MAYO CLINIC

CardiovascularUpdate

Cardiology, Pediatric Cardiology, and Cardiovascular Surgery News Vol. 18, No. 1, 2020

INSIDE THIS ISSUE

New Chair of Cardiovascular Surgery at Mayo Clinic in Rochester, Minnesota

Juan A. Crestanello MD

Juan A. Crestanello MD has been appointed as the new chair of the Department of Cardiovascular Surgery at Mayo Clinic in Rochester, Minnesota. Dr. Crestanello succeeds Joseph A. Dearani MD, who served in the role of department chair since 2011.

Dr. Crestanello joined Mayo Clinic in Rochester, Minnesota in 2017; he previously led the Division of Cardiac Surgery at The Ohio State University where he held the G.S. Kakos and T.E. Williams Professorship in Cardiac Surgery. He is board certified by the American Board of Surgery, the American Board of Thoracic Surgery, and holds the academic rank of professor. He is a member of the Society of Thoracic Surgeons and the American Association for Thoracic Surgery where he held several leadership roles.

Dr. Crestanello received his medical degree from the University of the Republic of Uruguay Medical School, and did postgraduate training at the Hospital de Clinicas, Hahnemann University School of Medicine, the University of Maryland Medical System, and Mayo Graduate School of Medicine.

New and Novel Treatments for Hyperlipidemia

R. Scott Wright MD

Statin drugs are very effective in reducing levels of low-density-lipoprotein cholesterol (LDL-C), one of the causal agents in the development of atherosclerotic disease. Statins lower cholesterol by inhibition of HMG-CoA reductase, the rate-limiting step in the synthesis of cholesterol. Nevertheless there are patients who have a suboptimal response to statin therapy or cannot tolerate effective doses, and the efficacy of statins in lowering LDL-C is variable. Additionally, many patients suffer recurrent cardiovascular events because of residual risk despite statin use. There is a compelling need to identify agents which specifically target LDL-C via other mechanisms as well as work with statins to more effectively lower LDL-C.

One approach has been to target biochemical pathways that impact LDL receptor availability. The human monoclonal antibodies evolocumab and alirocumab work by inhibiting the action of proprotein convertase subtilisin-kexin type 9 (PCSK-9). PCSK-9

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is a protein that binds to LDL-C when it binds to hepatic LDL receptors. Together, this complex of PCSK-9 and LDL-C are taken into the hepatocyte attached to the LDL receptor. The presence of this protein with the LDL receptor + LDL-C marks the receptor for degradation, and receptor degradation leads to increased circulating LDL levels as the LDL receptor is not recycled back to the hepatocyte surface where it will continue to bring LDL-C into the liver and out of plasma. It is also worth noting that the administration of statins upregulates synthesis of the PCSK-9 protein, as a counter-regulatory reaction to statin inhibition of cholesterol biosynthesis. The Nobel Prize winning work of Brown and Goldstein postulated the potential for a counter-regulatory mechanism tied to intracellular cholesterol levels. This mechanism was discovered to be mediated by the PCSK-9 protein, which is believed to limit the efficacy of statin agents in the treatment of hypercholesterolemia and is a counter-regulatory pathway to balance the LDL-C lowering efficacy of statins. Hobbs and co-workers discovered families with lower natural cholesterol levels and very low rates of coronary artery disease. Genetic analysis localized this trait to the gene encoding for PCSK-9 protein, thus sparking a decade-long effort to develop a new set of drugs to lower cholesterol. Loss of function of PCSK-9 protein, either through a genetic trait or by blocking the protein with a monoclonal antibody such as evolocumab and alirocumab dramatically reduces LDL-C levels when given with or independent of statins.

More recently, a small interfering RNA (siRNA) molecule was designed which harnesses the body's natural method of blocking RNA transcription of the mRNA for PCSK-9. Inclisiran, now undergoing FDA review, uses the RNA silencing mechanism (RISC) in liver cells to block the production of PCSK-9. Inclisiran has been engineered to only be taken up by hepatocytes and has been shown in Phase 2 trials to reduce LDL-C when given with a statin or independent of a statin. The agent is administered on average every six months as a subcutaneous injection.

