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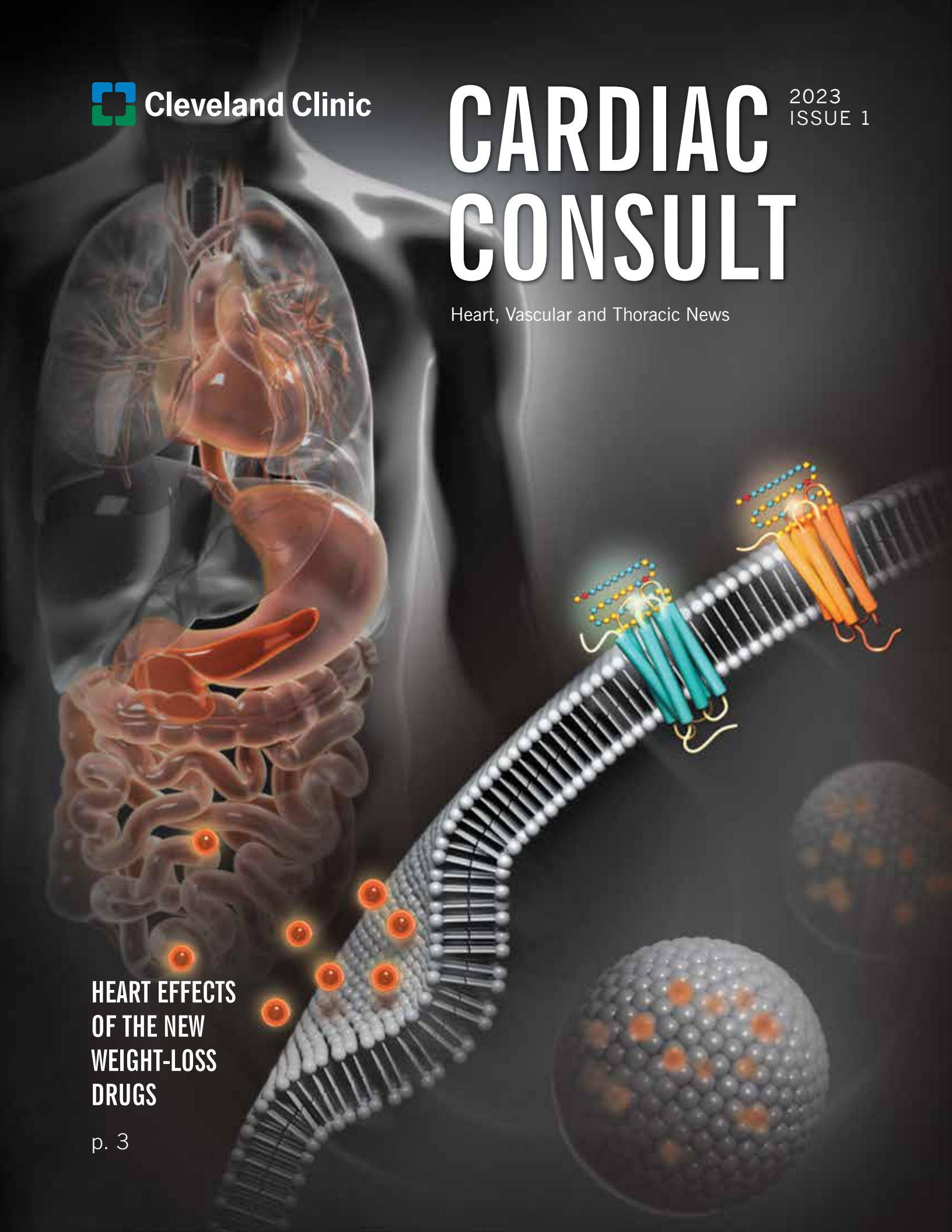

HEART EFFECTS OF THE NEW WEIGHT-LOSS DRUGS

p. 3

FROM THE CHAIR

Managing some of the world's most challenging cardiovascular and thoracic cases inspires the mind to imagine the best care possible — and then try to invent or help develop it.

Practice-fueled research has been fundamental to the leadership of Cleveland Clinic's Heart, Vascular & Thoracic Institute for many decades. As this issue of *Cardiac Consult* makes clear, it still is.

As profiled on page 14, our clinicians and scientists are using genomics — and omics more broadly — to develop a pipeline of repurposed medications for use in preventing progression of atrial fibrillation. This multifront research project has earned the support of a five-year, $14 million NIH grant.

As outlined on page 12, clinicians in our Hypertrophic Cardiomyopathy Center are leading a multitude of studies with potential to reshape the care of hypertrophic cardiomyopathy (HCM). These range from the pivotal VALOR-HCM trial supporting approval of the first medication for obstructive HCM to early investigations of a novel gene therapy for HCM to a study analyzing contemporary use of septal reduction therapy in the United States.

And as our cover story reports, Cleveland Clinic is honored to play leadership roles in both of the two large multicenter studies that promise to generate the first randomized trial evidence that weight loss can yield cardiovascular benefits independent of antidiabetic effects. Such evidence could upend preventive cardiology care in patients with overweight and obesity, particularly with the advent of the GLP-1 and GLP-1/GIP receptor agonist medications.

We remain inspired to invent and help develop tools to achieve the best care possible. We are grateful for your collaboration in those efforts.

Respectfully,

Lars G. Svensson, MD, PhD

Chair, Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute

Cleveland Clinic was named a top U.S. hospital in *U.S. News & World Report*'s "Best Hospitals" rankings for 2022-23, as well as the No. 1 hospital in cardiology and heart surgery for the 28th consecutive year.

ON THE COVER — Glucagon-like peptide-1 (GLP-1) receptor agonists and GLP-1 receptor/glucose-dependent insulinotropic polypeptide (GIP) receptor dual agonists bind to their respective receptors on pancreatic beta cells to stimulate glucose-induced insulin secretion. In addition to enhancing insulin secretion, binding to these receptors and downstream signaling slow gastric emptying and reduce appetite, leading to weight loss. See page 3 for cover story.

NEW WEIGHT-LOSS DRUGS ARE POISED TO UPEND PREVENTIVE CARDIOLOGY CARE IN PATIENTS WITH OBESITY AND OVERWEIGHT

Two major trials promise key progress against the last unaddressed major risk factor

Researchers and clinicians have long recognized a web of cause-and-effect relationships within the triad of cardiovascular disease (CVD), diabetes and obesity. Diabetes promotes development of CVD, and at least two classes of diabetes medications have been shown to improve CVD outcomes in patients with diabetes. Likewise, obesity raises the risk of type 2 diabetes, and randomized trial evidence shows that substantial weight loss in people with obesity can reverse diabetes or reduce its risk of development.

As for the third part of the triad — between obesity and CVD — a contributory role has been well established, with mounting data now indicating that excess body weight's association with CVD risk seems to be independent of its promotion of individual risk factors such as hypertension. Yet the "effect" aspect in this part of the triad has been more elusive. Growing evidence from observational studies indicates that treatment of obesity with bariatric surgery improves cardiovascular outcomes, but these findings have not been confirmed in randomized trials, largely because of randomization challenges with bariatric surgery.

But now the quest for randomized evidence of CVD benefits from treating obesity may soon yield dividends, thanks to two major multicenter trials of anti-obesity medications — one run by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and one with a Cleveland Clinic cardiologist as co-principal investigator. This article profiles these trials and their implications for management of CVD in people with obesity, after briefly tracing the path to the launch of these studies.

The obesity challenge

The past several decades have been boom times for innovation across multiple CVD risk factors, bringing forth an abundance of medications to regulate lipids, control blood pressure, lower blood sugar and improve inflammation. Yet one leading risk factor — obesity — has been largely untouched by this innovation wave. In this absence of therapeutic advances, the proliferation of societal factors that promote weight gain has resulted in a 41.9% prevalence of obesity and a 73.9% prevalence of overweight or obesity among U.S. adults, according to the National Center for Health Statistics.

"While we make progress on all these other CVD risk factors, obesity has continued unabated," says A. Michael Lincoff, MD, Vice Chair for Research in Cleveland Clinic's Department of Cardiovascular Medicine. "We don't have nonsurgical therapies that directly target cardiovascular risk-associated overweight or obesity and the related metabolic abnormalities. The profile of a typical heart disease patient has shifted over the past 30 years from the hypertensive, chain-smoking, type A personality to someone with overweight or obesity and concomitant diabetes. We can treat some of that latter patient's risk factors, but there's still much risk associated with body weight that we cannot directly target with medical therapy beyond lifestyle changes."

Insights from bariatric surgery

The "medical therapy" caveat in Dr. Lincoff's comment is important, as the growth and refinement of bariatric (metabolic) surgery over the past 30 years has resulted in significant gains for many patients — in life span, quality of life, reduction of diabetes risk and even reversal of diabetes — as well as compelling evidence suggesting cardiovascular benefits.

