAVACAMTEN

Additional analyses of the two trials presented at 2023 ESC Congress

Additional analyses of two major multicenter trials of newer cardiovascular medications — bempedoic acid (Nexletol®) and mavacamten (Camzyos®) — have strengthened evidence of the agents' clinical benefits.

The analyses were presented in late-breaking science sessions at the 2023 European Society of Cardiology Congress. Both studies analyzed were led by Cleveland Clinic and coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research).

One presentation focused on total cardiovascular events in the recent CLEAR Outcomes study of bempedoic acid in statin-intolerant patients, finding that the risk reduction conferred by the drug increased with each additional event among patients who experienced multiple cardiovascular events.

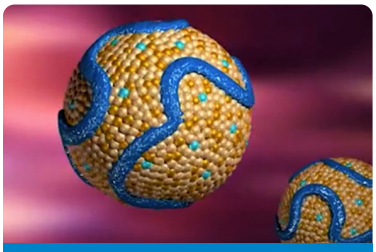
The other presentation shared longer-term results from the VALOR-HCM study of mavacamten in patients with highly symptomatic obstructive hypertrophic cardiomyopathy (HCM), extending follow-up to 56 weeks from the previously reported 32 weeks. The drug continued to reduce patients' need for septal reduction therapy and yielded sustained improvements in symptoms and left ventricular outflow tract (LVOT) gradients. These results were simultaneously published in *JAMA Cardiology*.

"Our C5Research academic research organization continues to provide the ability to take deep dives into clinical trials to provide scientific insights that extend beyond the primary publication. These two presentations are illustrative of this approach to clinical trial analysis," says Steven Nissen, MD, Chief Academic Officer of Cleveland Clinic's Heart, Vascular & Thoracic Institute and a co-investigator in both the CLEAR Outcomes and VALOR-HCM studies.

Total events in CLEAR Outcomes

The new report from CLEAR Outcomes was a prespecified analysis of total cardiovascular events.

As detailed in the primary study report earlier this year (*N Engl J Med.* 2023;388:1353-1364), CLEAR Outcomes randomized a mixed population of 13,970 primary and secondary prevention patients with statin intolerance to oral bempedoic acid (180 mg/day) or matching placebo. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke or coronary revascularization. Over median follow-up of 40.6 months, this endpoint occurred in significantly fewer patients in the bempedoic acid group than in the placebo group (11.7% vs. 13.3%; hazard ratio = 0.87 [95% CI, 0.79-0.96]; $P = 0.004$), a 13% relative risk reduction.



CLEAR Outcomes total events analysis

Bempedoic acid's protective effect increased with rising numbers of cardiovascular events, with a hazard ratio of 0.87 for first events versus 0.52 for fourth and subsequent events.

Across the study cohort, 1,134 patients had one primary endpoint event and 612 patients had more than one event over the course of the study. The new analysis examined bempedoic acid's effect relative to placebo on total events, including among patients with increasing numbers of events.

Among patients with more than one cardiovascular event, events beyond the first event broke down as follows: coronary revascularization, 69.4%; nonfatal MI, 14.3%; cardiovascular death, 10.9%; and nonfatal stroke, 5.4%.

When outcomes were analyzed according to first events versus total events, bempedoic acid demonstrated a statistically significant protective effect relative to placebo for the primary composite endpoint for both first and total events. This effect remained significant for all components of the primary endpoint except nonfatal stroke, where it trended toward significance for both first and total events.

The total incidence of the primary composite endpoint was reduced by 20% with bempedoic acid relative to placebo ($P = 0.0001$). Total incidences of secondary endpoints were also reduced significantly with bempedoic acid, as follows:

- 17% decrease in the composite of nonfatal MI, nonfatal stroke and cardiovascular death ($P = 0.002$)

- 31% decrease in nonfatal MI ($P = 0.0001$)
- 22% decrease in coronary revascularization ($P = 0.003$)

Notably, bempedoic acid's protective effect increased as events increased, with hazard ratios as follows:

- 0.87 (95% CI, 0.79-0.96) for first events ($P = 0.0037$)
- 0.74 (95% CI, 0.63-0.87) for second events ($P = 0.0002$)
- 0.69 (95% CI, 0.51-0.93) for third events ($P = 0.016$)
- 0.52 (95% CI, 0.31-0.88) for fourth and subsequent events ($P = 0.015$)

"Although this was a prespecified analysis, its results remain hypothesis-generating," notes Dr. Nissen. "That said, they suggest that in high-risk patients with statin intolerance, the benefits of lowering LDL cholesterol and high-sensitivity C-reactive protein with bempedoic acid extend to reduction of total cardiovascular events, including incrementally increasing protection against repeat events."

56-week results in VALOR-HCM

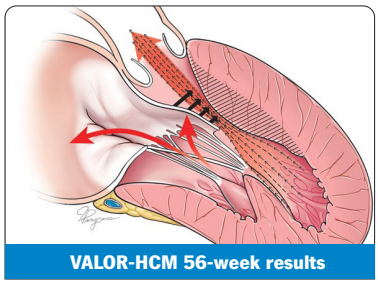
In April 2022, the cardiac myosin inhibitor mavacamten became the first FDA-approved drug for treatment of symptomatic obstructive HCM. Approval was supported by 16-week results of the VALOR-HCM trial, a multicenter study of 112 patients with obstructive HCM and severe symptoms despite maximally tolerated medical therapy with disopyramide, a beta blocker and/or a calcium channel blocker.

Patients were randomized in a double-blind manner to oral mavacamten 5 mg/day or placebo; the mavacamten dosage was titrated up or down based on echocardiographic assessment of LVOT and left ventricular ejection fraction (LVEF). The primary endpoint was a composite of the patient's decision to proceed with septal reduction therapy (SRT) or continued eligibility for SRT according to 2011 ACC/AHA guidelines.

Results at 16 weeks (*J Am Coll Cardiol.* 2022;80:95-108) showed a significant reduction in the share of patients meeting the primary endpoint with mavacamten relative to placebo. At that point, patients in the mavacamten group continued the drug and placebo recipients were crossed over to mavacamten.

Results from the next interim analysis, at 32 weeks (*Circulation*. 2023;147:850-863), bolstered those from 16 weeks. An even smaller share of patients in the original mavacamten group met the primary endpoint of undergoing or meeting criteria for SRT (10.7%, vs. 17.9% at 16 weeks), and just 13.5% of patients in the placebo-to-mavacamten crossover group now met this primary endpoint, down from 76.8% at 16 weeks.

