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INSIDE THIS ISSUE

3 COVID-19 Cardiac Involvement: Recognition and Management

6 TAILOR-PCI Narrowly Misses Primary Goal but Indicates Intriguing Trends

Congenital Cardiac Surgery: What's Next?

Joseph A. Dearani, M.D. *Elizabeth H. Stephens, M.D., Ph.D.*

In the 65 years since the first use of cardiopulmonary bypass at Mayo Clinic for the repair of a ventricular septal defect, the field of congenital cardiac surgery has reached a summit unimaginable at the time of the specialty's inception, tackling challenges in anatomy, physiology and technology that once appeared insurmountable. The care that our specialty is currently able to provide for people with congenital heart disease (CHD) from the cradle — and even the womb — to the grave has been revolutionized in recent decades. While the present is bright for those with CHD, with new technology and innovations on the horizon, the future is even brighter. This article briefly highlights the current state of care and looks to the future within various realms of CHD.

Changing Paradigm for Health Care

Health care as a whole in society continues to evolve. While today it is largely reactive and symptom based, in the next decade it will be preemptive and molecular based. Our interventions, while greatly improved compared with those of previous decades, are usually late stage, corrective and expensive, but are evolving to early stage, curative and affordable. These interventions are frequently invasive, but are moving toward becoming less invasive and increasingly utilizing technology such as robotics. These changes are fueled by surgical, technological and process innovations.

Imaging and Diagnostics

Imaging and diagnostic capabilities have revolutionized the capacity to care for patients of all ages with CHD. Increasingly the diagnosis of CHD is made during gestation; with increased resolution in imaging, identification of certain features, such as a restrictive or intact atrial septum in hypoplastic left heart syndrome (HLHS), can be anticipated and intervened on soon after delivery at centers with expertise in this area, improving outcomes. Advances in imaging and systematic study of quantified parameters, such as indexed right ventricular volumes on magnetic resonance imaging, have helped define thresholds for surgical intervention and improved outcomes. Development of diagnostic parameters such as liver "stiffness" has assisted the ability to evaluate patients for sequelae of CHD. Additionally, 3D modeling now aids in preoperative planning for patients with complex lesions. This modeling can be particularly helpful in adult patients with CHD who have had multiple previous repairs, not infrequently involving surgical techniques that are now extinct.

Virtual reality opens another world of possibility in both preoperative planning and education. The complex 3D structure of congenital heart defects can be more completely understood by "walking" through them and examining every angle. Diagnostic capabilities will also improve with increasing use of molecular and genetic markers, allowing earlier detection and earlier intervention when appropriate. Such advances

will make possible personalized treatment based on the molecular fingerprint of the patient's disease process.

Devices and Technology

Current state-of-the-art care of CHD includes a close collaboration between surgeons and interventional cardiologists, with transcatheter interventions assisting before and after surgical interventions, as well as being performed with surgery in "hybrid" procedures. Advances in devices and technology for transcatheter approaches now allow ductal stents as opposed to surgical shunts, percutaneous closure of certain atrial septal defects and percutaneous valve replacements in select patients. Refinement of cardiopulmonary bypass machines, including alterations in oxygenators, safety alarms, and tubing and priming to minimize systemic response to bypass, have improved outcomes. Ventricular assist devices have progressed to become smaller and optimize long-term support and are now available for children and even infants. Technological innovations have also led to minimal access surgery and robot-assisted surgery that can be applied in certain teenagers and adults with CHD. Now more than ever a multidisciplinary approach is needed for the care of patients with CHD, with a team of specialists determining the best combination of treatment strategies.

On the horizon are further advances in the areas of devices and technology. A subset of CHD progresses during gestation, worsening the severity of the condition and the prognosis for the baby after birth. Fetal cardiac intervention, however, gives the opportunity to stop or slow such progression, thereby improving the patient's overall prognosis. With technological advancements and refinement of interventional techniques such as ex utero intrapartum treatment, a subset of patients with HLHS has undergone fetal cardiac interventions with evidence of improvement compared with similar patients without intervention. Other congenital cardiac anomalies have the potential of benefiting from fetal cardiac intervention with further study and experience in this burgeoning realm.