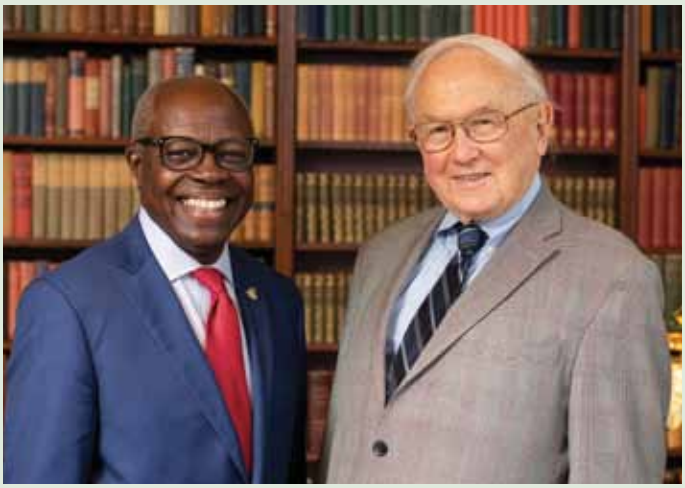
Two large, Phase III trials were reported at the 2019 American Heart Association Scientific Sessions in Philadephia. Mayo Clinic has played a pivotal role in the Phase II and Phase III development of inclisiran for LDL-C lowering through the work of R. Scott Wright MD, cardiologist at Mayo Clinic in Rochester, Minnesota. Dr. Wright led the Phase III ORION-10 trial, which examined the efficacy of inclisiran versus placebo in a large cohort of patients with atherosclerotic cardiovascular disease (ASCVD) who were already on statins or other lipid lowering therapy. In ORION-10, 1561 patients with ASCVD were randomized to placebo (n=780) or inclisiran (n=781) for approximately 18 months. Inclisiran or placebo was administered on days 1 and 90, then every six months thereafter. To be included, the patients had to have documented ASCVD, elevated LDL-C (> 70 mg/dL), and be on maximally tolerated statin therapy or other LDL-C lowering oral therapy (10% of patients in the study were also taking ezetimibe). The median LDL-C was 105 mg/dL in both groups. At the termination of the trial, there was a 58% reduction in LDL-C in the treated group compared to the placebo group on day 510 and a sustained 56% reduction over days 90 through 540, both $p<0.001$. There was no evidence of any difference in liver, muscle or hematological side-effects between placebo and inclisiran. The ORION-10 trial was not powered to detect changes in clinical event rates.

Although the effect on LDL-C by both the monoclonals and inclisiran has been quite dramatic, questions remain, such as how the drugs affect levels of high density lipoproteins, lipoprotein(a), and triglycerides. The use of the PCSK-9 monoclonal antibodies has been lower than expected, largely due to pricing issues and possibly due to the need for 26 injections annually. It is not yet known whether the treatment effect translates into a reduced incidence of coronary disease or reduced mortality. It is important to note that nearly all of the reduction in ASCVD mortality to date in clinical outcomes trials largely depends on the degree of reduction in LDL-C. Inclisiran is being specifically tested for its effect on cardiovascular outcomes in the 15,000 patient ORION-4 trial.

HONORS

Carole A. Warnes MD, cardiologist at Mayo Clinic in Rochester, Minnesota, received the American College of Cardiology 2020 Distinguished Teacher Award. This award is presented annually to a member of the college who has demonstrated innovative, outstanding teaching characteristics and compassionate qualities, and because of these attributes have made major contributions to the field of cardiovascular medicine at the national and international level.