A good deal of that cardiovascular evidence has come from Cleveland Clinic researchers. A Cleveland Clinic team led by cardiologist Amgad Mentias, MD, recently published a large database analysis showing that bariatric surgery in Medicare enrollees with obesity was associated with lower risks of mortality, new-onset heart failure and myocardial infarction (*J Am Coll Cardiol*. 2022;79:1429-1437).

Additionally, Cleveland Clinic cardiologist Steven Nissen, MD, has worked with bariatric surgeon Ali Aminian, MD, to publish a series of large retrospective cohort studies examining the effects of bariatric surgery on various clinical outcomes. Most notable is a study of cardiovascular outcomes among 2,287 patients with type 2 diabetes and obesity who underwent bariatric surgery at Cleveland Clinic and 11,435 matched controls (*JAMA*. 2019;322:1271-1282). The analysis showed that metabolic surgery significantly reduced major adverse cardiovascular events over 3.9 years of follow-up, with a hazard ratio of 0.61. The same researchers found similar effects on cardiovascular events

from bariatric surgery in patients with obesity and nonalcoholic steatohepatitis (*JAMA*. 2021;326:2031-2042).

"The average weight loss with sleeve gastrectomy, a common bariatric surgical procedure, is 20% to 25%," says Dr. Nissen, Chief Academic Officer of Cleveland Clinic's Heart, Vascular & Thoracic Institute. "We wanted to see if losing 20% or more of body weight would have a major effect on mortality, cardiovascular morbidity and other forms of morbidity. And it certainly did."

Enter the GLP-1 receptor agonists

Nevertheless, bariatric surgery — although low risk — is a highly invasive procedure that a limited number of patients are willing or able to consider. Even if all potential candidates chose to pursue it, their sheer numbers would swamp surgical capacity for many years to come. "We need pharmacological help to address the extraordinary effects and reach of the obesity epidemic," Dr. Nissen says.

Yet the track record of anti-obesity medications to date has been "uniformly disappointing," notes Dr. Lincoff, in terms of their effects on cardiovascular outcomes, their safety profiles or both.

However, around the time that bariatric surgery's positive effects on diabetes and cardiovascular outcomes were emerging from observational studies, researchers were taking note of the weight-loss and cardiovascular effects of the GLP-1 receptor agonist medications (GLP-1 RAs) used to treat type 2 diabetes.

GLP-1 stands for glucagon-like peptide-1, a gut hormone released in response to eating that serves as a satiety signal, stimulating insulin release, inhibiting glucagon secretion and regulating gastric emptying.

Consistent with these effects, GLP-1 RAs have been associated with substantial weight loss in clinical trials, leading to FDA approval of two of these agents — liraglutide and semaglutide — for chronic weight management in adults with obesity or with overweight and at least one weight-related comorbidity. "Semaglutide, which is the most potent pure GLP-1 RA available, has produced weight loss of up to 17% to 20% in clinical trials designed to assess its effect on weight," says Dr. Lincoff.

GLP-1 also produces effects that promise cardiovascular benefit, such as natriuresis, diuresis, and reduction of blood pressure and inflammation. Accordingly, GLP-1 RAs have reduced the risk of atherosclerotic cardiovascular events in a number of randomized outcomes trials in patients with type 2 diabetes. However, no completed trial has examined the effect of GLP-1 RAs on cardiovascular events in patients with established CVD and overweight/obesity *in the absence of type 2 diabetes*.

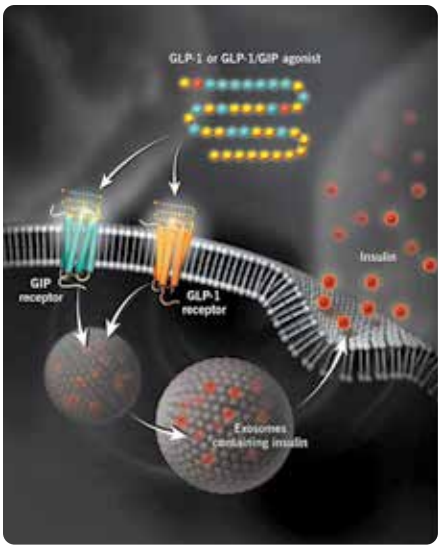

FIGURE — GLP-1 and dual GLP-1/GIP receptor agonists bind to their respective receptors on pancreatic beta cells to stimulate glucose-induced insulin secretion. Binding to these receptors also slows gastric emptying and reduces appetite, leading to weight loss.

That will change when results of the phase 3 randomized SELECT trial (NCT03574597) are released, perhaps as soon as 2023 or early 2024. This multicenter study has enrolled 17,500 adults aged 45 or older with a body mass index (BMI) of 27 kg/m^2 or greater and established CVD but without diabetes. Patients are randomized to 2.5 to 5 years of weekly semaglutide injections or placebo as an adjunct to standard care. The primary outcome measure is time to first major adverse cardiovascular event.

"The SELECT trial is designed to fill the gap in randomized trial evidence on cardiovascular outcomes with treatment of overweight or obesity independent of the effect that semaglutide has on diabetes," says Dr. Lincoff, who serves as co-principal investigator of the study.

Further promise from dual agonism

As the SELECT trial nears completion, a similar large trial was launched in autumn 2022, but this one involves a new wrinkle on GLP-1 receptor agonism that appears to yield even greater weight loss. It comes in the form of tirzepatide, a medication approved by the FDA in May 2022 to treat type 2 diabetes. Tirzepatide is the first in a class of drugs called dual GLP-1/GIP receptor agonists that activate the receptor for another gut hormone, glucose-dependent insulinotropic polypeptide (GIP), in addition to the GLP-1 receptor.

With this dual agonism, tirzepatide has demonstrated the largest weight loss in a randomized trial of any medication for obesity/overweight to date, with its highest dose achieving a 22.5% reduction relative to placebo at 72 weeks in the phase 3 SURMOUNT-1 trial (*N Engl J Med*. 2022;387:205-216). Submission of the drug for FDA approval for weight

"It's going to be very hard for people not to accept the value of these drugs…if we show they reduce cardiovascular morbidity and mortality…. For the first time, I have hope that we can actually reverse the obesity epidemic." — STEVEN NISSEN, MD

loss is expected after completion of a second phase 3 trial, SURMOUNT-2, in spring 2023.

Notably, SURMOUNT-1, which excluded patients with diabetes, showed improvements with tirzepatide in all prespecified cardiometabolic measures. That, together with the Cleveland Clinic studies showing cardiovascular outcome benefits from bariatric surgery, prompted Dr. Nissen to help launch the SURMOUNT-MMO trial (NCT05556512) in October 2022 ("MMO" stands for "Morbidity and Mortality in Obesity").

This phase 3 multicenter study, which is coordinated by Cleveland Clinic's C5Research academic research organization, is enrolling 15,000 adults with overweight or obesity (BMI ≥ 27) who do not have diabetes but do have either established CVD or multiple CVD risk factors. Patients are randomized in parallel fashion to subcutaneous tirzepatide once weekly or matching placebo. The primary outcome measure is time to first major cardiovascular event over five years of follow-up.

Dr. Nissen, who serves as study co-chair of SURMOUNT-MMO, notes that the exclusion of patients with diabetes will avoid confounding of results by favorable outcomes due to tirzepatide's antidiabetic effects. "If this trial is successful, we will have the evidence necessary to show the medical community that obesity is a reversible risk factor for atherosclerotic cardiovascular disease and other outcomes," he says.

He adds that SURMOUNT-MMO is also worth watching for a number of its secondary outcomes, including time to onset of type 2 diabetes, renal death or end-stage renal disease, and a variety of quality-of-life measures.

Overcoming reimbursement reluctance

Dr. Nissen expects tirzepatide to soon join the pure GLP-1 RAs with an FDA-approved indication for weight loss in addition to diabetes, although it may meet the same payer reluctance around reimbursement for weight loss that the pure GLP-1 RAs have. But Drs. Nissen and Lincoff suspect that reluctance will erode over time as more of these types of medications are approved for weight loss, particularly if the SELECT and SURMOUNT-MMO trials result in indications for atherosclerotic CVD.

"It's going to be very hard for people not to accept the value of these drugs, particularly tirzepatide and future dual agonists, if we show they reduce cardiovascular morbidity and mortality," says Dr. Nissen. "Tirzepatide produced weight loss at 72 weeks in the range of bariatric surgery, so a case can be made that this will be a cost-effective therapy. It may take time to convince payers, but it will happen. For the first time, I have hope that we can actually reverse the obesity epidemic."