Other technology and device developments are on the horizon with the potential to significantly improve the ability to care for patients. Refinement in transcatheter technology will enable smaller delivery systems — particularly important in small patients with CHD. Biomaterials development will lead to implanted materials with fewer issues related to clotting and scarring, with the potential for drug elution technology for specific diseases. Tissue engineering also is on the horizon, including biodegradable scaffolds and materials with the potential to grow with the patient. Robot-assisted technology will continue to evolve, allowing the potential for use in smaller patients and even in remote surgeries. Continued development in assist devices will create implantable devices (as opposed to extracorporeal devices) and smaller devices for the unique CHD anatomy and physiology.

Process Innovation

Increasingly the world is generating large amounts of data. Patient care is no exception. In recent years advancements in the ability to monitor patients has led to a body of research on patient management based on a constellation of parameters. Such data integration is currently impacting perioperative care. Other process innovation has included implementation of algorithms and protocols; as variability decreases, the quality of care increases. Such measures decrease length of hospital stay, decrease complications, and improve outcomes.

Data related to health care will only increase in ensuing years. Artificial intelligence and machine learning will be critical in optimizing the use of such data in the care of patients. In the near future, real-time analysis of patient-specific data will alert physicians of impending physiologic compromise before hemodynamic change is apparent to the patient or the physician. Artificial intelligence and machine learning will also become fundamental in the diagnosis of conditions. Remote monitoring, both for perioperative care that decreases hospital stays and in the intermittent or continuous monitoring and management of chronic conditions, will become routine.

Summary

Progress in the field of CHD has enabled us to conquer many challenges and correct many anomalies. What was once thought to be impossible has now become routine. We are now able to provide hope to patients with the most severe forms of CHD, the vast majority receiving corrective as opposed to palliative repairs and living with an excellent quality of life into adulthood. But loftier heights remain ahead, and with continuous surgical, technological, and process innovations, that goal of nearing perfection is getting closer every day.

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COVID-19 Cardiac Involvement: Recognition and Management

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Much emphasis has been placed on the respiratory complications of individuals with coronavirus disease 2019 (COVID-19). As the coronavirus has spread, cardiac complications have been recognized in a substantial number of individuals, sometimes occurring late in the course of the disease. Potential cardiac complications include acute coronary syndromes, acute myocardial injury without obstructive disease, arrhythmias, heart failure, pericardial effusion and thrombotic complications.

The responsible agent is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped, positive-sense, single-stranded RNA virus. Other coronaviruses include those causing the common cold or more-severe respiratory infections, including:

- Middle East respiratory syndrome (MERS), first identified in Saudi Arabia in 2012
- Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), which caused the SARS outbreak of 2002 to 2004

Characteristically, coronaviruses replicate by means of spike proteins expressed on the virus envelope attaching to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell. Transmembrane serine protease 2 (TMPRSS2), also expressed on the host cell, is required to perform protein conformational changes to enable viral entry and cell infection. These three critical components — the spike protein, the ACE2 receptor and TMPRSS2 — are all potential therapeutic targets, although only small in vitro studies have been completed to date.

Acute myocardial injury may be implied by typical ECG changes, increases in cardiac biomarkers or impaired function noted on imaging studies. Experience thus far suggests that myocardial damage may be due to acute myocarditis secondary to direct infection of macrophages and myocytes, systemic cytokine-mediated cardiomyopathy or microvascular thrombosis. Critically ill individuals are at higher risk of having cardiac complications. One multicenter report of 191 patients hospitalized with COVID-19 in China reported increased high-sensitivity troponins in 1 of 95 patients who survived, compared with 32 of 54 (59%) patients who did not. Research at Mayo Clinic is focused on the temporal nature of biomarker expression associated with COVID-19 cardiac involvement and treatment response.

Additional reports suggest that patients who died had elevated liver function values, d-dimer, interleukin-6 and prothrombin time, all suggesting an inflammatory profile similar to that of the cytokine release syndrome. The relative contribution of systemic cytokines is unclear at this time. The profound inflammatory response can lead to the development of disseminated intravascular coagulopathy (DIC). Microvascular coronary thrombosis due to DIC and endothelial dysfunction may be the mechanism behind myocardial infarction and stroke in young patients with COVID-19. Also unclear is whether SARS-CoV-2 infection leads to the production of cardiac autoantibodies.

