American Heart Association. | SCIENTIFIC SESSIONS 2015

Wednesday, November 11

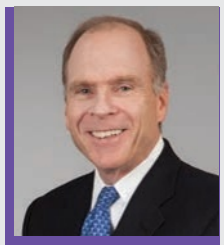
DailyNews

INSIDE

New PCI guideline for patients with STEMI released in October

The 2015 guideline update for percu-taneous coronary intervention in patients with STEMI includes two important changes. The routine use of thrombus aspiration prior to PCI is no longer recommended; and non-culprit artery PCI in hemodynamically stable patients, either at the time of primary PCI or later, can be considered in selected cases.

"These are updates we think will change practice, especially with regard to the issue of non-culprit artery PCI," said Patrick O'Gara, MD, senior physician at Brigham and Women's Hospital and professor of medicine at Harvard Medical School in Boston. O'Gara co-chaired the guideline writing committee along with Glenn M. Levine, MD, professor of medicine at Baylor College of Medicine and director of the cardiac care unit at the Michael E. DeBakey Medical Center in Houston.


Patrick O'Gara, MD

The guideline, which was jointly published in October by the AHA and the American College of Cardiology Foundation, downgrades the routine use of aspiration thrombectomy from Class IIa to Class III (no benefit). The prior recommendation was based on the results of observational studies and a single randomized trial. Two larger, more recent randomized controlled trials and a meta-analysis failed to demonstrate a benefit from aspiration thrombectomy.

In addition, the writing committee was not able to identify a sub-population of patients for which thrombectomy would be predictably beneficial, including those with larger thrombus burdens. Recognizing that there may be instances in which the operator feels thrombus aspiration could be helpful, such as a bail-out procedure, the committee noted that its utility in this context is not well-established (Class IIb).

GUIDELINE continued on page 14

In-ambulance troponin can improve time to final disposition versus in-hospital testing

Adding troponin to EMS ambulance care reduced the time to test by 100 minutes and the total time to final disposition by 20 minutes, according to a Canadian study reported during Tuesday's Late-Breaking Clinical Trials session.

The study, "Providing Rapid Out-of-Hospital Acute Cardiovascular Treatment (PROACT-4)," compared point-of-care troponin testing to traditional in-hospital troponin testing.


Justin A. Ezekowitz, MBBCh

"This was a large, prognostic trial with patients enrolled by paramedics," said lead author Justin A. Ezekowitz, MBBCh, associate professor of medicine at the University of Alberta in Canada. "The vast majority of patients with chest pain do not have cardiovascular issues. Just adding point-of-care troponin shortened the time to final disposition."

L. Kristin Newby, MD, MHS, professor of medicine at Duke University Medical Center in Durham, North Carolina, noted that point-of-care troponin testing is less sensitive than in-hospital testing, which could delay diagnosis for patients with less severe cardiac events. And while point-of-care testing cut just 20 minutes from the typical eight-hour emergency department visit, the study suggests potential to improve workflows in other areas as well, she said.

In another late-breaking presentation, researchers unveiled a new tool to help clinicians assess which patients are more likely to benefit from extending dual antiplatelet therapy beyond 12 months after implantation of a coronary stent. Extended DAPT reduces ischemic complications, but can increase bleeding.

"These are average treatment results, but some individuals are more likely to see benefit from extended therapy and others are more likely to be harmed," said Robert W. Yeh, MD, MSc, MBA, director of the Smith Center for Outcomes Research in Cardiology at the Beth Israel Deaconess Medical Center in Boston. "We have developed a scoring system to help individualize that determination."

Yeh is lead author of the study "Individualizing Treatment Duration of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: An Analysis of the DAPT Study." In the study, researchers

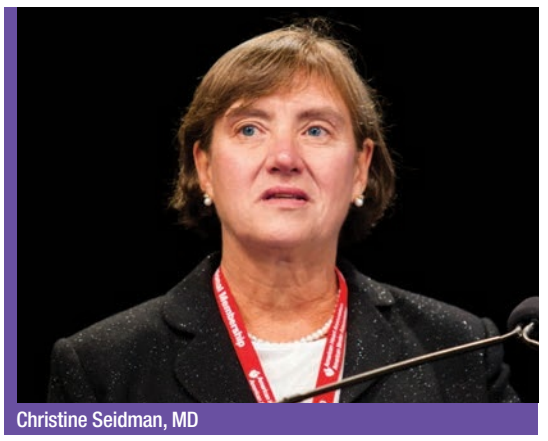
LATE-BREAKING continued on page 10

Genetic advances opening door to new therapeutic opportunities

Extraordinary technologic advances over the past two decades have provided unparalleled opportunities to sequence DNA, identify pathogenic mutations and recapitulate disease in model organisms and human cells. These innovations have fueled the discovery of genetic causes and mechanisms for human heart disease.