Dr. Lincoff is also optimistic, but he notes that cardiologists will need to gain familiarity with using the GLP-1 RAs and tirzepatide. "These drugs require dose titration, particularly to reduce adverse

THE TRIALS AT A GLANCE

	SELECT	SURMOUNT-MMO
Treatment	Subcutaneous semaglutide (GLP-1 receptor agonist) 2.4 mg once weekly	Subcutaneous tirzepatide (dual GLP-1/GIP receptor agonist) once weekly up to maximum tolerated dose
Duration/ design	5 years; randomized, double-blind, placebo-controlled, parallel-group	5 years; randomized, double-blind, placebo-controlled, parallel-group
Population	17,500 adults ≥ age 45 with BMI ≥ 27 kg/m^2 without diabetes but with established CVD	15,000 adults with BMI ≥ 27 kg/m^2 and without diabetes who are either ≥ age 40 with established CVD or ≥ age 50 (for men) or 55 (for women) with multiple CVD risk factors
Primary endpoint	Time to first major cardiovascular event over 5 years	Time to first major cardiovascular event over 5 years
Estimated completion date	Sept. 2023	Oct. 2027

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; BMI = body mass index; CVD = cardiovascular disease

"If patients start these medications without changing how they eat, the medications will be less effective, although they make it easier to eat less because they cause satiety."

— DENNIS BRUEMMER, MD, PHD

effects like nausea and diarrhea that are common soon after starting therapy," he says. "So cardiologists will need to counsel patients through that and acclimate them to giving these drugs by subcutaneous injection."

His colleague Dennis Bruemmer, MD, PhD, Director of Cleveland Clinic's Center for Cardiometabolic Health, already has considerable experience using these drugs for diabetes and weight loss. He says cardiologists will become increasingly comfortable using GLP-1 RAs and dual agonists, although they need to take care when starting them in patients with diabetes who are taking insulin. "In those cases," he says, "cardiologists may need help from a physician specializing in diabetes, because the insulin dose requires adjustment and management becomes more complicated."

Dr. Bruemmer notes that the medications are well accepted by patients. "These drugs are so powerful, and the injections and side effects compare so favorably with the invasiveness of bariatric surgery, that I think they will significantly reduce demand for bariatric surgery in the coming years," he predicts.

What to do in the meantime?

Despite the promise of these new therapies to address all parts of the CVD/diabetes/obesity triad, approval and broad reimbursement for all these uses are likely still a few years off. What can be done in the interim for the tens of millions of Americans with CVD related to obesity or overweight?

That's a question preventive cardiologists can find frustrating, for at least two reasons. First, the obesity epidemic fundamentally requires far more emphasis on prevention than on treatment. "We are reactive rather than proactive about this problem," says Dr. Bruemmer, noting a range of contributors to obesity that are not proactively addressed, from societal factors to health system and payer factors. Second, many effective tools are available to manage obesity, but they are not widely used, for a variety of reasons. Dr. Bruemmer cites the example of medically supervised weight loss programs. "These can be quite effective," he says, "but very few patients end up taking part," for reasons that range from coverage and access challenges to inertia on the part of providers or patients.

Bariatric surgery is another effective tool, yet only a fraction of eligible patients undergo it. The reasons are multifactorial, but a key one is limited access. While broader access is desired, Dr. Bruemmer cautions that bariatric surgery must be offered in a comprehensive way if it is to be safe and successful. "Patients need to be followed in a specialized bariatric surgery program," he explains. "Their medications need to be titrated. They need to be on certain supplements to help with nutrition. They require monitoring on a number of fronts and careful, regular follow-up after surgery. This type of care from a high-volume center with a comprehensive program is the way to ensure good outcomes from bariatric surgery."

What about lifestyle changes?

The milestone NIH-funded Look AHEAD trial (*N Engl J Med*. 2013;369:145-154) found that intensive lifestyle intervention focused on weight loss did not reduce cardiovascular events in a large cohort of adults with overweight/obesity and type 2 diabetes. Despite the reality that lifestyle change alone doesn't adequately address these conditions in most individuals, Dr. Bruemmer says it's an essential part of any ultimately successful treatment strategy, including use of tirzepatide and the GLP-1 RAs.

"If patients start these medications without changing how they eat, the medications will be less effective," Dr. Bruemmer says, "although they make it easier to eat less because they cause satiety. Initiation of these medications should always be accompanied by nutrition sessions to instruct patients on portion sizes and other dietary issues.

"Regardless of any other treatments," he concludes, "patients' best chances for a long, healthy life are going to come with exercise and eating healthy."

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Contact Dr. Lincoff at 216.444.2367, Dr. Nissen at 216.445.3224 and Dr. Bruemmer at 216.445.2332.

SURGICAL SOLUTIONS TO ANOMALOUS CORONARY ARTERIES AND MYOCARDIAL BRIDGES IN ADULTS

Growing awareness of impact at any age leads to proliferation of procedures

Anomalous aortic origin of a coronary artery (AAOCA) is an important cause of sudden cardiac arrest, most notoriously occurring in young athletes with no inkling of underlying problems. But awareness is increasing that this rare congenital malformation with multiple variants can also cause trouble in adults, as can myocardial bridges, a more common defect involving part of a coronary artery course embedded within the myocardium.

"Because most cardiologists and surgeons typically see few adults with AAOCA, or have the misconception that all myocardial bridges are benign, there is much uncertainty about what is benign or malignant and what intervention, if any, is needed," says cardiologist Joanna Ghobrial, MD, MS, Medical and Interventional Director of Cleveland Clinic's Adult Congenital Heart Disease Center. "Having gained more experience with these patients in recent years, we can recommend some optimal strategies for evaluation and management."

Cleveland Clinic has become one of the highest-volume centers in the country for handling these unusual and complex anomalies in adults. Over the past two decades, its clinicians have developed novel approaches — using noninvasive and invasive evaluation as well as surgical techniques — to address them.

How important is an incidental finding?

AAOCA and myocardial bridges can cause ischemia due to compression or kinking of the coronary artery. As a result, patients may present with fatigue, dizziness or fainting, shortness of breath, atypical chest pain or anginal symptoms. Since such symptoms can also arise from coronary atherosclerosis or aortic valve disease, teasing out the cause can be complicated in adults with cardiovascular comorbidities.

However, some patients may be asymptomatic, with AAOCA and/or myocardial bridges discovered incidentally, sometimes by CT evaluation after an injury or during workup for other causes. While AAOCA in adulthood was once thought to be not as malignant as AAOCA discovered in youth, this is now known to be inaccurate. It is now recognized that the first symptomatic manifestation may be cardiac arrest, which means that an incidental finding should be taken seriously. And although many myocardial bridges may indeed be benign, a portion of them can cause limiting symptoms and lead to myocardial infarction and malignant arrhythmias as well as cardiac arrest.

"Anyone who is discovered to have AAOCA, whether incidentally or during a workup for atypical symptoms, should have a thorough evaluation," says Dr. Ghobrial. "On the other hand, given that myocardial bridges are more common, patients who are asymptomatic may not require further investigation, while those presenting with concerning symptoms with no other clear etiology should undergo an investigative protocol like the one we use."

Thorough evaluation enables informed choices

To assess whether an intervention is indicated, Cleveland Clinic surgeons and cardiologists conduct a variety of tests, including:

- Coronary CT angiography to determine the course and caliber of an anomalous artery and the course and depth of a bridge within the myocardium
- Noninvasive stress PET with dobutamine or exercise to elicit dynamic obstruction, or treadmill ammonia PET imaging
- Invasive physiological evaluation that includes a dobutamine provocation stress catheterization, which measures the pressure difference across the anomalous coronary ostium or the myocardial bridge to assess blood flow, as well as intravascular imaging of the vessel to look for high-risk anatomy

Once the situation is thoroughly understood, the clinical team collaborates with the patient and family to determine next steps. The potential benefit of intervention is balanced against operative risk.

"Our approach is one of shared decision-making with our patients, integrating their desires for active lifestyles," says Tara Karamlou, MD, MSc, Surgical Director of the Adult Congenital Heart Disease Center. "We may treat a professional athlete more aggressively than an older patient who may not desire to be as physically active. That said, we have operated on patients as old as 75, including physically active grandparents who wanted reassurance that they wouldn't be limited caring for their grandchildren."

CABG is seldom indicated

Although Cleveland Clinic surgeons frequently see patients with AAOCA or myocardial bridges who were treated elsewhere with CABG and stents, they do not recommend this strategy unless the patient has concomitant coronary artery disease in the involved vessel.

"Bypass grafts are more at risk for competitive flow in AAOCA cases, and coronary stents may also be problematic in these situations," Dr. Karamlou notes. "Dynamic compression in these anomalous arteries and the competitive flow may lead to poor perfusion, making the graft or stent prone to failure and complicating further intervention."