HONORS



Ivor J. Benjamin MD, Professor of Medicine, Physiology, Pharmacology, Toxicology, Cell Biology and Surgery and Director of the Cardiovascular Center at the Medical College of Wisconsin in Milwaukee, Wisconsin (left) delivered the 24th Annual Robert L. Frye lecture. The title of his presentation was "Protein Misfolding Diseases: Lessons from Alzheimer's to Cardiomyopathy and the AHA." Dr. Frye is pictured on the right.

HONORS

Pharmacology trainee Duan Liu PhD and his mentor, Naveen Pereira MD, member of the Department of Cardiovascular Diseases at Mayo Clinic in Rochester, Minnesota received both the Top Poster Ribbon Award and the Presidential Trainee Award at the American Clinical Pharmacology and Therapeutics annual meeting in Houston, Texas. They have performed the first genome-wide association study to assess treatment response in patients with dilated cardiomyopathy and have identified genes that are primarily expressed in fibroblasts to be associated with myocardial recovery. They are currently evaluating the modulatory role of these genes on the development and progression of cardiac fibrosis to lay the foundation for development of these targets into novel heart failure drug therapy. These awards are presented for the very best abstracts of the meeting, and recognize Drs. Liu and Pereira's work in precision medicine for heart failure.

News from the Mayo Clinic Cardiovascular Research Center

Mackram R. Eleid MD

Mayo Clinic researchers are poised to test percutaneous coronary interventions (PCI) remotely by robotic tools controlled by an off-site doctor. In the initial test, the Mayo Clinic physician will be in the next room; however, if successful this trial run will lead to future procedures for patients miles away. This project is being spearheaded by Mackram R. Eleid MD, interventional cardiologist at Mayo Clinic in Rochester, Minnesota.

Thus far, only the final step of a PCI – dilating the artery and stent deployment – is done remotely. Arterial access and catheter insertion are performed on site. Lag time between the doctor's movements and the robot's corresponding actions have been the major technological challenge, though improvements in wireless networks are being addressed. Researchers have determined that 400 milliseconds of lag is acceptable, but that anything longer affects performance. This remote capability will have tremendous impact for patients in rural and isolated areas where emergency cardiac procedures can be delayed, resulting in worse outcomes for patients.

Genetic Testing Reveals Cause of Mysterious Deaths in Amish Children

Michael J. Ackerman MD PhD

In 2004, a medical examiner contacted Michael J. Ackerman MD PhD, pediatric cardiologist and director of the Windland Smith Rice Sudden Death Genomics Laboratory at Mayo Clinic in Rochester, Minnesota. The medical examiner had performed post-mortem studies on two children from an Amish family who had died suddenly while playing, their deaths occurring only several months apart. The autopsies were negative, and Dr. Ackerman was asked if genetic testing might shed light on the causes of death. Dr. Ackerman has pioneered the concept of the molecular autopsy; that is, using genetic testing to understand the cause of death and better predict risk for surviving family members. He suspected that the ryanodine receptor (RYR2) gene might be culpable, as mutations of this gene are frequently responsible for exercise-associated ventricular arrhythmias. However, initial testing was unrevealing. In subsequent years, two additional children from this family died, again while engaging in physical activity. An additional seemingly unrelated family was identified who had lost children under similar circumstances. Using new technology, Dr. Ackerman's team has recently able to identify the underlying genetic cause for these deaths.

The incidence of death in otherwise young, seemingly healthy individuals is 1.3 per 100,000 persons, and nearly half of these deaths remain unexplained after conventional autopsy. Families with multiple unexplained sudden deaths in young individuals are exceedingly rare. Post-mortem testing for inheritable cardiac channelopathy- and cardiomyopathy-associated genes sometimes identify the cause of death. In addition to providing closure for surviving family members, that information is critical to identifying additional at-risk family members.

Dr. Ackerman and his colleagues performed testing on autopsy samples from the deceased children from the first family and blood samples from living first degree relatives. Of note, the index child had been evaluated after an episode of exercise-associated syncope, and had a normal resting ECG and a normal exercise stress test without ectopy. The child died several years later during physical activity. A sibling experienced sudden cardiac arrest while playing and survived, but died a month later during another activity-related sudden cardiac arrest. Two other children died of sudden cardiac death, one of with documented ventricular fibrillation.