"These discoveries are setting the stage for new opportunities to target individuals who are at risk for disease with interventions that may delay or prevent clinical expression," said Christine Seidman, MD, the Thomas W. Smith Professor of Medicine at Harvard Medical School, and director of the Cardiovascular Genetics Center at Brigham and Women's Hospital in Boston.

Seidman delivered the Distinguished Scientist Lecture on Tuesday. She discussed the evolution of cardiovascular genetics in the context of congenital heart disease, citing pediatric cardiology pioneer Helen Taussig, MD, one of the first scientists to recognize that the likelihood of genetic etiologies for congenital malformations was considerable.


Christine Seidman, MD

"She recognized that neither exposure to toxic substances nor the health of the parents of young children were suitable to define the abnormalities that sometimes arise," Seidman said. "Despite her enormous insights into this likely etiology, her ability to tackle the problem was really quite limited. But after her death, the role of identifying familial causes of congenital heart disease began and has really flourished now for several decades."

Scientists soon recognized, Seidman said, that families in which these mutations are inherited are very rare. Because the defects are inherited, the malformations are generally mild and typically only involve minor septation defects.

DISTINGUISHED continued on page 6

TODAY AT SESSIONS

Don't miss today's highlighted presentations and events. For a complete schedule, download the Mobile Meeting Guide, see the Final Program or view the online program at scientificsessions.org.

9–10:15 a.m.
Navigating the Complex Landscape of Heart Failure
Chapin Theater

9–10:15 a.m.
Optimizing Outcome in Congenital Heart Surgery
W110A

9–10:15 a.m.
Updated Implementation of Multimodality Imaging Based on Guidelines (Joint Session with European Society of Cardiology)
W315AB

10:45 a.m.–Noon
Joint Session AHA/WHO: Ten Years to WHO 2025 Goals – Where do We Stand? How Far to Go?
W315AB

10:45 a.m.–12:15 p.m.
Late-Breaking Clinical Trials IV: Novel Therapies for Common Problems
Chapin Theater

Claiming CME/CE at Scientific Sessions

Healthcare professionals attending Scientific Sessions can claim and print CME/CE certificates.

- Sign in at **learn.heart.org** using your Professional Education Center (PEC) username and password. You can create an account if you don't have one.
- Find the activity you are registered for under the "Activities Catalog" tab or from the home page.
- Enter the authorization code you received with your attendee badge.
- Complete the evaluation.
- Claim your credit(s).

International attendees can obtain their attendance verification certificate at the registration center. For a full list of conference accreditation statements and credit hours, visit **scientificsessions.org**.

Attendee feedback

Scientific Sessions attendees will complete a survey evaluating Scientific Sessions in the process of claiming their CME/CE credit. The American Heart Association uses the surveys for feedback on programming, location, networking and more. Attendees who are not claiming CME/CE credit are invited to fill out a non-CME survey, which will be emailed following the meeting. Responses are anonymous.

HIGHLIGHTS FROM THE PROGRAM CHAIR

By Frank W. Sellke, MD, FAHA, Committee on Scientific Sessions Program Chair


Frank W. Sellke, MD, FAHA

It's hard to imagine, but this is the final day of Scientific Sessions 2015. I'm happy to report that some of the best programming has been saved for last.

We start with a plenary session, "Navigating the Complex Landscape of Heart Failure," which begins at 9 a.m. in the Chapin Theater. We also have a special joint session with the European Society of Cardiology this morning titled "Updated Implementation of Multimodality Imaging Based on Guidelines." The session begins at 9 a.m. in W315AB.

The final Late-Breaking Clinical Trials session begins at 10:45 a.m. in the Chapin Theater. The session, "Novel Therapies for Common Problems," will feature results from two heart failure trials, as well as results from a trial examining the prevention of cardiac dysfunction during adjuvant breast cancer therapy. It will also feature a trial examining the reversal of rivaroxaban-induced anticoagulation by a universal antidote for factor Xa inhibitors, a trial examining an inhibitor of PCSK9 with long-lasting effects and a handful of other outstanding late-breaking trials.