Instead, she recommends unroofing and rerouting procedures (see below), with approaches tailored to the specific anomaly. Postoperatively, intravascular ultrasound and cardiac catheterization with dobutamine stress testing are repeated to determine normalization of blood flow to the myocardium.

Surgical options offered at Cleveland Clinic

Electrocautery for unroofing. Over the years, the unroofing approach at Cleveland Clinic has changed from traditional sharp excision to electrical fulguration of the shared intramural wall segment (Figure 1). This method, which was developed by Cleveland Clinic surgeons, has been shown to be equally safe and effective with shorter cardiopulmonary bypass and cross-clamp times (*Ann Thorac Surg.* 2019;107:P823-P828).

Vouhé technique. For an anomalous left coronary artery arising from the right sinus with an intramural course between the pulmonary artery and aorta, the more difficult Vouhé technique is required. This involves suturing a fresh autologous pericardial patch to create a new coronary ostium in the appropriate left sinus.

Najm procedure for transseptal anomalies. Hani Najm, MD, Chair of Pediatric and Adult Congenital Heart Surgery at Cleveland Clinic, developed the first operation to address a rare AAOCA of the left coronary artery with a transseptal course behind the right ventricular outflow tract. The procedure involves complete unroofing of the anomalous coronary artery within the ventricular septum and bridging it with pericardium (Figure 2). It was described in detail in 2019 (*Ann Thorac Surg.* 2019;108:e383-e386) and recently updated with midterm outcomes from 14 patients (*Ann Thorac Surg.* 2023;115:e29-e31).

"Currently, with 18 Najm surgeries completed at Cleveland Clinic, there have been no deaths," says Dr. Najm. "Patients report resolution of symptoms, and postoperative testing indicates normalized perfusion."

Myocardial bridge unroofing. "While myocardial bridges are often a benign incidental finding, deep and long ones tend to be more dangerous," says cardiothoracic surgeon Shinya Unai, MD. "When the myocardium squeezes the embedded coronary artery with exercise, ischemia results."

To surgically address this, Dr. Unai painstakingly removes the myocardial fibers above the coronary artery (Figure 3). He reiterates that a myocardial bridge should not be treated with a distal bypass, as the graft will only receive blood flow intermittently and will soon fail.

Research advancing on multiple fronts

Cleveland Clinic is a member of the Congenital Heart Surgeons' Society AAOCA registry, a network of institutions that pools data on patients diagnosed with AAOCA up to age 30 years. To address the shortage of data on older adults, Cleveland Clinic

FIGURE 1 — Illustration of key steps in the Cleveland Clinic-developed electrical fulguration technique for coronary unroofing for AAOCA. Reprinted, with permission, from Vinnakota et al., *Annals of Thoracic Surgery* (2019;107:823-828), © 2019 by The Society of Thoracic Surgeons.

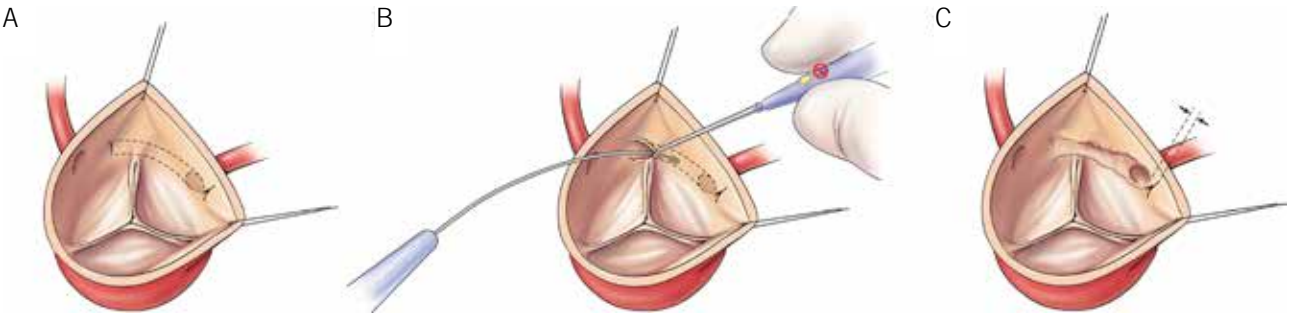
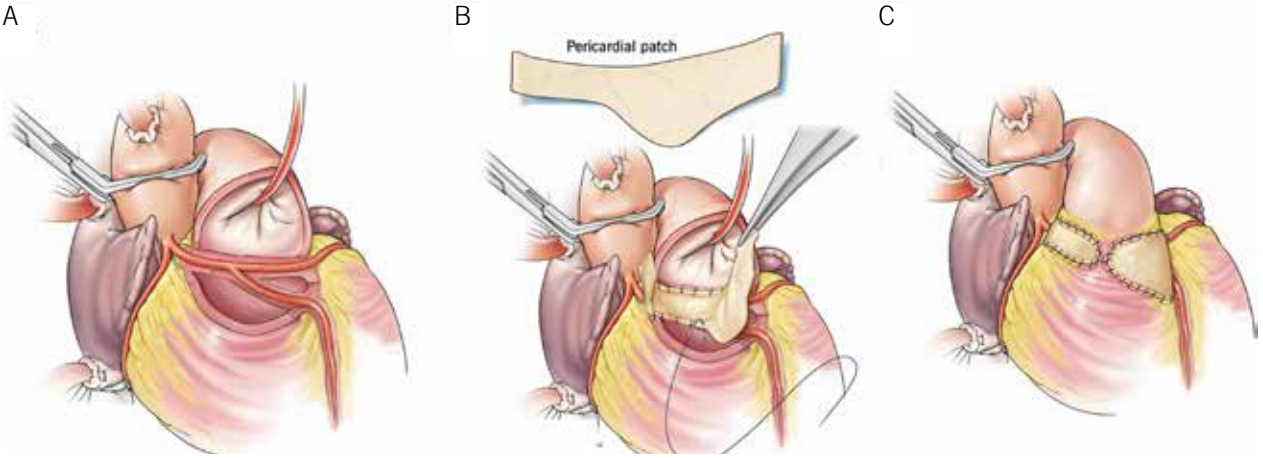


FIGURE 2 — Illustration of key steps in the Najm procedure. (A) Anomalous aortic origin of the left coronary artery with a transseptal course and early takeoff of the left anterior descending artery (LAD) from the left main coronary artery. (B) Modified autologous pericardial patch shape to accommodate the high takeoff of the LAD. The patch is straight on the superior aspect and wider inferiorly. (C) Completed repair with closure of the anterior right ventricular outflow tract with autologous pericardium. Reprinted, with permission, from Najm et al., *Annals of Thoracic Surgery* (2023;115:e29-e31), © 2022 by The Society of Thoracic Surgeons.



has developed a unique long-term database and registry to follow adults with AAOCA over time. These databases are enabling characterization of the multiple variants of AAOCA and outcomes of various surgical treatment strategies, including analysis of outcomes based on baseline imaging evaluation, noninvasive and invasive stress testing, and referral for surgery.

A review of 167 adults presenting with AAOCA during a two-year period at Cleveland Clinic was published in the *Annals of Thoracic Surgery* (2021;112[4]:1299-1305). Most patients presented with chest pain or shortness of breath. Right coronary artery anomalies were most common (57%), in contrast to the situation in pediatric patients. "This is probably a 'lethal bias' in that left coronary artery anomalies are likelier to be fatal or addressed in childhood," Dr. Karamlou observes.

Another study (*JTCVS Open.* 2022;10:205-221) characterized 763 patients with AAOCA from Cleveland Clinic databases and found no significant difference in the extent of coronary artery disease in anomalous coronary arteries versus normal arteries in the same individual.

Cleveland Clinic is also conducting novel research on the evaluative use of invasive dobutamine stress testing and the potential role of noninvasive fluid-structure interaction modeling (*JTCVS Tech.* 2022;13:144-162). Such techniques may one day inform the need for surgery in AAOCA and myocardial bridge settings, as well as evaluate successful reperfusion postoperatively.

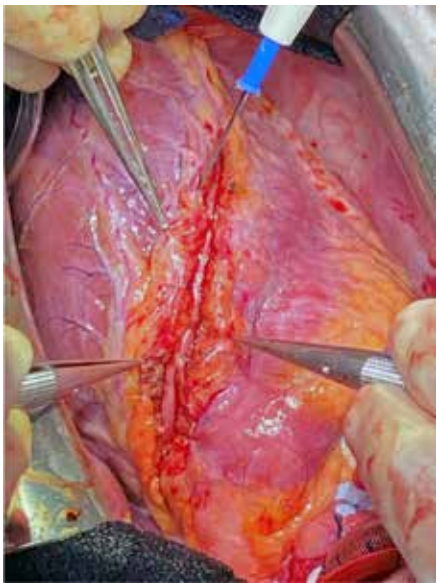


FIGURE 3 — Photo after completion of bridge unroofing of the left anterior descending artery.