Subsequently, a second Amish family reached out to Dr. Ackerman. This family consisted of more than 250 individuals, of whom 15 had experienced either exercise related-death or survived sudden cardiac arrest. As in the first family, no evidence of cardiomyopathy or channelopathy was observed in those affected individuals. One of those survivors in the second family had an ICD implanted after sudden cardiac arrest survival; this individual had three documented episodes of R-on-T ventricular ectopy that triggered *torsades de pointes* ventricular fibrillation, successfully treated by the device.

Dr. Ackerman and his team utilized copy number variation (CNV) analysis, which revealed a homozygous tandem duplication in the cardiac RYR2 promoter location in all affected individuals from both families (Figure). CNV alterations result in an abnormal number of gene copies, such as duplications, deletions, translocations, and inversions. The RYR2 gene is responsible for the functional integrity of the cardiac sarcoplasmic

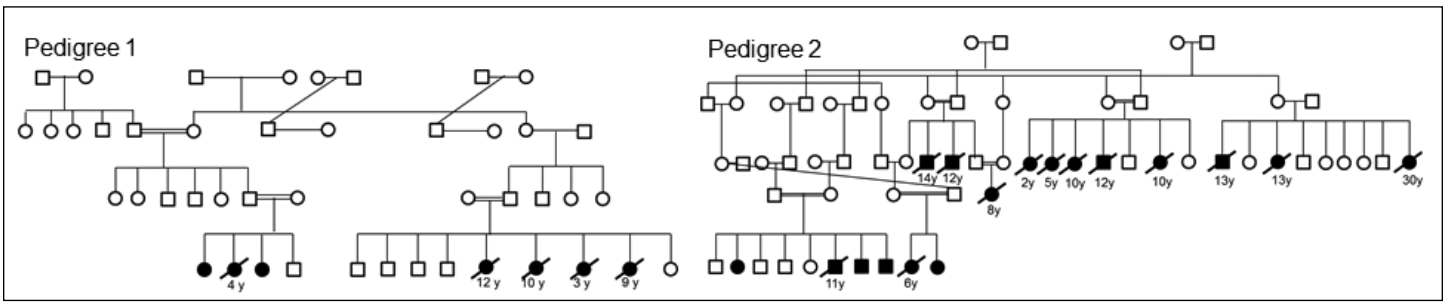


Figure. Pedigrees of two Amish families with homozygous tandem duplication of the RYR2 promoter location.

reticulum calcium release channel. Mutations of the RYR2 gene are associated with catecholaminergic polymorphic ventricular tachycardia and arrhythmogenic right ventricular cardiomyopathy.

This abnormality was identified in the heterozygous state in only four of approximately 70,000 tests performed at the Mayo Clinic Genomics Laboratory. The high incidence of this RYR2 gene abnormality in these affected Amish families and the extremely low incidence in the general population suggest that this duplication is likely an Amish founder mutation. "By identifying this genetic abnormality, we can test other family members and offer life-saving ICD therapy to protect affected individuals," says Dr. Ackerman.

For more information: *Tester DJ, Bombei HM, Fitzgerald KK, et al. Identification of a novel homozygous multi-exon duplication in RYR2 among children with exertion-related unexplained sudden deaths in the Amish community. JAMA Cardiol. Published online January 8, 2020. doi:10.1001/jamacardio.2019.5400*

HONORS

The American Heart Association awarded its Population Research Prize to Margaret M. Redfield MD, director of the Circulatory Failure Division, Department of Cardiovascular Diseases and co-director of the Cardiorenal Research Laboratory at Mayo Clinic in Rochester, Minnesota. The award was presented at the American Heart Association's Scientific Sessions 2019 in Philadelphia. "Dr. Redfield's seminal work with the population of Olmsted County, Minnesota, has greatly deepened our understanding of heart failure with preserved ejection fraction, or HFpEF, which can be a very challenging diagnosis," said American Heart Association President Robert A. Harrington MD, who presented the award.