There are limited treatment trial data and no expert recommendations (Figure 1), although early reports suggest that remdesivir may shorten recovery time, especially if administered early. However, a prospective trial of lopinavir and ritonavir in 199 severely ill patients with COVID-19 did not demonstrate reduction in viral load or clinical improvement. Antiviral therapies and hydroxychloroquine increase the heart rate-correct QT interval (QTc) and the risk of ventricular arrhythmias. Trials with the interleukin-6 inhibitors sarilumab, siltuximab and tocilizumab to treat cytokine release are in progress. Convalescent plasma from recovered patients is being collected and administered at Mayo Clinic.

At this time, patients with COVID-19 and evidence of myocardial injury who are hemodynamically and electrically stable can be followed until recovery from the acute viral syndrome. Patients with severe cardiogenic shock have been treated with extracorporeal membrane oxygenation (ECMO). Goal-directed medical therapy may be delayed until individuals are clinically stable and preparing for discharge. Patients are advised to abstain from competitive sports for at least three to six months.

Figure 1. Proposed assessment and management of COVID-19 with acute myocardial injury. (A) If the treating clinician has the ability to provide point-of-care cardiac ultrasonography without increasing COVID-19 exposure or personal protective equipment use, limited left ventricular ejection fraction (LVEF) assessment can be considered. A depressed systolic function would identify higher risk patients. (B) Repeat troponin testing is indicated with a deterioration of clinical status. (C) This pathway attempts to balance the imperfect trade-offs of increased diagnostic uncertainty without compromising patient outcomes while minimizing unnecessary staff exposures and testing that would not immediately change clinical care. (D) The 2015 Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities advise abstinence from competitive sports or aerobic activity for a period of three to six months until resolution of myocardial inflammation. (E) Assessment of LVEF should be considered at early follow-up for patients with abnormal troponin values during hospitalization to either identify patients with reduced systolic function or to complete a full cardiac assessment. Complete assessment should occur once a patient is no longer considered infectious in accordance with Centers for Disease Control and Prevention recommendations for the discontinuation of transmission-based precautions for patients with COVID-19. (F) There are currently no evidence-based therapies for COVID-19 with robust clinical evidence of efficacy. Enrollment in a clinical trial should be strongly considered if available at the treating center. Additional treatment with antiviral, anti-cytokine and additional investigational drugs should be completed. (G) Consideration of pulmonary arterial catheters and inotropic or mechanical support (that is, intra-aortic balloon pump, temporary left ventricular support device, VA-ECMO) should be completed on a case-by-case basis taking into account patient characteristics, availability of appropriately trained staff and the ability of the health care institution to safely manage a support device. (H) Evidence of acute myocarditis on imaging or biopsy of myocardial tissue may modify the choice and dosing regimen of therapies. Algorithm reprinted with permission from Circulation.

Risk of arrhythmias

Michael J. Ackerman, M.D., Ph.D.

There is a pressing need to identify safe and effective therapies to prevent and treat COVID-19. Although there are currently no specific drugs approved by the Food and Drug Administration (FDA), a number of agents are being evaluated in randomized clinical trials. In vitro results and anecdotal reports of clinical response to antivirals and antimalarial drugs have led some clinicians to treat patients with these drugs off-label. However, these agents may prolong the heart rate-correct QT interval (QTc), increasing the risk of drug-induced torsades de pointes and sudden cardiac death.

Chloroquine, hydroxychloroquine and azithromycin block the KCNH2-hERG/KV11.1 potassium channel and can prolong the QTc in susceptible individuals. The effects can be additive. Chloroquine and hydroxychloroquine are excreted unchanged in urine very slowly, with a half-life of 20 to 60 days; the half-life of azithromycin is two days. Antiviral agents may have independent effects on QTc through a yet uncertain mechanism.