"We are currently looking into impacts of concomitant cardiac pathology, such as coronary artery disease," Dr. Ghobrial notes. "Often such comorbidities make AAOCA patients develop symptoms after a lifetime of being asymptomatic, and they may complicate approaches to repair."

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Contact Dr. Ghobrial at 216.444.5923, Dr. Karamlou at 216.442.8278, Dr. Najm at 216.444.5819 and Dr. Unai at 216.445.5902.

OFF-LABEL ENDOVASCULAR INTERVENTION FOR GIANT AORTIC ARCH ANEURYSM: A CASE STUDY

Necessity breeds innovation when patient doesn't qualify for standard treatment or trials

A 65-year-old man presented to Cleveland Clinic's Aorta Center with an extremely large aneurysm bulging on top of the aortic arch (Figure 1). Several years prior, he had an acute aortic dissection repair at another institution, involving ascending aortic root repair and aortic valve replacement with a mechanical valve. Leakage into the aortic arch had slowly occurred since then.

He also had advanced-stage chronic obstructive pulmonary disease (COPD) that required continuous oxygen therapy at a stable rate for a couple of years. Otherwise, he was quite functional and able to participate in family and other activities.

Plan A: An investigational device trial?

Cleveland Clinic's Aorta Center is the largest in the U.S., with over 1,400 open and endovascular operations performed in 2021, including more than 1,000 involving the thoracic aorta.

Aorta Center Surgical Director Eric Roselli, MD, is principal investigator of the B-SAFER (Branched Stented Anastomosis Frozen Elephant Trunk Repair) physician-sponsored investigational device exemption (PS-IDE) clinical study focused on the outcomes of that innovative procedure, which he developed. Further work on an innovative device called PHASTER (Proximal Hybrid Aortic Stent Graft for Thoracic Extended Repair) to facilitate this operation is undergoing research and development with an industry partner. The Aorta Center team has consistently performed more than 120 total arch replacements using these novel hybrid techniques for the past several years. This patient was not a candidate for these techniques, which require an open surgical approach as part of the repair.

Management of aortic arch disease is rapidly improving, as a variety of single- and double-branch devices are under investigation that can be implanted with less-invasive hybrid surgical/endovascular procedures. They provide the possibility of lifesaving interventions to patients who are not candidates for traditional or hybrid open surgery, such as this patient with severe COPD. Cleveland Clinic is a participant in ongoing trials of all these devices, but this patient did not qualify for these trials either, due to his mechanical aortic valve and other anatomical limitations.

"The large volume of cases we treat gave us confidence that we could come up with a creative solution to help this man who had no traditional path to intervention." — ERIC ROSELLI, MD

"For patients who could potentially benefit from aortic arch repair but do not qualify for clinical trials of new devices or techniques, options are severely limited," says Dr. Roselli, Chief of Adult Cardiac Surgery. "But the large volume of cases we treat gave us confidence that we could come up with a creative solution to help this man who had no traditional path to intervention."

Plan B: A custom-made device

In collaboration with Aorta Center colleagues in vascular surgery and cardiothoracic surgery, Dr. Roselli embarked on a two-stage intervention using readily available, but modified, tools.

Stage 1: Prepare patient for a single-branch device. An incision was made from the base of the neck to the top of the manubrium to expose the upper part of the thoracic inlet and all branch vessels where they originate from the aortic arch. The left subclavian artery was transposed to the left common carotid artery, and an interposition bypass was created between the left common carotid and innominate arteries. The origins of the innominate and subclavian arteries were then ligated. The brain was now supplied by inflow from the left common carotid artery. The upper manubrium was reapproximated with a titanium plate.

The patient tolerated this procedure well. He was extubated in the operating room and had a good recovery, with no increase in oxygen requirements after a three-day hospital stay. He was discharged home, as the team hoped to enroll him in one of the single-branch stent graft trials.

Stage 2: Construct single-branch device inside patient. After several unsuccessful attempts to gain the patient access to one of the branched stent graft trials, the decision was made to proceed

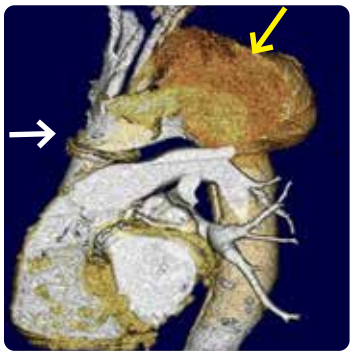

FIGURE 1 — Preoperative volume-rendered CT demonstrating a seam at the distal anastomosis of the prior repair (white arrow) and a massive arch aneurysm of the false lumen in the aortic arch (yellow arrow).

FIGURE 2 — Volume-rendered 3D reconstruction of the completed hybrid aortic repair demonstrating a patent branch that feeds into the left common carotid artery and then supplies the debranched head vessels above. Note that the aneurysm is no longer being opacified with contrast.

with completion endovascular aortic repair with a modification of a commercially available device a few months after the initial debranching procedure.

For this stage, the patient was put on partial cardiopulmonary bypass, draining blood from the right atrium via the femoral vein and returning arterial blood from the oxygenator through an inflow cannula to the right axillary artery. Brain perfusion was carefully monitored throughout the procedure using near-infrared spectroscopy. A commercially available stent graft was then delivered from percutaneous access in the femoral artery to the ascending aorta graft, bridging across the arch and into the upper part of the descending aorta. Once deployed, the stent graft covered the entire arch, including the new "pitchfork" branch vessel reconstruction, and sealed off the aneurysm. Brain flow was adequately supplied via the axillary artery cannulation and the cardiopulmonary bypass pump.

Next, a long spinal needle was delivered via neck access using X-ray guidance through the left common carotid artery, and the stent graft was punctured from above. A wire was delivered through the needle into the arch and snared from access via the femoral artery.

This through-and-through wire access provided a wire pathway commonly called a "body floss" technique. The hole in the graft was then enlarged serially with successively larger balloons, and a covered stent 10 mm in diameter was delivered into the left common carotid artery. This was also serially dilated across the orifice in the graft to reestablish blood flow to the brain. After the endovascular arch reconstruction was accomplished (Figure 2), the patient was easily weaned from partial cardiopulmonary bypass with no change in cerebral oximetry measures.

The patient was again extubated in the operating room and discharged home after a four-day hospital stay without respiratory or other complications. He was noted to be doing well at one-year follow-up. The aneurysm has shrunken on CT with no evidence of endoleak and a widely patent arch branch. Although the patient is still limited by his COPD, his risk of an aortic rupture has been alleviated.

Tailored precision care

Dr. Roselli urges colleagues to not give up on patients who need aortic repair and are not surgical candidates without first exploring other possibilities.

"Ideally, we can use an investigational device and avoid the need for cardiopulmonary bypass," he says. "But even if a patient is not a candidate for one, we might still have some options." Since the time of this procedure, one of the single-branch endograft devices has been approved by the FDA for commercial use in more distal arch aneurysms.

"Patients with advanced arch aneurysms who are not fit for traditional aortic surgery and do not meet criteria for clinical trials are often left in a clinical limbo," observes Francis Caputo, MD, Vascular Surgery Director of the Aorta Center. "We've found that by drawing on our vast experience with multidisciplinary approaches, taking what we have learned by working together, we can develop solutions tailored to patients' complicated problems."

Dr. Roselli adds that although just about any aneurysm can be fixed technically, doing so might not always be advisable. In addition to aorta and valve details, noncardiac comorbidities must be considered. Moreover, the surgical team's experience with new techniques and access to newer technology are critical to optimize outcomes. "It's important to keep in mind that we treat the whole patient, not just the aorta we see on a CT scan," he concludes.

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Contact Dr. Roselli at 216.444.0995 and Dr. Caputo at 216.445.9580.

ADVANCES IN HYPERTROPHIC CARDIOMYOPATHY THERAPY: VALOR-HCM MAY BE JUST THE BEGINNING

An abundance of promising studies are on the horizon

When Cleveland Clinic cardiologist Milind Desai, MD, MBA, presented findings from the pivotal VALOR-HCM study of the cardiac myosin inhibitor mavacamten at last year's American College of Cardiology and American Heart Association meetings, it was just the start of a wave of emerging data from hypertrophic cardiomyopathy (HCM) investigations.

In addition to VALOR-HCM substudies and long-term follow-up of the trial's enrollees, reports are anticipated from a registry of real-world use of mavacamten, a Cleveland Clinic-led trial of mavacamten for nonobstructive HCM, a phase 3 study of a second cardiac myosin inhibitor for obstructive HCM and early studies of a novel gene therapy for *MYBPC3*-associated nonobstructive HCM. These come on the heels of a newly published Medicare database analysis with implications for the use of new drug therapies in the mix of therapeutic options for HCM. Cleveland Clinic has a role in all these investigations, which are outlined below.