ANNOUNCEMENT

Elizabeth H. Stephens MD PhD has joined the Division of Cardiovascular Surgery specializing in congenital cardiac surgery. She received her medical degree from Baylor College of Medicine and PhD in Bioengineering from Rice University focusing on heart valve tissue engineering. Her adult cardiothoracic training was completed at Columbia University and congenital training at Lurie Children's Hospital in Chicago. Her clinical areas of expertise include the treatment of neonates, infants, children, and adults with complex congenital heart disease, valvular disease including Ebstein's anomaly, mechanical circulatory support, and heart transplantation. In addition to her clinical areas of expertise, Dr. Stephens is active in outcomes research relative to congenital heart disease and is extensively published on various cardiac surgery conditions. She has a particular interest in education, including serving on national committees and mentoring trainees of all levels.

HONORS

Blase A. Carabello MD (left), chair of the Division of Cardiology at the East Carolina Heart Institute in Greenville, North Carolina presented the 2019 Carole A. Warnes Lecture entitled "What Do You Want To Be When You Grow Up? Doctor or Physician: Lessons From Secretariat, Nolan Ryan and Sir William Osler." Dr. Warnes is pictured on the right.

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MitraClip™ Treatment of Mitral Regurgitation after Cardiac Transplant: Case Report

Abdallah El Sabbagh MD

Peter M. Pollak MD

Parag C. Patel MD

Mitral regurgitation is a common finding in the transplanted heart. Re-do surgical valve repair or replacement incurs higher risk in these patients due to immunocompromised state, prior sternotomy, and frequently other comorbidities. Cardiac procedures in this patient population are challenging because of the distorted anatomy of the transplanted heart. Abdallah El Sabbagh MD and Peter M. Pollak MD, interventional cardiologists at Mayo Clinic in Florida, recently treated a heart transplant patient who had developed severely symptomatic, medically refractory mitral regurgitation.

The patient is a 72-year-old male with a history of nonischemic cardiomyopathy who underwent orthotopic cardiac transplantation 18 months previously. He reported that after his transplantation, he was feeling much better, but a few weeks later he noticed dyspnea on exertion and drop in functional capacity during cardiac rehabilitation. Echocardiography revealed severe mitral regurgitation secondary to leaflet malcoaptation. His medical therapy was optimized, but he continued to have severe symptoms. There was no evidence of active rejection. Coronary angiography was unremarkable. He was referred to Mayo Clinic in Florida for consideration of percutaneous intervention of his mitral valve.

There are scattered case reports of MitraClip™ (Abbott, Abbott Park, Illinois) being used to treat mitral regurgitation in transplanted hearts, although this population has not been specifically studied in a randomized clinical trial. This patient underwent uncomplicated MitraClip™ placement, with almost complete resolution of symptoms within weeks of implantation.