The new interim analysis reported results at 56 weeks as well as outcomes stratified by sex. Of the 112 enrolled patients, 108 qualified for assessment at 56 weeks. Results from 32 weeks were sustained through this time point, as follows:



VALOR-HCM 56-week results

Only 8.9% of patients in the mavacamten group and 19.2% in the placebo-to-mavacamten crossover group underwent septal reduction therapy or remained eligible for it.

- 8.9% of patients in the original mavacamten group met the primary endpoint of undergoing or meeting criteria for SRT at week 56.
- 19.2% of patients in the placebo-to-mavacamten crossover group met the primary endpoint at week 56.

Both groups also showed sustained improvements in resting and provoked LVOT gradients, New York Heart Association (NYHA) class, biomarkers, left ventricular mass index, left atrial volume and quality-of-life scores at week 56.

Stratification by patient sex showed that mavacamten's effects on eligibility for SRT, NYHA class improvement and LVOT gradients were comparable in men and women.

Notably, while 11% of patients experienced LVEF < 50% during the study, after temporary therapy interruption, 75% of these patients were able to resume mavacamten at a lower dose with sustained LVEF recovery. "This underscores the need for careful echocardiographic monitoring during therapy and the need for further long-term safety data," says principal investigator Milind Desai, MD, MBA, Director of Cleveland Clinic's Hypertrophic Cardiomyopathy Center.

Echocardiograms were read at the study's core lab for the first 32 weeks and on-site thereafter. "We found significant correlation of LVEF and LVOT gradients between echocardiograms read on-site and those read at the core lab," he adds, "which suggests that echocardiographic monitoring will be a safe strategy in clinical practice."

Overall, only four patients decided to proceed with SRT while on mavacamten therapy during the study's first 56 weeks. "This suggests a strong patient preference for medical therapy over an invasive procedure," Dr. Desai says, "although we must continue to monitor safety and need for SRT over the longer term." Follow-up will continue through at least 128 weeks.

Contact Dr. Nissen at 216.445.3224 and Dr. Desai at 216.445.5250.

PACLITAXEL-COATED DEVICES: HOW THE PROCESS OF RULING OUT SAFETY CONCERNS HAS IMPROVED VASCULAR SURGERY RESEARCH

Benefits of the new FDA safety determination go beyond expanding patients' options

When the FDA announced in July that it determined paclitaxel-coated devices are not associated with excess mortality risk for patients with atherosclerotic lesions in the femoropopliteal artery, the decision did more than expand many patients' treatment options.

It also established a model for how the FDA, physicians and the medical device industry can collaborate to efficiently address pressing clinical questions. It even appears to be improving how vascular surgery trials will be conducted moving forward.

That's the perspective of Sean Lyden, MD, Chair of Vascular Surgery at Cleveland Clinic. "The FDA's decision came in the wake of a flood of research and effort to ensure that the vascular surgery and vascular medicine communities were putting our patients' safety first," says Dr. Lyden, who is a member of the board of directors of the not-for-profit VIVA Foundation, which helped coordinate the FDA/physician/industry collaboration to scrutinize the safety of paclitaxel-coated devices.

"This represents a huge win that involved getting all the players together to thoroughly examine all the data and get answers for our patients," he continues. "The FDA should be applauded for the speed of their reaction and their sustained collaboration with physicians and industry. Vascular surgery research has evolved for the better as a result of this experience."

Paclitaxel-coated devices: The controversy in brief

The FDA decision came in the form of an update letter to healthcare providers that states, "Based on the FDA's review of the totality of the available data and analyses, we have determined that the data does not support an excess mortality risk for paclitaxel-coated devices."

The suggestion of such a risk arose from a meta-analysis published by Katsanos and colleagues in December 2018 (*J Am Heart Assoc*. 2018;7:e011245). These researchers pooled summary-level data from 28 randomized controlled trials (RCTs) of paclitaxel-coated balloons and stents for treating femoropopliteal peripheral artery disease (PAD). They reported a significant increase in all-cause death at two and five years in patients with claudication who received paclitaxel-coated devices (relative to controls), as well as a potential dose-related signal.

This prompted the FDA to update labeling for paclitaxel-coated devices in 2019 and to advise providers that "alternative treatment options should generally be used for most patients" while the agency further studied the question.

The findings also prompted controversy, due to the lack of a plausible mechanism of harm and the fact that up to 30% of patients had been lost to follow-up, as the studies in the meta-analysis were not designed to assess long-term mortality. A subsequent meta-analysis (*Circulation*. 2020;141:1859-1869) used individual patient-level data and captured more of the patients lost to follow-up. That analysis, facilitated by VIVA and co-authored by Dr. Lyden, showed a smaller increase in mortality with the paclitaxel-coated devices and no dose-response relationship.

Meanwhile, the FDA worked with physicians and device manufacturers on analysis plans as data accumulated from additional studies and from longer follow-up and more-complete vital status information from prior studies. This culminated in an updated patient-level meta-analysis with follow-up from most studies out to five years. That prompted the FDA to conclude in July that "the updated RCT meta-analysis does not indicate that the use of paclitaxel-associated devices is associated with a late mortality risk."

Near-term effects of FDA's determination

The updated patient-level meta-analysis, which will soon be published in a peer-reviewed journal, "was the tipping point for the FDA," Dr. Lyden says. "It proved that the initial meta-analysis was flawed due to incomplete data. But when the safety signal was first suggested, we did the right thing for patients. Use was restricted, we studied the question as thoroughly as possible and the concern was ultimately proven unfounded."

The FDA is now working with manufacturers of paclitaxel-coated devices to revise their labels to remove warnings about potential late mortality risk and any recently added use restrictions. But raising broad awareness of the changes may take a while.

"The FDA should be applauded for the speed of their reaction and their sustained collaboration with physicians and industry. Vascular surgery research has evolved for the better as a result of this experience." — SEAN LYDEN, MD

"At Cleveland Clinic, we swiftly went back to using drug-coated devices as our primary therapy for appropriate patients," Dr. Lyden says, noting that it is well established that these devices increase the chance of vessel patency by 30% at one and two years, with sustained benefit out to five years. But hesitancy is greater in community practice, he notes, especially in light of the FDA's initial 2019 guidance to use alternative therapies for most patients. "Physicians were told to use these devices only for high-risk lesions in high-risk patients, but 'high-risk' was never defined. As a result, many physicians were wary of using them at all."