What's next from VALOR-HCM?

Mavacamten's FDA approval last spring as the first medication for treatment of symptomatic obstructive HCM was based largely on VALOR-HCM, which randomized 112 patients with symptomatic obstructive disease to mavacamten or placebo. Through the latest follow-up, at 32 weeks, mavacamten had significantly reduced patients' eligibility for septal reduction therapy (SRT) relative to placebo, the study's primary endpoint, as detailed in *Circulation* (Epub 6 Nov 2022).

Follow-up of the study's participants will continue through at least 128 weeks, says Dr. Desai, the study's national principal investigator and Director of the Hypertrophic Cardiomyopathy Center at Cleveland Clinic. He notes that one-year data will be available later this year. "We are focused on confirming whether the impressive safety and efficacy results with mavacamten are sustainable over the long term," he says.

"Now that we have evidence of symptom improvement with mavacamten over eight months, we are eager to learn whether its long-term use reduces life-threatening arrhythmias and sudden death," adds Nicholas Smedira, MD, MBA, Surgical Director of Cleveland Clinic's Hypertrophic Cardiomyopathy Center. "An effective noninvasive alternative to septal reduction therapy would provide a much-needed option for highly symptomatic patients and expand our toolbox of offerings."

Meanwhile, VALOR-HCM substudies are emerging. One led by Cleveland Clinic cardiologist Paul Cremer, MD, MS, showed that mavacamten improved measures of diastolic function independent of its effects in reducing left ventricular outflow tract gradients and mitral regurgitation (*Circ Cardiovasc Imag.* Epub 6 Nov 2022). "This has important implications for the use of diastolic assessment to determine prognosis and evaluate treatments," says Dr. Cremer. Another substudy will soon be presented on mavacamten's effects on Kansas City Cardiomyopathy Questionnaire results.

Real-world registry insights

Additional insights on mavacamten will be coming from DISCOVER-HCM (NCT05489705), a prospective U.S. registry study of the drug's real-world use that launched in late 2022. "From this we will learn things like how many patients receiving mavacamten have declines in ejection fraction and how many continue to feel good symptomatically over time," Dr. Desai notes.

He also will be watching whether mavacamten's effects are ultimately shown to extend beyond symptoms, diastolic function and avoidance of SRT to include structural changes in the heart, such as regression of mass. "A key question is whether this can modify the disease to a point where we can change patients' life trajectory in a positive way," he says.

A window into current use of SRT

Meanwhile, an administrative database study by Dr. Desai and Cleveland Clinic colleagues (*J Am Coll Cardiol.* 2023;81:105-115) suggests a role that drugs like mavacamten might play in the future therapeutic landscape for obstructive HCM. The researchers analyzed more than 5,000 Medicare beneficiaries who underwent SRT — i.e., septal myectomy or alcohol septal ablation — from 2013 through 2019. They found that while both forms of SRT significantly reduced readmissions for heart failure, septal myectomy was associated with lower redo rates and better long-term survival relative to alcohol septal ablation.

"A key question is whether [cardiac myosin inhibition] can modify the disease to a point where we can change patients' life trajectory in a positive way."

— MILIND DESAI, MD, MBA

Notably, the analysis also showed that despite better SRT outcomes at high-volume centers, 70% of SRT procedures in the U.S. were performed at low-volume centers. "Despite guideline recommendations, many patients are still undergoing SRT at low-volume centers," Dr. Desai observes. He says this suggests particular potential utility for cardiac myosin inhibitor therapy in patients who cannot easily access a high-volume SRT center, "given that outcomes are inferior at low-volume centers."

Other ongoing trials of note

Such patients may ultimately benefit from additional choice in cardiac myosin inhibitor therapy, as a second drug in the class — aficamten — is now in phase 3 testing for symptomatic obstructive HCM. The SEQUOIA-HCM study (NCT05186818), in which Cleveland Clinic is a participating center, is expected to be completed later this year.

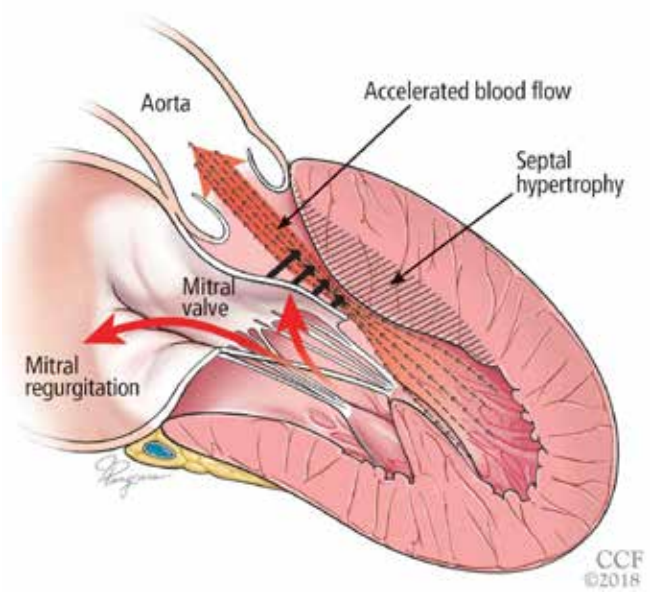
Additionally, Cleveland Clinic is leading a phase 3 multicenter trial of mavacamten in a different patient population — those with nonobstructive HCM. ODYSSEY-HCM (NCT05582395) is a randomized, double-blind, placebo-controlled study run by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research). The trial is enrolling several hundred patients with symptomatic nonobstructive HCM for treatment over one year to evaluate effects on quality of life, functional capacity and biomarkers.

If the results are positive, mavacamten could become the first medical therapy approved for nonobstructive HCM, which rarely is treated with SRT. "Patients with nonobstructive disease are more challenging to treat," says Dr. Desai, who is chair of the ODYSSEY-HCM executive committee. "We are looking to see if cardiac myosin inhibition improves functional quality of life in a setting where there is no obstruction to relieve."

The next frontier: Gene therapy

Cleveland Clinic is also one of a small number of centers involved in early studies of a gene therapy approach to HCM. The strategy is targeted at HCM due to *MYBPC3* mutation, a protein deficiency mutation and the most prevalent genetic form of HCM.

FIGURE — Illustration showing obstructive HCM — specifically, left ventricular outflow tract obstruction due to ventricular septal hypertrophy. Noninvasive treatment of obstructive HCM was the initial indication pursued for mavacamten and other cardiac myosin inhibitors. Now mavacamten is also being studied for use in nonobstructive HCM.



The approach involves TN-201, an investigational adeno-associated virus-based gene therapy designed to address the underlying cause of *MYBPC3*-associated HCM by delivering a functional *MYBPC3* gene to restore normal levels of myosin-binding protein C3. "The virus is administered as a single injection to stimulate protein formation and theoretically result in normal myocardial thickness," Dr. Desai explains, noting that animal studies have shown successful mass regression. "If it's 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."

Contact Dr. Desai at 216.445.5250, Dr. Smedira at 216.445.7052 and Dr. Cremer at 216.444.6765.

TRANSLATING GENOMICS TO THERAPEUTICS FOR ATRIAL FIBRILLATION

$14M NIH grant supports research toward medications to prevent progression

The prevalence of atrial fibrillation (AF) in the U.S. is projected to double by 2030, yet few effective therapies for AF exist. No new pharmacologic agents have been approved for the condition in more than 10 years.

Building on nearly 20 years of research on AF, clinicians and scientists in Cleveland Clinic's Heart, Vascular & Thoracic Institute and Lerner Research Institute are aiming to fill that gap through four synergistic projects that have their roots in — but go well beyond — genetics.

Funded by a five-year, $14.2 million National Institutes of Health grant, the work by the multidisciplinary team is designed to advance existing genomics — and omics more broadly — and develop a pipeline of repurposed drugs that can prevent progression of AF in adults.

A multipronged research endeavor

To achieve that goal, the researchers will address gaps in five knowledge areas:

- Functional mechanisms and causative genes and variants linking AF genome-wide association (GWA) loci with AF
- The role of mitochondrial dysfunction and obesity in AF pathophysiology and progression of AF
- The role of dietary/nutrition interventions and the microbiome in AF
- Targetable factors and pathways contributing to AF progression
- Genomics-based repurposable drugs and drug combinations that can prevent AF progression

"The need for novel targets for AF is substantial, but genetic findings have yet to yield clinically actionable results," says project lead Mina Chung, MD, a cardiologist in Cleveland Clinic's Section of Cardiac Electrophysiology and staff in the Department of Cardiovascular and Metabolic Sciences. "Our team's goal is to bring basic research on genomic mechanistic discoveries in AF to the bedside by identifying mechanisms and targets underlying the condition that may lead to personalized therapies."