A special joint session with the World Health Organization also begins at 10:45 a.m. in W315AB, bringing the meeting to a close. The session is titled "Ten Years to WHO 2025 Goals – Where do We Stand? How Far to Go?"

This year's Scientific Sessions has featured some outstanding clinical trials, including the SPRINT trial, an outstanding series of plenary and special sessions and other educational programs, and the much-anticipated 2015 resuscitation guidelines. These and other presentations will undoubtedly have long-lasting implications on the treatment of our patients with cardiovascular disease. The clinical, population and basic science presentations clearly helped make this the premier cardiovascular meeting in the world.

I would like to thank the staff of the American Heart Association and the Committee of Scientific Sessions Program for their skill and hard work putting this meeting together. See you next year for Scientific Sessions 2016, Nov. 12-16, in New Orleans, Louisiana. ▼

Late-Breaking Clinical Trials — LBCT.04
10:45 a.m.–12:15 p.m. Wednesday | Chapin Theater

Novel Therapies for Common Problems

TRIAL	DESCRIPTION
One Year Follow-up Results From AUGMENT-HF: A Multicenter Randomized Controlled Clinical Trial of the Efficacy of Left Ventricular Augmentation With Algisyl-LVR in the Treatment of Heart Failure	This is a multicenter, randomized, controlled clinical trial testing a novel heart failure therapy as a potentially effective treatment for patients with advanced HF.
The First-in-Man Randomized Trial of a 3-adrenoceptor Agonist in Chronic Heart Failure – The BEAT-HF Trial	This trial was designed to evaluate the effect on heart pump function and safety of a beta-3 receptor agonist in patients with chronic heart failure.
Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2 x 2 Factorial, Placebo-Controlled, Double-Blind Clinical Trial	This randomized, placebo-controlled, double-blind trial assessed the effect of the beta blocker metoprolol and the angiotensin receptor blocker candesartan as preventive cardioprotective therapy in women treated with an anthracycline-containing early adjuvant breast cancer regimen with or without trastuzumab and radiation.
ANNEXA™-R Part 2: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Sustained Reversal of Rivaroxaban-Induced Anticoagulation in Older Subjects by Andexanet Alfa (PRT064445), a Universal Antidote for Factor XA (FXA) Inhibitors	ANNEXA™ is a four-part, Phase 3, double-blind, placebo-controlled program comprised of two studies of AnXa in older subjects treated with rivaroxaban or apixaban; ANNEXA-R Part 2, which investigated a bolus of AnXa followed by a two-hour continuous infusion, will be presented.
Prevention of Acute Kidney Injury by Nitric Oxide During and After Prolonged Cardiopulmonary Bypass: A Double Blind Randomized Controlled Trial	In the NITRIC trial, nitric oxide was delivered during and after prolonged cardiopulmonary bypass to prevent acute kidney injury caused by plasma-Hb induced NO scavenging.
A Randomized, Placebo Controlled Trial of Late Na Channel Inhibition (ranolazine) in Coronary Microvascular Dysfunction (CMD): Impact on Angina and Myocardial Ischemia	RWISE was a randomized, double-blinded, placebo-controlled crossover trial of oral ranolazine 500 mg–1,000 mg twice daily for two weeks in women and men with symptoms and signs of myocardial ischemia, no obstructive CAD and abnormal CFR or abnormal myocardial perfusion reserve index (MPRI) on CMRI.
ALN-PCSsc, an RNAi Investigational Agent That Inhibits PCSK9 With Potential for Effective Quarterly or Possibly Bi-Annual Dosing: Results of Single-Blind, Placebo-Controlled, Phase 1 Single-Ascending Dose (SAD), and Multi-Dose (MD) Trial in Adults With Elevated LDL-C, on and off Statins	This study looked at ALN-PCSsc, an RNAi investigational agent that inhibits PCSK9, with potential for effective quarterly or bi-annual dosing.

Walking Challenge

Congratulations, Walking Challenge participants. You've already logged enough steps to walk to New Orleans, the site of next year's Scientific Sessions, and back… several times over! As of 4 p.m. Tuesday, Walking Challenge participants had logged a grand total of 20,527,162 steps. Using 3 feet as an average stride length, that comes out to more than 11,663 miles. The driving distance between the Orange County Convention Center and the Ernest N. Morial Convention Center in New Orleans is 645 miles, so that's more than nine round trips.