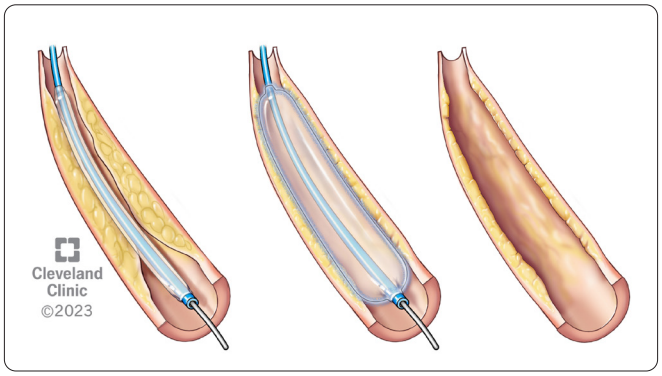
Dr. Lyden suspects it will take a year or two — and consistent education of providers — for use of paclitaxel-coated devices to return to pre-2019 levels. "Once a warning is out there, it's difficult to walk it back," he says. "This makes the FDA's commitment to resolving this issue all the more remarkable."

His Cleveland Clinic colleague Aravinda Nanjundappa, MBBS, MD, concurs. "Establishing the long-term safety of paclitaxel-eluting balloons and stents has changed the scope of practice for the endovascular management of PAD," says Dr. Nanjundappa, staff cardiologist in the Section of Interventional Cardiology. "Ongoing and future research on the safety and efficacy of drug-coated devices for critical limb ischemia will accelerate wound healing, reduce amputations and save lives."

Broader long-term impacts too

Meanwhile, the episode has yielded broader positive changes in at least three aspects of vascular surgery research, according to Dr. Lyden:

- **A model for research collaboration.** The experience has yielded a model of enhanced collaboration among the FDA, physicians and the device industry that can benefit how future research questions are addressed. In particular, the cooperation and data-sharing efforts among competing device manufacturers "were unheard of before this happened," Dr. Lyden notes. "Now there are standards for this type of cooperation going forward."
- **Endpoints and follow-up duration.** Prior to this controversy, studies of combined device/drug therapies like paclitaxel-coated devices hadn't been designed to assess for a long-term mortality signal. "Every trial from now on is going to look at patients for five years, in terms of any mortality signal in addition to other standard safety and efficacy measures," Dr. Lyden predicts.
- **New strategies for long-term follow-up.** Clinical trials typically lose 15% to 20% of patients to follow-up. The methods used to capture more complete data in the patient-level analysis done following the initial summary-level analysis have yielded lasting lessons, Dr. Lyden says. "We went back and contacted more patients and their families to find out if patients were still alive," he explains. "If they weren't, we tried to get information from their death certificate or from an autopsy to learn the cause of death to improve the safety data for the analysis. That was unheard of." But now, the Society of Vascular Surgery's Vascular Quality Initiative (VQI) has launched a project called VQI Vision to extend patient follow-up from one year to up to five years through new uses of Medicare billing data and the Social Security Death Index. "These changes will revolutionize how we study vascular procedure outcomes over the long term," Dr. Lyden concludes.



ABOVE — Illustration of key steps in paclitaxel-coated balloon deployment. Paclitaxel is delivered from the balloon (middle panel) to prevent scar tissue formation and reduce the risk of restenosis.

Contact Dr. Lyden at 216.444.3581 and Dr. Nanjundappa at 216.445.5846.

NOVEL TOOL HOLISTICALLY ASSESSES PATIENT-REPORTED OUTCOMES IN ESOPHAGEAL CONDITIONS

Cleveland Clinic Esophageal Questionnaire goes beyond Eckardt symptom score to evaluate dyspepsia, eating and symptom "bother"

Cleveland Clinic researchers have developed and validated a new point-of-care tool that clinicians can use to objectively quantify and longitudinally track outcomes in patients with benign and malignant esophageal conditions.

Development and validation of the Cleveland Clinic Esophageal Questionnaire (CEQ) were recently described in the *Journal of Thoracic and Cardiovascular Surgery*, and now a study reported at the American College of Surgeons Clinical Congress 2023 shows that the CEQ detects important differences in eating and dyspepsia in achalasia patients that are not captured by the Eckardt symptom score (ESS). The study also demonstrated the utility of the CEQ's novel "bother" T-score aimed at determining the impact of symptoms on a patient's quality of life.

"Our research shows that the CEQ provides a better objective quality-of-life assessment in achalasia patients than the Eckardt symptom score," says thoracic surgeon Monisha Sudarshan, MD, principal investigator of the study. "It takes under five minutes to complete and can be used to reliably surveil patients with a wide variety of esophageal conditions."

What makes the CEQ different

Written at a third-grade level, the CEQ is the only validated patient-reported outcome measure applicable to all esophageal diseases. It was developed beginning in 2020 based on an extensive literature review, expert opinion and previously unpublished Cleveland Clinic research. A pilot version of the questionnaire was tested at Cleveland Clinic's thoracic surgery outpatient clinic, after which it was further refined based on patient feedback.

The final 34-item instrument spans six domains:

- Dysphagia
- Eating
- Pain
- Reflux and regurgitation
- Dyspepsia
- Dumping (rapid enteral emptying)

Patients are asked to rate each symptom on a frequency scale from "never" to "several times a day" and to rate the "bother" caused by

"We were surprised that [the CEQ] also documented significant improvements in dyspepsia post-surgery, which is not part of the Eckardt score."

— SADIA TASNIM, MD

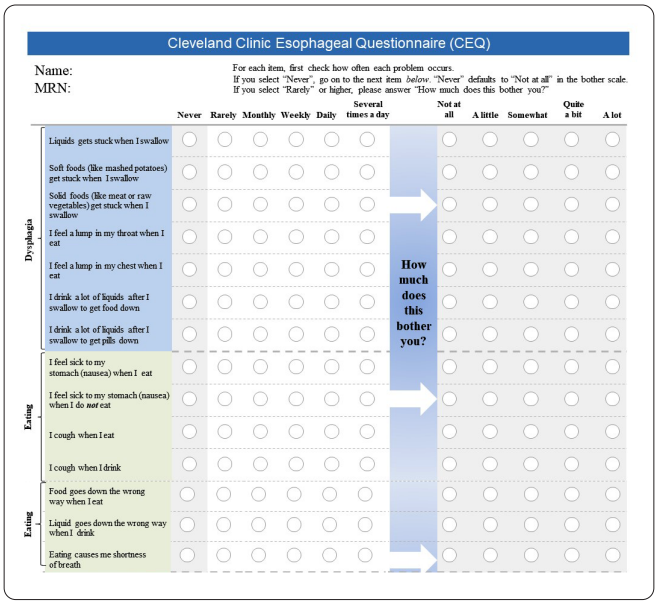


FIGURE — A sample portion of the Cleveland Clinic Esophageal Questionnaire (CEQ).