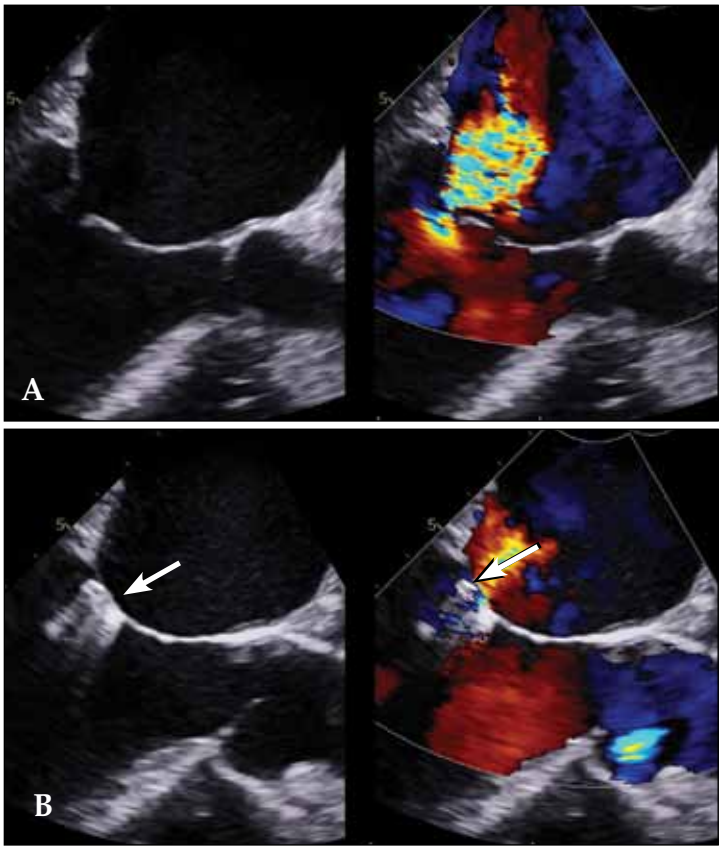

Figure. 2-D and color-flow Doppler images of mitral regurgitation before (A) and after (B) MitraClip™ (arrows) placement.

HONORS

Joseph A. Dearani MD was elected President of The Society of Thoracic Surgeons during the organization's 56th Annual Meeting in New Orleans, Louisiana. Founded in 1964, The Society of Thoracic Surgeons is a not-for-profit organization representing more than 7,500 cardiothoracic surgeons, researchers, and allied health care professionals worldwide who are dedicated to ensuring the best possible outcomes for surgeries of the heart, lung, and esophagus, as well as other surgical procedures within the chest. The society's mission is to enhance the ability of cardiothoracic surgeons to provide the highest quality patient care through education, research, and advocacy.

After completing his undergraduate education at Fordham University in New York City, Dr. Dearani earned his medical degree from Georgetown University School of Medicine in Washington, DC. He completed research and clinical residencies and fellowships at Harvard Medical School, Brigham and Women's Hospital, Georgetown University Medical Center, Mayo Clinic, and Loma Linda University. Dr. Dearani recently completed his tenure as chair of cardiovascular surgery at Mayo Clinic in Rochester, Minnesota. Additionally, he has served as medical director of Children's HeartLink for 20 years, leading efforts to train medical teams and work with government officials in low- and middle-income countries, providing education and transforming health care in underserved parts of the world.

HONORS

Vidhu Anand MBBS, cardiology fellow at Mayo Clinic in Rochester, Minnesota received the 2019 American Society of Echocardiography Foundation Top Investigator Award held at the foundation's scientific sessions for her presentation "Prognostic value of cardiac power output in patients with normal left ventricular ejection fraction referred for stress echocardiography." She was also one of three finalists for the 2019 European Society of Cardiology Young Investigator Award – Clinical Cardiology for her presentation "Prognostic value of cardiac power reserve in patients with normal left ventricular ejection fraction undergoing exercise stress echocardiography." The award winners are selected based on the exceptional scientific merit of their research projects.

CONTEMPORARY CASES IN CARDIOLOGY

NEXT WEBINAR PROGRAM

CARDIAC ELECTROPHYSIOLOGY: IN 2020 – WHAT IS NEW AND WHAT IS TO COME?

CVEDUCATION.MAYO.EDU

Mayo Clinic Cardiovascular Digital Education presents the next program in the new webinar series "Contemporary Cases in Cardiology." This non-credit program will be offered free of charge, and it will cover a broad range of topics of cross-disciplinary interest. The program "Cardiac Electrophysiology: In 2020 - What is New and What is to Come?" is lead by faculty members Christopher V. DeSimone MD PhD, Abhishek J. Deshmukh MD, and Suraj Kapa MD.