The winners of this year's Walking Challenge will be displayed by 10 a.m. Wednesday in the Walking Challenge app and on the leaderboard in the Walking Challenge Booth in the Hall C Lobby. Winners must pick up their prizes by 1 p.m. at the Walking Challenge booth.

Surgeon General seeks to redefine success in healthcare

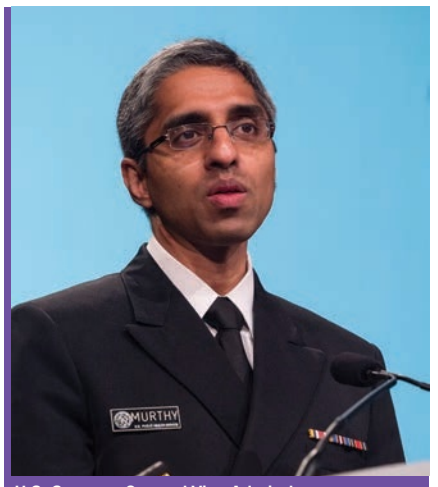
As a youngster in Miami, Vivek Murthy enjoyed hanging out at his dad's primary-care practice. Being around those patients prompted him to realize that so much of what brought them into the office was preventable.

These days, as Surgeon General of the United States, Murthy is doing something about it. And he wants the rest of the healthcare community to join him. Speaking Tuesday at Scientific Sessions, Murthy encouraged clinicians and researchers to find more, and more modern, ways to help.

"Now is the time for us to expand our definition of success when it comes to health," he said. "Success should be the patient who never has to walk through the door of a clinic or a hospital in the first place."

Murthy cited an explosion of chronic disease that's responsible for seven out of 10 deaths in America and well over $1 trillion in healthcare costs, because prevention efforts have fallen short. He urged healthcare providers to help build "a culture of prevention," focusing on information and environment.

"We have to be creative about using different messages, using different messengers and employing different platforms to reach people where they are, to ensure that the maximum number of people are getting the information about health that they need," he said.



U.S. Surgeon General Vice Admiral Vivek Murthy, MD, MBA

Yet information is only a start, since most people know they should exercise more or eat better. The struggle is getting them to do it. That's where the environment comes into play, such as cities and workplaces making healthy choices easier and more affordable.

For example, in Wabasso, Florida, community leaders fixed up sidewalks, turned vacant lots into parks and added better lighting. Two years later, 95 percent of residents surveyed had increased their activity levels, Murthy said.

Murthy acknowledged that many healthcare professionals haven't been taught how to change environments, and it's not easy. But he urged them to try, offering the story of Dr. David Sagbir, a cardiologist from Westerville, Ohio, as an example.

After years of counseling patients about diet and exercise, he found that only a handful of patients were getting the recommended 150 minutes per week of physical activity. So he began asking patients to meet him in a park so they could walk together. More than 100 showed up the first time. Now, there are more than 160 chapters nationwide of an organization he built called Walk With A Doc.

"The patients who participate in this program are 80 percent more likely to increase their level of physical activity," Murthy said. "The walks they do also provide time for doctors and patients to talk freely and to strengthen their relationship in ways that are often quite difficult in the hustle and bustle of a busy clinic."

Murthy encouraged medical professionals to provide the guidance patients need.

"Dr. Sagbir's example teaches us that we, too, have the potential to bring good health to millions of people by building a prevention-based society," he said. "That's what our country needs. And that's what I hope we can create together." ▼

CAREER PROGRESSION

NANCY M. ALBERT, PHD, CCNS, CCRN, NE-BC, FAHA, FCCM

Each day, we're profiling an investigator at a different career stage, from early career to distinguished veteran.

Nancy Albert got involved with the American Heart Association in 1999 when she was asked to co-direct a program at a heart failure conference.

"A year later, I assisted the Council of Cardiovascular Nursing (now called the Council on Cardiovascular and Stroke Nursing) with program planning for Scientific Sessions, and since then I have been involved with multiple committees and working groups," said Albert, associate chief nursing officer for the Office of Nursing Research and Innovation at the Nursing Institute for the Cleveland Clinic Health System.

For her extensive volunteer work, Albert was recently named the AHA Healthcare Volunteer of the Year.