"The CEQ provides a better objective quality-of-life assessment in achalasia patients than the Eckardt symptom score. It takes under five minutes to complete and can be used to reliably surveil patients with a wide variety of esophageal conditions." — MONISHA SUDARSHAN, MD

each symptom on a scale from "not at all" to "a lot." The figure on the prior page presents a sample portion of the CEQ and bother questionnaire.

In contrast, the gold-standard ESS is written at a higher reading level (dependent on the clinician administering it), grades the frequency of only four symptoms (dysphagia, regurgitation, chest pain and weight loss) and has no "bother" component.

"It was particularly important to us to measure bother because the impact of a symptom can vary from patient to patient," Dr. Sudarshan says. "Mild dysphagia, for example, may be very troubling to some individuals, whereas even significant dysphagia is not a problem for other patients."

According to study co-author Sadia Tasnim, MD, a Cleveland Clinic thoracic surgery research fellow, the researchers also believed the CEQ should measure ability to eat. "Ability to eat is a better assessment of achalasia symptoms than weight loss, which can be influenced by several other confounding factors," she says.

Comparing the CEQ and ESS

For the study presented at the American College of Surgeons meeting, use of the CEQ and the ESS was compared in 28 English-speaking adults with achalasia scheduled to undergo either Heller myotomy with Dor fundoplication or per oral endoscopic myotomy (POEM). Patients had a mean age of 59 years and were predominantly female (57%) and white (93%). The two questionnaires were administered to the cohort before and approximately three months after their respective procedures, which were performed from January 2022 through January 2023.

Differences in pre- and post-surgery scores were calculated using a paired t-test, with effect size measured using Cohen's *d* (0.2 = small effect, 0.5 = medium, 0.8 = large).

On the three symptom domains that are common to all three scores — dysphagia, pain and reflux/regurgitation — the CEQ, its bother T-score and the ESS all detected statistically significant large effect size differences between the pre- and post-surgery time points (Cohen's *d* range, 0.88-2.59; $P < 0.001$).

Additionally, the CEQ and the bother T-score detected statistically significant effect size differences before and after surgery in the eating and dyspepsia domains (Cohen's *d* range, 0.76-1.19; $P < 0.001$).

"The CEQ was comparable for the same domains measured by the Eckardt symptom score," says Dr. Tasnim, "and we were surprised that it also documented significant improvements in dyspepsia post-surgery, which is not part of the Eckardt score."

Clinical applications of the CEQ

As reported in the *Journal of Thoracic and Cardiovascular Surgery* study (Epub 23 Aug 2023), validation of the CEQ was performed among 546 patients (mean age, 62 years; 53% male, 86% white), of whom > 90% completed it within five minutes. Construct validity was demonstrated by differentiating scores across conditions including esophageal cancer, achalasia, hiatal hernia and others.

To date, the CEQ has been used in more than 1,100 patients with esophageal complaints at Cleveland Clinic. Next steps are to incorporate it into the institution's electronic medical record and to seek multi-institutional validation of the instrument.

"Every patient with an esophageal disease who walks through our clinic's doors is completing this questionnaire, and we intend to administer it at every visit so we can amass longitudinal data," Dr. Sudarshan notes. "We are also working to extend use of the CEQ to other departments that see patients with esophageal disease and to surgeons in our local Veterans Affairs hospital."

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LORUNDROSTAT SAFELY LOWERS BLOOD PRESSURE IN UNCONTROLLED HYPERTENSION IN PHASE 2 TRIAL

Results inform dose selection for further trials of the aldosterone synthase inhibitor

Lorundrostat (MLS-101) — an investigational medication that works by lowering aldosterone production — safely and effectively lowered blood pressure (BP) in patients with hypertension refractory to standard medical treatment.

So reported investigators with the placebo-controlled Target-HTN phase 2 clinical trial in a late-breaking clinical trials session at the American Heart Association Hypertension Scientific Sessions 2023. The study was simultaneously published in the *Journal of the American Medical Association*.

"We saw a very robust blood pressure lowering response, particularly in study participants with obesity, a major driver of hypertension in this country," says first author Luke Laffin, MD, staff cardiologist in Cleveland Clinic's Section of Preventive Cardiology. "Lorundrostat has the potential to become an important new tool to help this hard-to-treat population and others with uncontrolled hypertension."

Possible new way to treat hypertension

Excess aldosterone has been implicated in contributing to hypertension in patients with obesity, metabolic syndrome and obstructive sleep apnea. In such individuals, the normal feedback loop of elevated aldosterone leading to increased renin activity — which inhibits further aldosterone synthesis — is disrupted.

If the standard three-drug regimen for treating hypertension (a thiazide diuretic, a calcium channel blocker, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) does not adequately control BP, a mineralocorticoid receptor antagonist (MRA), typically spironolactone, is added. While spironolactone binds intracellular aldosterone receptors, leading to BP lowering, its use is limited by side effects. In addition, circulating aldosterone levels may actually *increase* as a result of receptor blocking, enhancing nongenomic effects of aldosterone and leading to excess sympathetic activation, disrupted glucose homeostasis and negative vascular effects.

Lorundrostat (Figure) is in a novel class of drugs that lower aldosterone by inhibiting aldosterone synthase rather than blocking mineralocorticoid receptors. The orally administered medication has the potential to lower BP without the adverse effects of an MRA. The first aldosterone synthase inhibitor, osilodrostat, interfered with cortisol production. Baxdrostat, a more specific drug similar to lorundrostat, has performed well in a phase 2 clinical trial.

The current Target-HTN trial was designed to test lorundrostat's safety and efficacy, especially among patients with suppressed renin activity, and to help determine dosages for future trials.