Genetic underpinnings

More than 100 genetic loci relevant to AF have been identified. The locus with the strongest association with AF is near *PITX2*, which codes for the PITX2 transcription factor expressed early in development. PITX2 appears to suppress a left atrial sinus node program and is involved with formation of the pulmonary veins.

"*PITX2* is a tantalizing candidate gene because of its association with the pulmonary veins, which are the target of ablation," Dr. Chung explains. "Patients with AF may be born with a susceptibility to the condition, but it may manifest only in adulthood after exposure to stressors such as aging and obesity."

From genomics to multi-omics

Using human tissue samples from the pulmonary vein and left atrial appendage, Cleveland Clinic researchers are studying the leading pathways implicated by candidate AF risk genes. They have identified novel upstream pathways using transcriptomics and identified genetic effects on nearby gene expression. That has led them to propose — and pursue via the NIH-supported projects — a dual risk model (Figure) that may explain AF's association with heterogeneous cardiovascular stressors.

"Thanks to our collaboration with cardiothoracic surgeons, we developed a bank of human left atrial tissues that has allowed us

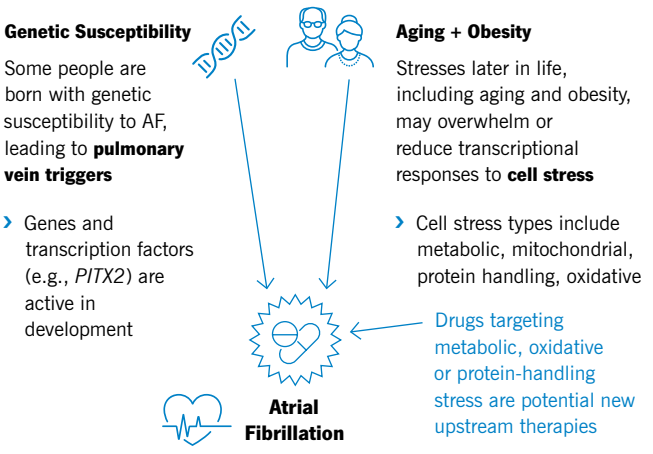


FIGURE — A model of how inadequate transcriptional responses to stress might predispose genetically susceptible people to atrial fibrillation (AF) in later life. Based on a proposal in Chung et al., *Cardiol Rev.* 2019;27(6):302-307.

Transcriptomics-Based Study Suggests Metformin Is Repurposable for AF

A transcriptomics-based study by Cleveland Clinic researchers in collaboration with colleagues at Northwestern University suggests that metformin is a top repurposable drug candidate for AF. The results — based on application of network-medicine methodologies analysis and analysis of electronic health record (EHR) data — show that the diabetes medication is significantly associated with reduced risk of AF.

"We harnessed drug-target interactions to assemble a drug-target network, used gene set enrichment analysis to nominate candidate drugs, and performed a large-scale pharmacoepidemiologic analysis to validate metformin as a repurposable drug for AF," says Dr. Chung, senior author of the study, which was published in *Cell Reports Medicine* (2022;3[10]:100749).

The researchers began by harnessing gene expression data from 251 patients to generate an AF genetic expression network or disease module. They then identified drug targets from a list of 2,891 FDA-approved drugs and calculated network proximity of drug targets to the AF disease module.

Gene expression data from drug-treated human cell lines were used to further narrow the repurposed drug list. Gene set enrichment analysis identified nine drug candidates, including metformin. Functional testing of metformin in human induced pluripotent stem cell (hiPSC)-derived atrial-like cardiomyocytes provided validation of the in vitro drug candidates.

For the population-based validation, the researchers leveraged data collected in the Northwestern Medicine Enterprise Data Warehouse between 2011 and 2021. Five drug cohort comparison analyses were performed, as was propensity score matching for age, gender, race and comorbidities.

"Our analysis of the EHR data showed that metformin was significantly associated with a 52% reduced likelihood of AF compared with the combined drug cohort," Dr. Chung says. "A subgroup analysis showed that the effect size for metformin was stronger in women than in men."

The Cleveland Clinic research team is currently enrolling patients in the TRIM-AF trial (NCT03603912), a prospective 2×2 factorial study comparing metformin with lifestyle/risk factor modifications for reducing AF burden and progression. The secondary aim is to determine clinical, genomic and biomarker predictors of AF progression that may be used to personalize upstream therapies.

to make the links from DNA to mRNA to protein to function," Dr. Chung explains. "Now we'll be using a network systems biology approach and layering on various omics to identify disease modules, as well as performing network-based proximity analysis to identify existing drugs that act on those modules."

The researchers will integrate new single-nucleus RNA sequencing with AF recurrence GWA studies, bulk RNA sequencing, and proteomic and metabolomic data to identify interactome-mediated gene regulatory networks underlying AF progression in the human AF tissue. They hypothesize that in AF, an interplay exists between systemic inflammatory, metabolic and fibrotic mechanisms and gene regulatory networks.

End goal of therapeutic discovery

Understanding this interplay, they believe, is essential to gain insights into AF progression and inform therapeutic discovery. As part of the research, artificial intelligence and systems biology approaches will be applied to identify repurposable candidate drugs and drug combinations. (As detailed in the sidebar, related efforts have already yielded published results with the diabetes drug metformin.) Validation will be performed with beating cardiomyocytes derived from inducible pluripotent stem cells from healthy subjects and patients with AF. Leading candidate drugs will be tested in mouse models of spontaneous AF and progression.

The research program's four individual projects also aim to enhance understanding of the function of selected candidate AF risk genes; the interplay of metabolic, mitochondrial and obesity pathways in AF; and the effect of diet and the microbiome on AF. These projects ultimately will be integrated to identify drugs or drug combinations that have potential to advance to clinical trials in patients with AF.

"This is a huge team effort focused on working toward personalization of treatment and shortening of the development timeline for new AF therapies," says Dr. Chung.

"We are honored to receive this significant grant from the NIH that will support our ongoing investigation of AF on multiple levels," adds Oussama Wazni, MD, MBA, Section Head of Cardiac Electrophysiology.

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Contact Dr. Chung at 216.444.2290 and Dr. Wazni at 216.444.2131.

CASE STUDY IN COLLABORATION

USING RAPID IMPROVEMENT EVENT METHODOLOGY TO ENSURE RELIABLE REGISTRY DATA COLLECTION

How our HVTI Advisory Services team facilitated swift improvements for an affiliated health organization

Standardizing quality across a health system is critical to integrated and efficient care delivery. That is the experience of three hospitals in the Nuvance Health organization that collaborated to coordinate best practices around collecting, analyzing and applying their cardiovascular care data to promote continuous improvement in quality and patient outcomes.

Nuvance at a glance

Nuvance Health is a network of more than 2,600 physicians serving 1.5 million patients in New York's Hudson Valley and Connecticut. The Nuvance Health Heart and Vascular Institute is an affiliate of Cleveland Clinic's Heart, Vascular & Thoracic Institute (HVTI). As a result of this relationship, Cleveland Clinic's HVTI Advisory Services team works with clinicians and multidisciplinary teams at three Nuvance Health hospitals — Vassar Brothers Medical Center in Poughkeepsie, New York, and Danbury Hospital and Norwalk Hospital in Connecticut — to assist with selected clinical and operational needs.

Identifying the need

Reliable data allow clinicians to analyze their outcomes and focus improvement efforts where they are needed most. The Nuvance Quality and Registry (NQR) team is charged with providing clinicians with outcomes and process metrics related to the quality of patient care. Nuvance's leadership team recognized that they needed to make changes to their data abstraction processes. They determined that their workflows and pace were not sustainable, so they engaged Cleveland Clinic for assistance.

The Cleveland Clinic HVTI Advisory Services continuous improvement team conducted a rapid improvement event (RIE), also known as a Kaizen event, with NQR team members, including front-line caregivers, quality department leaders, director-level leaders and executive leaders. The process involved use of the Lean Six Sigma continuous improvement methodology and tools to empower the team to develop a vision and move from passively acknowledging the problem to actively engaging in solution design. RIEs are driven by cross-functional teams to ensure buy-in. They are designed to rapidly yield measurable results through analyzing and improving a narrowly defined process where solutions are not known.

The Lean tools employed in the event are most successful when used by experts in the field with a proven record. The HVTI Advisory Services continuous improvement team used these tools to help the NQR team fully see its work, analyze the root cause of the problem, design experimental solutions, implement systems-based thinking, develop process efficiencies and outline standard work.