"Volunteerism for the AHA opened up my professional world," she said. "After becoming involved in the AHA, I went back to college to work toward a PhD and my career path became much more focused on leading research."

As a clinical nurse, Albert always had an interest in cardiac disease, but the focus has changed over time.

"I spent many years caring for patients after open-heart and vascular surgeries," she said. "My goals were to ensure smooth transitions out of the intensive care unit, so the focus was primarily on ensuring optimal hemodynamics, managing intravenous medications and devices, and ensuring optimal healing."

When she took a job as a nurse manager of a high-intensity coronary care unit, Albert began to appreciate the delicate balance of aggressive and palliative care for patients with advanced heart failure, post-STEMI cardiogenic shock and post arrest due to arrhythmic events.

"In this setting, I learned that I had an affinity for helping patients suffering from heart failure," she said. "When an opportunity arose to become a clinical nurse specialist in heart failure, dysrhythmias and cardiac transplantation, it was a perfect fit."

Since then, her research work has helped her career evolve in new directions. Most recently, she has become increasingly focused on identifying and understanding patients' perspectives.

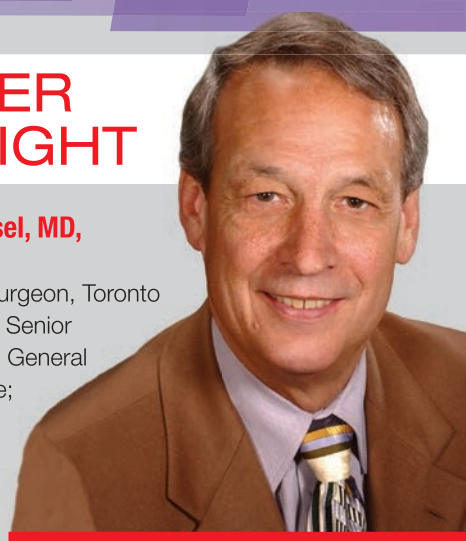
"I became interested in novel methods of mobile or electronic health monitoring that could be important to patients with heart failure," said Albert, who is also a clinical nurse specialist at the Kaufman Center for Heart Failure at the Cleveland Clinic's Heart and Vascular Institute. "As population health becomes more ingrained and as national research goals evolve, I expect my research work will continue to transition."

Albert acknowledges that many factors have influenced her career progression, including healthcare trends, governmental and economic forces, patient factors and her hospital's strategic plans. One constant has been her volunteer work for the AHA and other organizations.

Albert currently volunteers with the AHA's Clinical Workgroup of the Get With The Guidelines: Heart Failure program. She also serves on the Consumer Health & Quality Coordinating Committee as Professional Education Committee liaison; the Quality Care and Outcomes Research Leadership Committee as Cardiovascular and Stroke Nursing (CVSzN) Council member; the CVSN Council's Leadership Committee; the Science Advisory and Coordinating Committee; the Corporate Relations Review Committee; and as chair of the Professional Education Committee.

"There are so many expert volunteers at the AHA whose opinions are valuable, contemporary and forward thinking," she said. ▼

MEMBER SPOTLIGHT



Richard D. Weisel, MD, FRCSC, FAHA
Cardiovascular Surgeon, Toronto General Hospital; Senior Scientist, Toronto General Research Institute; Professor of Cardiac Surgery, University of Toronto

How long have you been an AHA/ASA Professional Member?
I have been a member of the AHA since 1978.

Why did you join?
I joined the AHA in order to attend Scientific Sessions and present our research on myocardial protection for heart surgery. I have attended nearly every meeting since 1978. In the last 20 years, our group has focused on stem cell research from the bench to the bedside and back.

Are you involved in AHA councils?
I have been a member of the Surgery Council — now called the Council on Cardiovascular Surgery and Anesthesia — since I joined the AHA. My involvement has evolved over the years. First I was an attendee at the council meetings and dinner. Then I was asked to join the Council Program Committee.

I became the chairman of the Council Program Committee and finally I was selected to be the council chairman. Since that time, I have continued to serve on the leadership committee in various roles. In addition, I have been a member of the Basic Cardiovascular Sciences Council as my second council.

What do you enjoy most about these roles?
The AHA meetings provide opportunities to meet and interact with clinicians and basic scientists with similar research interests. Each year I learn more about what is really going on in my field than from reading the literature. The discussions with investigators from around the world provide unique insights that focus our research efforts.