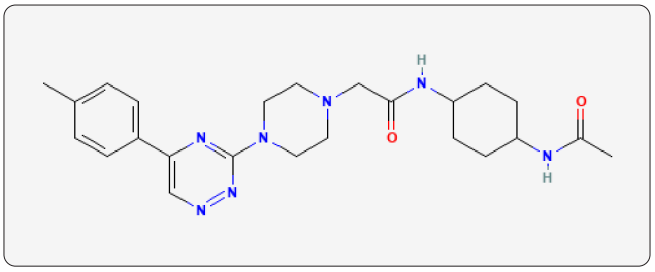

FIGURE — Chemical structure of lorundrostat, a member of a novel class of drugs that lower aldosterone by inhibiting aldosterone synthase rather than blocking mineralocorticoid receptors. This promises the potential to reduce blood pressure without the adverse effects of a mineralocorticoid receptor antagonist such as spironolactone.

"The development of lorundrostat is important because no new class of blood pressure-lowering drugs has been introduced for many years," says the study's senior author, Steven Nissen, MD, Chief Academic Officer of Cleveland Clinic's Heart, Vascular & Thoracic Institute. "Blood pressure is difficult to control in some patients, particularly those with obesity and diabetes, so new options will be valuable."

A dose-ranging study design with two target groups

The prospective, randomized, double-blind Target-HTN study was conducted at 43 U.S. sites, including Cleveland Clinic.

The Cleveland Clinic Coordinating Center for Clinical Research (C5Research) independently confirmed the primary endpoint analysis.

To qualify, patients had to have a minimum systolic BP of 130 mmHg despite taking at least two antihypertensive medications. The study's 200 patients were enrolled into two cohorts, with the initial cohort (cohort 1) consisting of patients with suppressed plasma renin activity (≤ 1.0 ng/mL/h) and elevated serum aldosterone (> 1.0 ng/dL) and a subsequent smaller cohort (cohort 2) consisting of patients without suppressed plasma renin activity (> 1.0 ng/mL/h). The cohorts were treated as follows:

- **Cohort 1** (n = 163; mean baseline BP of 142.2/81.5 mmHg): Participants were randomized in equal numbers to placebo or one of five lorundrostat doses (12.5 mg, 50 mg or 100 mg once daily, or 12.5 mg or 25 mg twice daily) for eight weeks.
- **Cohort 2** (n = 37; mean baseline BP of 139.1/79.1 mmHg): In a 1:6 ratio, patients were randomized to placebo or 100 mg lorundrostat once daily for eight weeks. This small cohort was considered exploratory to see whether patients without suppressed plasma renin activity might also respond to the drug; no formal statistical analysis was performed.

Patients continued their existing background antihypertensive medications during study treatment. Mean age of the study population was 65.7 years; 60% were women, 48% were Hispanic and 36% were Black.

Nearly half of participants (48%) had a body mass index of more than 30 kg/m^2 and 40% had type 2 diabetes.

All participants underwent a two-week placebo run-in period. After randomization, they were monitored with automated office BP measurements weekly throughout the study. The primary efficacy endpoint was change in systolic BP from baseline to week 8.

Results

Key efficacy findings were as follows:

- In cohort 1, observed reductions from baseline systolic BP were 14.1 and 13.2 mmHg with lorundrostat 100 mg and 50 mg once daily, respectively, compared with 4.1 mmHg with placebo. The least square mean difference in systolic BP change versus placebo was −9.6 mmHg for lorundrostat 50 mg once daily (90% CI, −15.8 to −3.4; $P = 0.01$) and −7.8 mmHg for lorundrostat 100 mg once daily (90% CI, −14.1 to −1.5; $P = 0.04$).
- Reductions in systolic BP with the twice-daily dosages, relative to placebo, were similar to those with the once-daily regimens.
- In cohort 2 (patients without suppressed plasma renin activity), lorundrostat 100 mg once daily reduced systolic BP by 11.4 mmHg.
- Patients with obesity had the largest BP-lowering response to lorundrostat.

Most adverse events were classified as mild. No cases of cortisol insufficiency occurred. One serious adverse event was believed to be treatment-related: a patient in cohort 2 on lorundrostat 100 mg developed worsening hyponatremia, requiring drug discontinuation. Mean serum potassium increases were similar across all doses of lorundrostat. Serum potassium rose above 6.0 mmol/L in six patients but was corrected with dose reduction or drug discontinuation and required no further intervention.

"The 50-mg daily dose lowered blood pressure to a similar degree as 100 mg, but with fewer adverse events," Dr. Laffin observes.

Keep an eye out for further trials

Dr. Laffin notes two trials using lorundrostat that Cleveland Clinic and C5Research are helping to lead:

- ADVANCE-HTN (NCT05769608) is testing lorundrostat as add-on therapy to standardized background treatment of patients with uncontrolled and resistant hypertension. About 300 participants are being randomized to placebo, lorundrostat 50 mg once daily, or lorundrostat 50 mg daily with titration at four weeks to 100 mg daily as needed. The 12-week trial is currently enrolling patients and is expected to issue preliminary results in 2024.
- A larger phase 3 international trial of lorundrostat is expected to begin enrolling participants soon, with early results anticipated in mid-2025.

"Target-HTN has found lorundrostat to be well tolerated and to confer significant and clinically meaningful blood pressure reduction in patients with hypertension refractory to standard therapy," Dr. Laffin summarizes. "These findings suggest that a targeted approach to blood pressure management might be useful, especially for those with elevated aldosterone."

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EARLY SURGERY FOR ISOLATED SEVERE TRICUSPID REGURGITATION IMPROVES OUTCOMES

Cleveland Clinic study argues against waiting for symptoms to develop

Surgery should be considered for isolated severe tricuspid regurgitation (TR) before overt symptoms develop. So concludes a retrospective study of 159 patients who underwent isolated surgical tricuspid valve (TV) repair or replacement at Cleveland Clinic. The study was published in the *Journal of Thoracic and Cardiovascular Surgery* (2023;166[1]:91-100).

The investigation found higher operative mortality and significantly worse composite morbidities in patients who had symptomatic severe TR preoperatively compared with asymptomatic patients with severe TR and right ventricular dilation and/or dysfunction. The study is one of the largest single-center series of isolated TV surgery to date, and the first to compare surgeries by indication.

"We found that taking an earlier approach to intervening for isolated TR saves lives," says senior and corresponding author Milind Desai, MD, MBA, a cardiologist and Vice Chair of Cleveland Clinic's Heart, Vascular & Thoracic Institute. "Waiting for symptoms to appear is associated with many comorbidities and higher patient risk for surgery."