Given the number of individuals worldwide with congenital long QT syndrome (LQTS), and the number of patients who may be eventually treated with one or more of these agents, the absolute number of individuals at risk of lethal ventricular arrhythmias is substantial. Given the nature of the pandemic, serial 12-lead ECG monitoring of the QTc during initiation of drug therapy may be impractical. The FDA has recently provided emergency approval for select mobile devices to be used to monitor QTc. Additionally, many inpatient telemetry systems have real-time QTc monitoring capacity.

The average QTc values for healthy men and women are approximately 410 msec and 420 msec, respectively, in the absence of exogenous aggravating factors. A QTc value in excess of 470 msec in men and 480 msec in women may indicate an increased risk of QT-dependent arrhythmias. Patients with a resting QTc higher than 500 msec, whether congenital or acquired, have a significantly greater risk of torsades de pointes and sudden cardiac death.

Ultimately, the risk-benefit calculation of using these drugs independently or in combination will depend on clear evidence of efficacy as determined by clinical trials. In the meantime, a simple red-yellow-green-light QTc algorithm has been developed at Mayo Clinic to determine individual risk of life-threatening arrhythmias to assist with risk assessment (Figure 2) when considering treatment with any of these agents (www.covidqtc.com). The algorithm was published in the April 2020 issue of Mayo Clinic Proceedings.

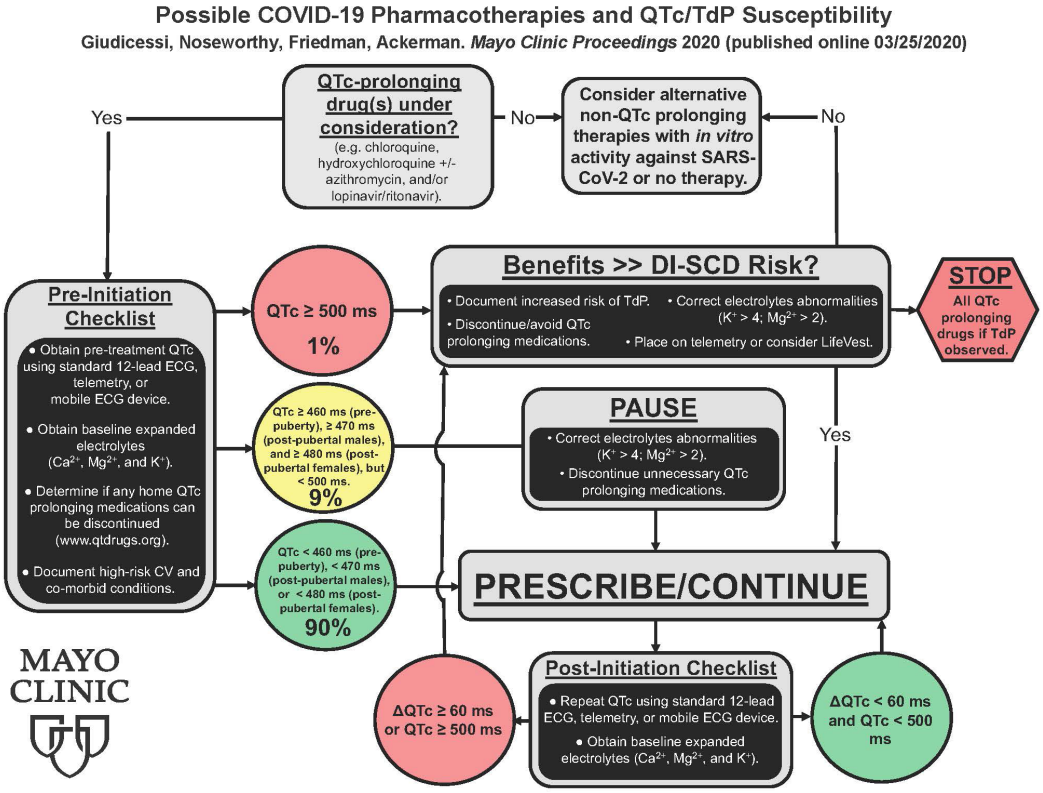

Figure 2. Red-yellow-green-light approach to mitigating risk of drug-induced torsades de pointes and sudden cardiac death in patients with COVID-19 treated with QT-prolonging drugs. Algorithm reprinted with permission from Mayo Clinic Proceedings.