How else are you involved with the AHA?
I have served on a variety of AHA national committees.

Why is membership valuable to you?
My involvement with the AHA has provided me an opportunity to know the leaders in my areas of research interest. I learned how to get grants funded and papers published through my participation in AHA review activities. Many of these associations continue to be important today for my activities as editor of *The Journal of Thoracic and Cardiovascular Surgery* and chair of the Cardiothoracic Surgical Trials Network.

What message would you like to convey to your colleagues about being an AHA member?
Participation can be extremely rewarding. Spend the time and learn what you can. The opportunities afforded by AHA membership are exceptional.

Health Tech Competition

In the second annual Health Tech Innovation Competition at Scientific Sessions, the People's Choice Award went to Constant Therapy and the Judge's Award went to Remedy. Congratulations to the winners!

Study finds no J-curve in sodium intake, CVD, mortality rates

A study of dietary sodium intake and mortality presented Tuesday at Scientific Sessions showed no association between reduced sodium intake and increased risk at the low end of the sodium spectrum. Earlier observational studies had raised the possibility of a J-curve association, but the analysis presented Tuesday showed a linear association between increased dietary sodium and increased risk of future mortality over 20 years at all levels of sodium intake.

"We had a healthy group of individuals and showed that there is a straight line relationship for dietary sodium intake with both cardiovascular disease incidence and now total mortality," said lead author Nancy R. Cook, ScD, professor of medicine at Harvard Medical School and professor of epidemiology at Harvard T.H. Chan School of Public Health in Boston. "All the evidence points to lower sodium being better."

The AHA recommends that most adults consume no more than 1,500 mg of sodium per day.

"That is very difficult to achieve, given that most of our dietary sodium is found in prepared foods," Cook said. "Not many people have sodium intake that low. But it seems it would be beneficial for total mortality as well as cardiovascular disease."

Cook presented findings from a post-trial follow-up of the two phases of the Trials of Hypertension Prevention (TOHP), randomized clinical trials of various blood pressure control strategies in the 1980s and 1990s. A total of 744 phase I participants and 2,382 phase II participants were randomized to either 18 months or 36 months of dietary sodium restriction or control and compared to 3,021 usual-care participants.


Nancy R. Cook, ScD

Participants were between 30 and 54 years of age at baseline. None had frank cardiovascular disease and none had hypertension. The participants had what was called at the time "high normal" blood pressure and might now be assessed as prehypertensive, Cook said.

Because TOHP was a randomized clinical trial, all of the participants had multiple clinical assessments, including between three and six 24-hour urine specimens during the trial phases to assess their true sodium intake. More than 3,000 participants were not assigned to a sodium-reduction intervention and were classified by average sodium intake for the analysis of average sodium levels. The participants were then followed for between 23 and 26 years for cardiovascular disease and for all-cause mortality in the post-trial period.

"This study utilized the breadth and depth of clinical measurements collected during the two phase I and II clinical trial periods," said Donna K. Arnett, PhD, MSPH, chair and professor of epidemiology at the University of Alabama Birmingham School of Public Health and a past AHA president. "Rather than relying on self-reported sodium intake, these participants had multiple 24-hour urine samples, the gold standard of sodium intake. They were randomized to a wide range by sodium intake and they were followed for up to 26 years. There is no evidence of harm and, most importantly, no evidence of any J-shaped relationship within this very well-done study."


Donna K. Arnett, PhD, MSPH

Earlier studies assessed TOHP participants for cardiovascular disease 10 to 15 years following the trial, Cook said. In addition to statistically significant reductions in cardiovascular disease associated with lower sodium intake, there was a trend for lower overall mortality associated with reduced dietary sodium.

The current analysis is based on more than 20 years of mortality follow-up through the end of 2013. Active intervention to reduce sodium intake was associated with a hazard ratio of 0.85 with a nonsignificant p value of 0.19. Participants were also classified by dietary sodium intake: less than 2,300 mg/day; 2,300 to 3,599 mg/day; 3,600 to 4,799 mg/day; and 4,800 mg/day or higher.

"Of particular interest to us was the bottom of the curve, to see whether there was any evidence of an uptick, a J shape, or if the dietary sodium-mortality relationship remained linear," Cook said. "We saw a very linear relationship throughout. Using the best measure of sodium available, 24-hour urine, we saw no evidence of a J-shaped curve." ▼

New imaging techniques being developed to identify catastrophic plaque ruptures

The conventional ideas about plaque formation and rupture are wrong, according to Keith A.A. Fox, MB, ChB, who presented the Paul Dudley White International Lecture on Tuesday at Scientific Sessions.