Established indications for isolated TV surgery are few

Isolated TV surgery entails higher risk of operative mortality than isolated operations on other heart valves or on coronary arteries. For this reason, it is not often performed, even at high-volume centers like Cleveland Clinic, despite poor outcomes associated with severe TR.

The latest American College of Cardiology/American Heart Association guideline for valvular heart disease has no class I indications for isolated TV surgery, while European Society of Cardiology (ESC) guidelines have just one such indication — for severe symptomatic isolated TR.

Study design and findings

The study comprised 159 patients who underwent isolated TV surgery at Cleveland Clinic between 2004 and 2018. Of those, 115 were symptomatic ("class I group," per the ESC guidelines) and 44 were asymptomatic ("early surgery group") at the time of surgery. At baseline, all patients in the early surgery group had one of the following: both right ventricular dilation and dysfunction (n = 12; 26.8%), right ventricular dilation alone (n = 23; 52.7%) or right ventricular dysfunction alone (n = 9; 20.5%).

Seventeen surgeons performed the procedures. Valve repair was performed in 73.0% of class I patients and 79.5% of early surgery patients ($P = 0.54$). More than 90% of valve replacements were done using bioprosthetic valves.

The two groups differed significantly at baseline in several respects: class I patients were older than early surgery patients (mean age of 61.7 vs. 54.4 years; $P = 0.016$); had a higher prevalence of secondary TR (65.2% vs. 38.6%; $P = 0.004$); had more symptoms (by definition), including right heart failure, higher New York Heart Association class and greater likelihood to be in a critical preoperative state; and more often had a history of cardiac surgery, cardiac implantable electronic device, heart failure, atrial fibrillation or chronic lung disease.

Key findings were as follows:

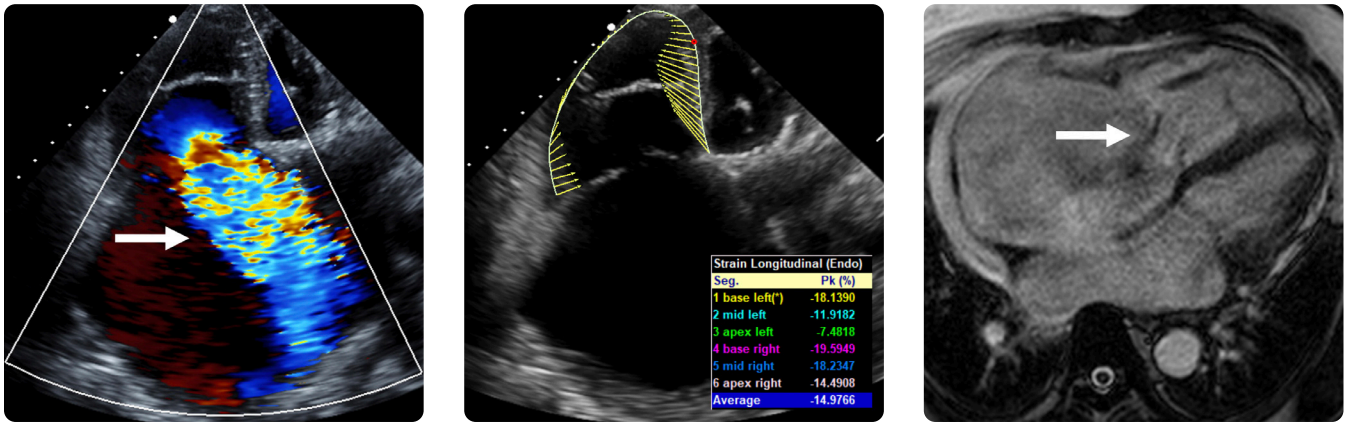
- Operative mortality occurred in eight patients (7.0%) in the class I group versus no patients (0.0%) in the early surgery group ($P = 0.107$).
- Composite morbidity occurred in 41 patients (35.7%) in the class I group versus eight patients (18.2%) in the early surgery group ($P = 0.036$).

The early surgery group had superior survival rates over the length of the study (mean follow-up, 5.1 ± 4.0 years). Multivariable analysis revealed that mortality during follow-up (the primary endpoint) was associated with the following factors:

- Class I indication (vs. early surgery) — hazard ratio (HR) = 4.62 (95% CI, 1.09-19.7); $P = 0.038$
- Age (per year) — HR = 1.03 (95% CI, 1.00-1.07); $P = 0.046$
- Diabetes mellitus — HR = 2.50 (95% CI, 1.13-5.55); $P = 0.024$

"Although differences in outcomes between the two groups were mostly explained by baseline clinical differences, the early surgery

BELOW — The study authors recommend that patients who have isolated tricuspid regurgitation without overt symptoms should be monitored with multimodality imaging such as transthoracic echocardiography (TTE) (left), right ventricular longitudinal strain evaluation by TTE (middle) and cardiac MRI (right) so that surgery can be considered once certain imaging thresholds are met. Arrows in these images point to findings of severe tricuspid regurgitation.



group was still better off after adjustment for these differences," Dr. Desai observes.

Guidance for improving outcomes

The study authors emphasize several takeaways from their findings, as outlined below.

- **Don't wait for symptoms.** "Patients with isolated TR before having overt symptoms should be monitored with quantitative right heart and TR measures on cardiac imaging — such as tricuspid regurgitant volume (≥45 mL on echocardiography, >35 mL on cardiac MRI) or regurgitant fraction (>30% on cardiac MRI) and right ventricular strain (less negative than −19% on echo)," says first author Tom Kai Ming Wang, MBChB, MD, staff cardiologist in Cleveland Clinic's Section of Cardiovascular Imaging. "This was shown in two of our group's recent studies (*Circ Cardiovasc Imaging*. 2021;14[9]:e012211 and *JACC Cardiovasc Imaging*. 2023;16:13-24), and it is recommended so that surgery can be considered once the aforementioned imaging thresholds are met. To further aid patient management and surgical selection, we recently developed a novel risk score (*JACC Cardiovasc Imaging*. 2022;15:731-744) for predicting one-year mortality in isolated TR to assist in risk stratification for these high-risk patients."
- **Concentrate surgeries at centers of excellence.** "Isolated tricuspid valve surgery is high-risk and infrequently performed, so we strongly recommend that it be done at a high-volume institution for the best results," says co-author A. Marc Gillinov, MD, Chair of Thoracic and Cardiovascular Surgery at Cleveland Clinic. The authors note that morbidity and mortality outcomes in this study compare favorably with those in other recent reports, likely due to surgeon experience in all TV operations, patient selection and attentive perioperative management.
- **Consider transcatheter approaches, especially for high-risk surgical candidates.** "Percutaneous approaches to TV repair and replacement are emerging in an effort to improve outcomes and widen the candidate pool to safely undergo intervention," says Amar Krishnaswamy, MD, Chair of Interventional Cardiology at Cleveland Clinic, who wasn't involved in the study. "Outcomes from this study can provide surgical benchmarks for studies of isolated TV catheter-based approaches."