Convalescent plasma

Robert F. Rea, M.D.

Mayo Clinic is the lead center of over 2,000 institutions providing access to convalescent plasma for hospitalized patients with severe or life-threatening COVID-19, or those at high risk of progression. This is a blood product obtained from patients who have recovered from COVID-19 and who meet certain criteria; plasma donors must be recovered for 14 days from swab-proven COVID 19 and subsequently test negative for COVID-19, or be 28 days out from the end of symptoms (follow-up test not required) to qualify. Physicians at any institution who are treating hospitalized patients with COVID-19 can register their institution and patients at https://uscovidplasma.org/.

Digi-ceuticals and contact tracing

Suraj Kapa, M.D.

The term "digi-ceuticals" describes mechanisms to provide health care at a distance. These tools have been extremely helpful in providing health care to individuals during the pandemic, reducing exposure risk to patients, medical staff and families. Patients expect increased connectivity with their medical providers. Even before COVID-19, patients were becoming more comfortable with the digi-ceutical concept, especially individuals with chronic conditions. Additionally, digital tools are useful in measuring fitness, monitoring health issues, assessing medication compliance and sending alerts. Data can be aggregated to monitor overall population health. For example, automatic daily digital temperature average measurements in one of the New York City boroughs increased immediately prior to the COVID-19 outbreak in the city.

In addition to mobile devices for ECG monitoring, which received FDA emergency use approval, devices that can acquire various physiologic variables remotely are in the pipeline or under review by the FDA. Devices that perform components of the virtual physical examination are in various stages of development. Loosened interstate licensing restrictions, reduced HIPPA restrictions and equivalent reimbursement rates have all facilitated the dramatic growth of virtual visits.

Beyond individual telemedicine encounters, digi-ceuticals offer the possibility of improved population health measures. Mayo Clinic is participating in multicenter efforts exploring the use of digital tools in the public health sphere, such as exposure tracking, quarantine maintenance and resource distribution.

Contact tracing typically identifies the original point source of the infection and maps how it spreads. Also helpful would be the ability to identify exposure by infectious but asymptomatic individuals. Smartphones track location and can identify an individual's "trail." If an individual subsequently develops infection, contacts can be identified based on the intersection of their trails with that of the infected individual. This approach could monitor and manage spread of infection without the need for strict social isolation.

Unlike data collection tools being developed by large technology companies, the Mayo Clinic collaboration is developing platforms that anonymize, aggregate and encrypt data to preserve individual privacy. Data can be used not only to advise individuals of potential exposure but also to identify early hot spots while maintaining individual anonymity.

For more information

Ackerman MJ, et al. Recognition and management of cardiac complications of COVID-19 infection and treatment (https://medprofvideos.mayoclinic.org/videos/recognition-and-management-of-cardiac-complications-associated-with-covid-19-infections-and-treatment). Medical Professional Video Center. Mayo Clinic. 2020.

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TAILOR-PCI Narrowly Misses Primary Goal but Indicates Intriguing Trends

Naveen Pereira, M.D.

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One of the keys to delivering personalized medicine is the use of information from the genome — the set of chromosomes in an individual — and its variation to guide medical decision-making. By identifying individual genetic profiles, the hope is that therapies can be targeted, dosages can be optimized and side effects can be reduced.

Patients who undergo percutaneous coronary intervention (PCI) are commonly prescribed anti-platelet agents such as clopidogrel for up to one year after the procedure to reduce the risk of stent thrombosis. Clopidogrel is a prodrug, absorbed by the intestine and converted to its active metabolite in the liver via two oxidative steps that involve the cytochrome P450 superfamily enzyme system, of which the CYP2C19 enzyme is the most important component. Individuals who have a loss-of-function (LOF) variant of the CYP2C19 gene are unable to fully metabolize the prodrug into the active metabolite, reducing its effectiveness and increasing the risk of ischemic events. The most common LOF alleles are CYP2C19*2 and CYP2C19*3, occurring in approximately 30% of the U.S. population. Studies have shown that patients who carry these LOF alleles have an increased incidence of ischemic events when they take clopidogrel compared with those without the alleles who take clopidogrel. This risk is mediated by many factors, not just genotype including systemic factors such as diabetes mellitus and chronic kidney disease as well as technical factors such as arterial and stent size and flow. It is unknown whether routinely genotyping for CYP2C19 LOF alleles and prescribing anti-platelet therapy based on the results can reduce the incidence of ischemic events.