Plaque does not build over time, rupture catastrophically and generate a thrombus that blocks the artery. Plaque does build over time, but small ruptures are common occurrences that pose little risk, he said. Only selected plaques are vulnerable to catastrophic rupture with potentially fatal consequences.

"Blockage of arteries is a stochastic progression with abrupt, destabilizing changes sometimes resulting in death," said Fox, the Duke of Edinburgh Professor of Cardiology at the University of Edinburgh in Scotland. "We have a series of small ruptures all the time. In most of us, the balance is tipped toward repair. In vulnerable plaques, repair cannot keep pace and we die."

The concept of vulnerable plaque is hardly new, Fox noted in his lecture, "Identification of the Vulnerable Plaque: From Bench to Bedside." The first recorded observation of plaque rupture dates back to an 1844 autopsy in Denmark.

What's new is the realization that plaque is ubiquitous and rupture is only sometimes catastrophic. Data from heart donors show increasing atherosclerosis with increasing age. Most older individuals in developed economies have atheromatous plaques, and most plaques are benign and asymptomatic.

That benign profile changes in cardiovascular disease. Not all coronary lesions are equally prone to catastrophic rupture, Fox explained. But standard imaging techniques cannot distinguish between vulnerable plaque and asymptomatic plaque.

The need for improved imaging techniques comes into sharp focus when seen through the lens of long-term survival from acute coronary syndromes. ST elevation is responsible for most deaths during the acute phase. But ST depression is the leading cause of death beyond the first 15 days, Fox noted.

Data from the Global Registry of Acute Coronary Events (GRACE) show roughly similar five-year death rates from STEMI, non-STEMI and unstable angina. But the proportion of post-discharge deaths is significantly higher for both non-STEMI and unstable angina than for STEMI events. Data on recurrent events from the U.K. cohort of GRACE showed significant numbers of readmissions for recurrance of the index event: 12.7 percent had at least one recurrent MI, 7.7 percent had at least one recurrent stroke and 53.6 percent had one or more ACS readmissions.

"Much has been done to improve outcomes in the acute phase," Fox said. "I want us to refocus on longer-term outcomes. The acute phase is only the start of the problem. Some 86 percent of deaths occur after the acute phase, after the initial discharge."

Cardiovascular events after an initial ACS are almost evenly divided between events related to the culprit lesion and events not related to the culprit lesion. That makes it even more important to devise methods to identify and treat vulnerable plaque.

Fox has devised ultrasound microbubbles that can be linked to monoclonal antibodies to target activated endothelial cells by CD54 on cells that have been activated by TNF. The microbubbles selectively attach to activated endothelial cells to enhance imaging. The same technique might be used to deliver therapeutic agents directly to target cells. Oncologic researchers are developing similar techniques to target, identify and treat specific tumor types.

Keith A.A. Fox, MB, ChB

New imaging techniques are being developed that can identify deposits of vulnerable plaque. One such technique, ^{18}fluro-deoxy glucose PET, can identify pockets of aortic inflammation but it is less useful in picking out inflamed coronary lesions. Peak plasma troponin correlates well with aortic ^{18}F-FDG uptake, but the technique does not work for coronary arteries because myocardial uptake of glucose obscures the culprit plaque in most images.

A newer technique, sodium ^{18}F-fluoride, highlights calcification activity. In patients with myocardial infarction, ^{18}F-fluoride clearly distinguished the culprit lesion from the highest non-culprit lesion in both *ex vivo* and *in vivo* experiments.

"There is progress in identifying the pathways leading to plaque rupture and progression," Fox said. "But we need more research into patient phenotypes, identifying and imaging those vulnerable plaques and finding novel targets to limit progression." ▼

Study finds that Life's Simple 7 has implications beyond CVD

The American Heart Association's Life's Simple 7 index may identify vulnerability for multiple chronic conditions beyond cardiovascular disease, according to a study presented at Scientific Sessions that suggests achieving the AHA's national goal of ideal LS7 health metrics will reduce the burden of many diseases.

The research was presented Tuesday by Oluseye Ogunmoroti, MD, MPH, postdoctoral research fellow at Baptist Health South Florida in Miami.