"Although this study has the limitations of a single-center observational investigation, it has the advantage of reflecting real-world practice," Dr. Desai notes. "Randomized controlled trials are now needed to compare outcomes of surgical, transcatheter and medical management, along with their timing and indications."

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FIRST PATIENT TREATED WITH INVESTIGATIONAL GENE THERAPY FOR HYPERTROPHIC CARDIOMYOPATHY

One-time infusion of adenovirus-based therapy is designed to restore heart muscle function

Human clinical testing of TN-201, an experimental gene therapy for hypertrophic cardiomyopathy (HCM) associated with myosin binding protein C3 gene (*MYBPC3*) mutation, has begun with infusion of the therapy in the first patient in a phase 1b trial at Cleveland Clinic in early October.

The goal of treatment with TN-201, a first-in-class adenovirus-based therapy, is to deliver a working copy of the *MYBPC3* gene to the heart muscle in hopes of halting disease progression. In preclinical studies, a one-time intravenous infusion restored normal levels of myosin binding protein C3, which regulates contraction of heart muscle, reversing HCM.

"TN-201 is given as a single injection to stimulate protein formation with the aim of achieving normal myocardial function," says investigator Milind Desai, MD, MBA, Director of Cleveland Clinic's Hypertrophic Cardiomyopathy Center. "If it is ultimately shown to be safe and effective in humans, it could prove to be a one-time solution for a fairly common form of HCM."

Targeting the genetic cause of one-fifth of HCM cases

HCM, the leading cause of sudden cardiac death before age 30, often has a genetic etiology. The most frequent genetic cause is *MYBPC3* mutation, accounting for an estimated 20% of all HCM cases.

"This mutation essentially results in a protein deficiency state," Dr. Desai says. "People with a defective *MYBPC3* gene produce only 60% to 70% of the myosin binding protein C3 needed for heart function. Patients with *MYBPC3*-associated HCM are at higher risk for accelerated decline and serious disease complications."

Trial at a glance

The new trial is an open-label, multicenter investigation of TN-201 among patients with *MYBPC3*-associated nonobstructive HCM who are symptomatic and have an implantable cardioverter defibrillator.

Investigators are targeting an enrollment of six to 15 adults. All patients will receive the therapy as a two-to-three-hour infusion, be monitored on an inpatient basis for a week, and then be followed for treatment response over five years.

Primary outcome measures are safety and tolerability over five-year follow-up. The secondary outcome measure is change in quality-of-life measures at week 52. Patients also will undergo heart biopsies at post-infusion weeks 8 and 52 to assess expression levels of vector genomes, transgene messenger RNA and myosin binding protein C3 in the right ventricular septum. Changes in N-terminal pro-BNP and high-sensitivity cardiac troponin I levels will be assessed over five years, as will changes in echocardiography measures, peak exercise capacity and New York Heart Association class.

ABOVE — A Cleveland Clinic research nurse coordinator readies the infusion of TN-201 for the trial's first patient.

Quest for an additional noninvasive tool

The study's first patient, a 27-year-old woman, was discharged after a week and is doing well so far, Dr. Desai says. Trial results are expected in 2024. If TN-201 is found to be safe and effective, a phase 2 trial will be launched in a larger population.

"Our understanding of HCM has progressed to the point where we are developing novel medical treatments that will, hopefully, avoid the need for septal reduction therapy," says Dr. Desai. "We are now focused on determining whether the impressive preclinical results seen with TN-201 can be translated into a safe and efficacious treatment for patients."

Disclosure: Dr. Desai is a paid consultant to Tenaya Therapeutics, which is sponsoring the study.

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RESEARCH ROUNDUP

RECENT STUDIES OF NOTE FROM CLEVELAND CLINIC

Monomorphic VT Electrical Storm: Is Ischemic or Coronary Evaluation Needed?

Ischemic or coronary evaluations often needlessly delay lifesaving ablation therapy in patients who have monomorphic ventricular tachycardia (VT) electrical storm with no indication of an acute coronary syndrome (ACS). So concludes a retrospective study of 97 patients from Cleveland Clinic's VT ablation registry, which showed that such evaluations (conducted in 45% of patients) resulted in few findings of causative coronary occlusions and had little impact on procedural and mortality outcomes. The study, the first to address this issue, was published in *JACC: Clinical Electrophysiology* (2023;9[9]:1890-1899). "In the setting of monomorphic VT electrical storm without ACS, we found that time and resources are generally better spent focused on prompt rhythm control than on coronary assessment," says co-author Ayman Hussein, MD. "Ischemia assessment not only delays therapy but involves risks inherent to invasive coronary angiography."

Patient Sex Linked With Progression and Outcomes of Early Aortic Stenosis

A large retrospective cohort study of patients with mild to moderate aortic stenosis finds that, compared with men, women had slower hemodynamic progression, greater chance of having preserved left ventricular (LV) ejection fraction and concentric LV hypertrophy, and a lower incidence of aortic valve replacement (AVR). The findings are from a propensity-matched analysis of 2,548 patients (57.5% men, 42.5% women) from the Cleveland Clinic echocardiography database from 2008 through mid-2016, with follow-up until 2018. "Women's slower hemodynamic progression may help explain their lower incidence of AVR versus men," says co-author Venu Menon, MD. "Our findings support the need for sex-specific clinical assessment and follow-up surveillance of early-stage aortic stenosis." The study appeared in *JACC: Cardiovascular Imaging* (Epub 26 July 2023).

Increased HF Risk Lingers Among Black Residents of Redlined Neighborhoods

Older Black Americans currently living in ZIP codes that were heavily redlined by the U.S. government in the 1930s have a significantly elevated risk of heart failure (HF) compared with Black Americans residing in other areas. That's the conclusion of a Cleveland Clinic-led study (*Circulation*. 2023;148[3]:210-219) of data from over 2 million Medicare beneficiaries between 2014 and 2019. Even after adjusting for age, sex, comorbidities and social deprivation factors, contemporary risk of HF was significantly higher among Black residents in ZIP codes with the highest proportion of historic redlining in real estate lending practices. No such effect was seen for white Medicare beneficiaries. "Significant health effects were found even many years after the discriminatory policies officially ended," says co-author Amgad Mentias, MD, MS. "This points to structural racism's role in cardiovascular health disparities."