To test this hypothesis, the largest genotype-guided cardiovascular trial was designed and initiated by researchers at Mayo Clinic in collaboration with an international network of sites to determine if anti-platelet therapy guided by CYP2C19 genetic metabolizer status could reduce the incidence of ischemic events after PCI. The Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention (TAILOR-PCI) study was a multicenter (40 centers in the U.S., Canada, Mexico and South Korea), randomized, prospective clinical trial. Patients undergoing PCI for stable or unstable angina were randomized to a genotype-guided strategy (n = 2,652), in which patients without CYP2C19 LOF alleles received clopidogrel 75 mg daily and patients with the LOF alleles received ticagrelor 90 mg twice daily. Ticagrelor is not a prodrug and is not dependent upon CYP2C19 metabolic activation for therapeutic effect. The standard therapy (n = 2,650) group received clopidogrel 75 mg once daily without prospective genotyping.

To test the hypothesis that altering anti-platelet therapy based on CYP2C19 LOF status would lead to improved outcomes, the primary analysis was conducted only in the 1,849 patients with LOF alleles, 903 in the genotype-guided group compared with 946 in the standard therapy group. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis and severe recurrent ischemia at 12 months. Investigators hypothesized that genotype-guided therapy would reduce the incidence of the primary endpoint in the genotype-guided group by 50% compared with the standard therapy group.

At the end of the trial, the composite endpoint occurred in 4.0% (35/903) of the genotype-guided group, and in 5.9% (54/946) of the standard therapy group (p = 0.056). The genotype-guided strategy yielded a 34% reduction in cardiovascular events, but did not reach the 50% reduction target, and was not statistically beneficial compared with standard therapy. Based on the statistically not significant P value of 0.056, if one assumed that genotype-guided therapy had no effect in reducing ischemic events as compared to standard therapy, then less than 3% of studies would have an effect of 34% reduction in ischemic events as observed in TAILOR-PCI. Therefore making it highly probable that genotype-guided treatment was associated with improved outcomes.

"Although these results fell short of the effect size that we predicted, they nevertheless provide a signal that offers support for the benefit of genetically guided therapy, with approximately one-third fewer adverse events in the patients who received genetically guided treatment compared with those who did not," said Naveen L. Pereira, M.D., cardiologist at

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Mayo Clinic in Rochester, Minnesota, and co-principal investigator of the study with Michael Farkouh, M.D., from the Peter Munk Cardiac Centre, University of Toronto.

While the primary outcome was not statistically different between treatment groups at 12 months, interestingly a post hoc analysis revealed a 79% reduction in adverse events in the first three months in the genotype-guided group compared with those who did not, which may indicate a particularly high-risk window of time after stenting. Similarly, a pre-specified analysis demonstrated a 39% ($p = 0.01$) reduction in cumulative or multiple ischemic events per patient with genotype-guided therapy.

Assuming a more modest effect of genetic testing which would have translated to enrolling more patients may have resulted in the trial achieving its primary endpoint. When the TAILOR-PCI trial was designed in 2012, around 10% to 12% of patients who received a stent could be expected to have a major adverse cardiovascular event within a year. Over the course of the trial, the standard of care evolved through greater use of drug-coated stents and other treatments, which reduced the expected rate of adverse events in a year to about 5%. This change in technology substantially improved care for patients, but at the same time may have made it more difficult for the trial to reach its goal of a 50% reduction in adverse events with the number of patients enrolled.

Due to the current pandemic, all live courses sponsored by Mayo Clinic Cardiovascular Continuing Medical Education have been cancelled for 2020. Nevertheless, we remain committed to our educational mission. Please continue to regularly visit our cardiovascular education website (**https://cveducation.mayo.edu/**) for updates on live and digital courses, offerings, and resources.

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