Current state vs. target state

The group used Lean Six Sigma methodologies to identify current-state data collected by the NQR team. These data revealed that 70.3% of the work performed by team members was outside the scope of their primary role as data abstractors. For example, other caregivers at the three hospitals asked NQR team members to prepare agendas for meetings in which their role was minor. These out-of-scope requests caused the team members to fall behind with their time-sensitive data duties and New York state regulatory requirements.

The process led to defining a target state (left side of Figure), which was set in collaboration with Nuvance leadership — Mark Warshofsky, MD, Senior Vice President and System Chair of the Heart and Vascular Institute, and Kelli Stock, Vice President of the Nuvance Health Heart and Vascular Institute — and in consultation with Cleveland Clinic HVTI's best practices for data and quality registries.

The NQR team and leaders together implemented the RIE methodology and visualized their work, which enabled them to clearly identify their gaps. The multidisciplinary team identified 164 gaps in the eight-step data abstraction process. The gaps were broadly described as follows: lack of standard work, lack of systems thinking, siloed teams, missing education and training, need for support from vendors and organizational development, and prioritization in the information technologies queue.

FIGURE — Baseline (current) and target-state values for the Nuvance NQR team's 12 key metrics (left side) and actual performance values (right side) following the rapid improvement event (RIE) project.

Category	Metric	Baseline (Current State)	Target State	Actual at 30 Days	Actual at 60 Days	Actual at 90 Days
Quality	Standardized abstraction process	0	1	1	1	1
	Aligned data and registry team across sites	0	1	1	1	1
	Abstractor standard work	0	1	1	1	1
	Abstractor workflows	5	1	1	1	1
	Individual reports (number created per person)	43	↓50% (20)	19	23	16
	Individual meeting attendance	72	↓50% (35)	30	12	11
Time	Time spent on troubleshooting abstractions/ registry follow-up and adjudication (min/wk)	71	30	25	28	12.7
	CathPCI® abstraction time (min) – Non-STEMI	95*	60	47.5	49.2	45
	CathPCI® abstraction time (min) – STEMI	95*	90	26	57.6*	22
	STS abstraction time per case (min)**	120	90	180	56	75
	ICD abstraction time per case (min)	90	30	55	29.1	30
	TVT abstraction time per case (min)**	120	90-120	180	60	20

STEMI = ST-elevation myocardial infarction; STS = Society of Thoracic Surgeons; ICD = Implantable Cardioverter Defibrillator; TVT = Transcatheter Valve Therapy
* Skewed by combining diagnostic and interventional cases.
** QCentrix at Vassar Brothers Medical Center.

The team then proposed solutions and designed rapid experiments to meet its vision using Cleveland Clinic best practices and structured facilitation by a Cleveland Clinic continuous improvement specialist.

The team discovered the opportunity to eliminate abstracting of data that was not valuable for National Cardiovascular Data Registry quality outcomes. "This had a very big impact for the abstractors, who were constantly struggling to keep current," says Barbi Lizak-Hart, Nuvance's Director of Quality and Data Registries. "It freed them up to work on other department registries and enabled an improvement in productivity for the STS, ICD and CHF registries."

Within 30 days of the project, the NQR team met targets for 75% of its metrics by applying nine of the easier rapid experiments, known as "Just Do Its." The team members engaged in multiple supporting projects, which enabled them to meet targets for 100% of their metrics and make the solutions standard within 90 days (Figure).

Secrets to success

A key to success was the engagement and support of Nuvance executive leadership. Dr. Warshofsky and Ms. Stock supported the RIE and committed the necessary time for the team to participate in it. This enabled an overwhelmed NQR team — which faced many deadlines and staffing challenges — to pause its work to complete this initiative.

Executive leaders trusted the process, fostered a sense of teamwork and instilled confidence in the NQR team members. "The key to the success of a project is having an executive leader who assumes the role of coach and is actively present, aligning teams around a common goal and empowering them to make decisions while showing modesty and removing barriers," says Edward Soltesz, MD, MPH, HVTI's Director of Cardiac Surgery Affiliate and Alliance Programs. "Nuvance's Dr. Warshofsky and Kelli Stock exemplified these behaviors, which increased the rate of successful outcomes."

The abstraction metrics through 90 days demonstrate the success of the Nuvance team and the RIE methodology in this setting. Similar results can be achieved across a variety of clinical areas when continuous improvement facilitators are paired with teams and executive leaders who will invest the required time and energy.

For information on affiliation or alliance opportunities with Cleveland Clinic's Heart, Vascular & Thoracic Institute, email Amanda Lesesky at leseska@ccf.org.

CME PREVIEW

GET CURRENT ACROSS THE SPECTRUM OF CARDIOLOGY PRACTICE THIS SUMMER

'State-of-the-Art Topics in Cardiology' covers the latest in all major subspecialty areas

State-of-the-Art Topics in Cardiology

Fri.-Sun., Aug. 4-6, 2023

InterContinental Hotel, Bank of America Conference Center, Cleveland

Information/registration: **ccfcme.org/cardiologyreview**

If you're a cardiology practitioner struggling to keep up with the latest developments in contemporary practice, have no fear. This powerhouse two-and-a-half-day CME course offers an efficient and engaging way to get up to speed across the spectrum of major subspecialty areas.

The course, held on Cleveland Clinic's main campus, is a successor to the long-standing Cleveland Clinic Intensive Review of Cardiology, which the course directors wanted to refresh with a program focused more on the latest research and practice updates and featuring more opportunities for interaction with a vast faculty of 42 expert physicians from Cleveland Clinic's Heart, Vascular & Thoracic Institute.

"Comprehensiveness is still the watchword for this course, which also retains a focus on complex patient management and clinical decision-making," says course co-director Venu Menon, MD, Section Head of Clinical Cardiology at Cleveland Clinic. "We have simply put more of a spotlight on the very latest clinical trial data and guideline recommendations."

Come hear what's new

These data and recommendations are a particular focus of the course's first day, which kicks off with takeaways from four recent major clinical trials presented by their lead trialists: the CLEAR Outcomes trial of bempedoic acid in patients with statin intolerance, the VALOR-HCM study of mavacamten for symptomatic obstructive hypertrophic cardiomyopathy, the PROTECTED TAVR study of cerebral embolic protection during TAVR, and the SPORT trial directly comparing six dietary supplements with statin therapy for LDL cholesterol reduction.

The day proceeds to overviews of major professional society guidelines for coronary artery revascularization, aortic disease management and evaluation of chest pain. Those are followed by expert recaps of the top five trials of 2022 in five subspecialty areas: electrophysiology, interventional cardiology, heart failure/transplant, cardiac imaging and preventive cardiology.

The first day concludes with reviews of new developments in six evolving specialty topics: pericarditis, amyloidosis, sarcoidosis, heart failure with preserved ejection fraction, pulmonary hypertension and sports cardiology.

Current issues in the subspecialty areas

The remainder of the course — all day Saturday and Sunday morning — consists of sessions exploring a handful of timely topics in each of seven subspecialty areas: interventional cardiology, heart failure, preventive cardiology, vascular medicine, cardiothoracic surgery, cardiac critical care and electrophysiology.

Presentations during these sessions range from general updates (e.g., "Contemporary Management of Cardiogenic Shock") and practical recommendations (e.g., "Current Considerations in Hypertension Guideline Implementation") to focused discussions of timely clinical questions (e.g., "Impact of Coronary Calcium Score for Heart Risk") and snapshots of specialized clinical programs (e.g., "Insights and Outcomes from a CRT Optimization Clinic").

All presentations are 20 minutes, with faculty asked to devote 40% of that time to Q&A or other forms of attendee interaction.

"This event is designed for reviewing key concepts and learning the latest developments in all major areas of contemporary cardiovascular medicine," says course co-director Samir Kapadia, MD, Chair of Cardiovascular Medicine at Cleveland Clinic. "Cardiologists, trainees, advanced practice providers, nurses and midlevel providers all stand to benefit."

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Course and registration details are available at ccfcme.org/cardiologyreview.

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

CARDIAC CONSULT STAFF

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

Medical Editors
Lars G. Svensson, MD, PhD | svenssl@ccf.org
Brian Griffin, MD | griffib@ccf.org
Oussama Wazni, MD, MBA | waznio@ccf.org

Managing Editor
Glenn R. Campbell

Art Director
Chip Valleriano

Marketing
Colleen Burke | **Jackie Riggle** | **Suzanne Anthony** | **Morgan Bischof**

Photography
Russell Lee

Cover Illustration
Amanda Mendelsohn

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Cleveland, OH 44195

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Fri., Nov. 3, 2023
Hyatt Regency Columbus, Columbus, Ohio
Information/registration: ccfcme.org/columbusCVcare23

Mastering the Management of the Aortic Valve

Fri.-Sat., Dec. 15-16, 2023
InterContinental New York Barclay, New York
Information/registration: ccfcme.org/aorticvalve

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

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