Novel Approach to Transcaval Type II Endoleak Embolization Shows Safety and Efficacy

For embolization of type II endoleak after endovascular aneurysm repair, use of a 0.014" guidewire and continuous current electrocautery allows crossing of the inferior vena cava/aortic sac junction without puncturing or damaging the endograft or nearby structures. Cleveland Clinic vascular surgeons reported their experience with this novel approach to transcaval type II endoleak embolization in 12 patients in a retrospective cohort study in *Annals of Vascular Surgery* (2023;93:300-307). "The big advantage of this technique is the sole use of a 0.014" guidewire to gain access to the aortic sac, making inadvertent perforation of the endograft very unlikely," says co-author Sean Lyden, MD. "In all cases, access was successful without significant acute morbidity or mortality."

CAC Scoring Improves CVD Risk Screening Accuracy

Adding coronary artery calcium (CAC) scoring to traditional screening for cardiovascular disease (CVD) increases the precision of 10-year risk calculations in individual patients. So suggests a study by Cleveland Clinic researchers in the *American Journal of Cardiology* (2023;206:303-308). Analysis of data from 5,324 asymptomatic middle-aged adults found that adding CAC scoring from the Multi-Ethnic Study of Atherosclerosis (MESA) to two traditional CVD risk scores — the Atherosclerotic Cardiovascular Disease Risk Calculator (ASCVD) and the Reynolds Risk Score (RRS) — resulted in significant stratification in nearly half of study participants. Overall, the ASCVD overestimated CVD risk while the RRS underestimated CVD risk compared with MESA-CAC scoring. However, a differential reclassification emerged when participants were divided by number of calcified coronary arteries. "Adding CAC results to traditional CVD risk models provides important and synergistic value, reducing the risk of under- or overprescribing of preventive therapy," says co-author Milind Desai, MD, MBA.

CME PREVIEW

DON'T MISS THE DEFINITIVE COURSE ON VALVE DISEASE, STRUCTURAL INTERVENTIONS AND IMAGING

26th annual offering will mix the tried and true with emerging developments

Valve Disease, Structural Interventions and Diastology/Imaging Summit

Thu.-Sun., March 7-10, 2024
Fontainebleau Miami Beach | Miami Beach, Florida
Information/registration: ccfcme.org/echo

This popular annual CME course, which was offered for the 25th time in early 2023, will begin its second quarter century in March 2024 by combining its established strengths with explorations of emerging practice developments.

"This year, in addition to addressing the latest in valvular heart disease, structural interventions and new advances in imaging, we will explore the role of artificial intelligence as well as timely controversies in clinical practice," says summit director Allan Klein, MD, a cardiologist who directs Cleveland Clinic's Pericardial Diseases Center. "Many presentations will be case-based, featuring a practical approach to management. These will be complemented by debates, hands-on workshops and panel discussions."

Structural heart disease through an imaging lens

Topically, the focus will be on mitral, aortic and tricuspid valve disease as well as developments in structural interventions, including transcatheter aortic valve replacement (TAVR), transcatheter edge-to-edge repair (TEER), valve-in-valve procedures and left atrial appendage occlusion. Additional sessions are devoted to diastology, myocardial and pericardial diseases, and a combination of sarcoid disease, congenital heart disease, mechanical support in heart failure and contrast echocardiography.

The faculty of over 20 expert clinicians from Cleveland Clinic and other top centers includes leaders in cardiovascular imaging, interventional cardiology, electrophysiology and other cardiology subspecialties as well as cardiothoracic surgeons, sonographers and researchers.

A focus throughout will be practical application of the latest relevant practice guidelines and consensus statements on valves, structural interventions, pericarditis, hypertrophic cardiomyopathy and amyloid disease. "This course offers attendees the best opportunity to get up to date on issues in cardiovascular imaging and structural heart disease," says summit co-director Leonardo Rodriguez, MD, Program Director of Cleveland Clinic's Advanced Imaging Fellowship.

Diverse and well-paced agenda

The summit's pace will be brisk, featuring presentations five to 12 minutes in length and often organized around illustrative cases. These focused talks will be integrated into interactive panel discussions at the end of each of the seven broad topical sessions.

The agenda is punctuated by a series of case workshops and a pair of hands-on "how to" sessions — one on 3D reconstruction and cropping in valve disease, and one on strain imaging and diastology.

The format will be further diversified by a series of pro/con debates — on TEER versus surgery for primary mitral regurgitation, on TAVR versus surgical AVR for an active 65-year-old, and on whether artificial intelligence will replace echocardiographers in the future.

"Our program is updated every year to provide state-of-the-art reviews across all areas of valve disease, structural interventions and diastology," says summit co-director Christine Jellis, MD, PhD, of Cleveland Clinic's Section of Cardiovascular Imaging. "With a focus on innovation and drawing on Cleveland Clinic's vast experience, we are able to showcase new technologies, provide practical clinical pearls and give hands-on technical training through interactive workshops."

Another opportunity for hands-on instruction is a two-hour "Learning Lab for Interventional Echo" on Thursday evening, March 7, before the start of the summit the next morning. This lab — limited to 25 attendees — provides hands-on practice in 3D transesophageal echo and multiplanar reconstruction to inform structural heart interventions.

The meeting itself takes place Friday through Sunday, with early starts each day and adjournment by 1 p.m. to allow attendees to enjoy the Miami Beach sunshine. Attendees will have abundant opportunities to interact directly with expert faculty at breaks and meals throughout the summit.

"Structural intervention and cardiovascular imaging are evolving at an unprecedented pace," says summit co-director Samir Kapadia, MD, Chair of Cardiovascular Medicine at Cleveland Clinic. "This course will feature thought leaders' takes on these innovations and provide ideal opportunities for interaction at a great venue."

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

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Information/registration: ccfcme.org/congenital

Valve Disease, Structural Interventions and Diastology/Imaging Summit

Thu.-Sun., March 7-10, 2024

Fontainebleau Miami Beach
Miami Beach, Florida

Information/registration: ccfcme.org/echo

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

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