This webinar will:

- Provide an overview of pulsed-electric field electroporation as an emerging ablative approach to improve safety and efficacy of atrial fibrillation procedures
- Demonstrate the utility of His bundle and left bundle pacing, and other newer approaches in patients in need of cardiac resynchronization therapy
- Provide an overview on the utility of needle-based catheter ablation for mid-myocardial substrate for PVC and VT ablation, as well as future approaches using non-invasive external beam therapies

Join us for this webinar on April 30, 2020 11:00 AM-12:00 PM Central Time
Please register at our website: https://cveducation.mayo.edu/CARDIAC-EP

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June 4-7, 2020 Manhattan, NY

Cardiac Rhythm Device Summit: Implantation, Management, and Follow Up
June 18-20, 2020 New York, NY

Heart Failure Up North: Practical Approaches to the Management of Congestive Heart Failure
June 27-28, 2020 Brainerd, MN

Echo Alaska: Frontiers of Multimodality Imaging Including Echo, Cardiac CT, and MRI
July 13-17, 2020 Anchorage, AK

Current Applications and Future of Artificial Intelligence in Cardiology
July 23-25, 2020 San Francisco, CA

Success With Failure: Strategies for the Evaluation & Treatment of Heart Failure
July 26-28, 2020 Whistler, BC, Canada

Cardiology Update: The Heart of the Matter
July 30-August 2, 2020 Sedona, AZ

Cardiovascular Review Course for Initial Certification and Recertification
August 22-26, 2020 Rochester, MN

Echo Focus Session
August 27, 2020 Rochester, MN

Internal Medicine Review for Nurse Practitioners, Physician Assistants & Primary Care Physicians
September 9-11, 2020 Rochester, MN

Advanced Catheter Ablation: New Tips, Techniques and Technologies for Complex Arrhythmias
September 12-15, 2020 Boston, MA

Interventional Cardiology Board Review
September 18-20, 2020 Rochester, MN

The Genetics of Heart & Vascular Disease
September 24-26, 2020 Phoenix, AZ

Challenges in Clinical Cardiology: A Case-Based Update
September 25-27, 2020 Chicago, IL

Echocardiography in Pediatric & Adult Congenital Heart Disease Case Studies: Including Multimodality Imaging
October 1-4, 2020 Phoenix, AZ

Echo Revolution: Adult Echocardiography for Physicians and Sonographers
October 11-13, 2020 Boston, MA

Innovations in Atrial Fibrillation: Impacting Quality of Life and Stroke Risk
October 16-17, 2020 Seattle, WA

Cases in Echocardiography, Cardiac CT and MRI
October 21-24, 2020 Napa, CA

Coronary Artery Disease: Case-Based Learning
October 30-November 1, 2020 Dana Point, CA

Cardiovascular Review in Bahrain: Case-Based Approach
November 4-7, 2020 Manama, Bahrain

Echo Best Practice I Echocardiography in Patient Care and in Clinical Trials: When to Use Multimodality Imaging
November 19-22, 2020 Scottsdale, AZ

The Heart Beat of Cardiology: Practical Application of Echocardiography
December 10-12, 2020 Chicago, IL

Echo on Marco Island: Case-Based Approach
December 17-20, 2020, 2021 Marco Island, FL

Cardiovascular Conference at Snowmass: Cases, Controversies, and Challenges
January 9-13, 2021 Snowmass Village, CO

Cardiology Update at Puerto Vallarta: A Focus on Prevention
January 18-22, 2021 Puerto Vallarta, Mexico

Hawaii Echo with Multimodality Imaging
January 25-29, 2021 Maui, HI

Arrhythmias & the Heart: A Cardiovascular Update
February 1-5, 2021 Kohala Coast, HI

Cardiovascular Conference at Snowbird
February 9-12, 2021 Snowbird, UT

Cardiology at Cancun: Topics in Clinical Cardiology
February 22-26, 2021 Cancun, Mexico

Ski the Summit@Copper: Echo Imaging in Colorado
February 28-March 4, 2021 Copper Mountain, CO

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