Oluseye Ogunmoroti, MD, MPH

"The findings emphasize the importance of primordial prevention as a means to reduce the burden of chronic diseases," Ogunmoroti said. "The risk of chronic diseases, such as cancer and chronic kidney disease, is lower among individuals with ideal Life's Simple 7 scores."

The AHA initiated Life's Simple 7 with the goal of improved health by educating the public on how to live a healthy lifestyle. The program measures have three common denominators. Any person can make the changes, the steps are not expensive to take and even modest improvements to an individual's health will make a big difference.

"Educating the public on achieving ideal cardiovascular health has the potential to improve overall well-being and reduce healthcare costs," Ogunmoroti said.

Ogunmoroti's study included 6,506 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). Participants were followed for a median 10.2 years.

Each component of the LS7 metrics (smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and blood glucose) was assigned a score: 2 (ideal), 1 (intermediate) or 0 (poor). A total score for all seven components of 11 to 14 was considered ideal; 9 to 10 was considered intermediate; and 0 to 8 was poor.

Cox proportional hazard ratios and incidence rate per 1,000 person-years were calculated for hospital ICD-9 diagnoses of cancer, chronic kidney disease, pneumonia, chronic obstructive pulmonary disease, deep vein thrombosis/pulmonary embolism, dementia and hip fracture. Analyses were adjusted for age, gender, race/ethnicity and socioeconomic status.

Overall, all non-CVD event rates were lower with improved LS7 health status, Ogunmoroti said.

In multivariable adjusted models, with the poor category of the LS7 health index as reference, individuals in the ideal category had a lower hazard for the following non-CVD events: 20 percent lower for cancer, 62 percent lower for CKD, 43 percent lower for pneumonia and 49 percent lower for COPD. ▼

Using data from the MESA trial, researchers have concluded that AHA's Life's Simple 7 health metrics may identify vulnerability for chronic conditions beyond cardiovascular disease. The study results, which were presented Tuesday in abstract 11907, suggest that achieving the AHA's national goal of ideal health may reduce the burden of many diseases as well as healthcare costs.

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"Despite these rarities, they were very informative mutations because all of them resulted in a loss of function of the encoded protein and turned out to interrupt the function of a class of molecules — cardiac conscription factors," Seidman said.

Unfortunately, this insight is not applicable to much more severe forms of congenital heart disease, such as tetralogy of Fallot, transposition of the great arteries and hypoplastic left heart syndrome.

The National Heart, Lung, and Blood Institute funded the creation of the Pediatric Cardiac Genetics Consortium in 2009. It comprises some of the leading cardiovascular research labs in the U.S. to address the potential genetic etiologies of more severe cardiac malformations, Seidman said.

"What we have postulated over the past five years is that *de novo* mutations arise in the embryonic egg or sperm, ultimately resulting in a child with critical congenital heart disease that obviously was absent from either of the parental genomes," Seidman said. "What we were looking for in our sequence analyses was a Mendelian error, if you will."

Ongoing research has led to the identification of specific mutations that perturb genes involved in anatomic structure, morphogenesis and developmental processes. The details will be published in the journal *Science* later this year.

"What we're learning is enormously informative of a new genetic cause of congenital heart malformation and is going provide a wide range of opportunities to discover the developmental signals that are critical for shaping the normal human heart," Seidman said. ▼

LPIR score may be an early biomarker for type 2 diabetes

In initially healthy women, lipoprotein insulin resistance (LPIR) score is strongly associated with incident diabetes, independent of risk factors that include body mass index, hemoglobin A1c levels and lipids, according to research presented Tuesday at Scientific Sessions.

The study also indicated that the LPIR score had a stronger association than BMI with diabetes, said Paulo Henrique Nascimento Harada, MD, MPH, a research fellow in the divisions of preventive and cardiovascular medicine at Brigham and Women's Hospital in Boston.

The LPIR score is a composite of six lipoprotein parameters measured by nuclear magnetic resonance spectroscopy that reflects the lipoprotein derangements of insulin resistance, which may be apparent years before the onset of overt hyperglycemia. The parameters are: very-low-density lipoprotein (VLDL), high-density (HDL) and low-density (LDL) lipoprotein particles of average size, and concentrations of large VLDL, large HDL and small LDL subclasses.

Harada said this more-sensitive biomarker might allow for earlier detection of type 2 diabetes risk.

"Type 2 diabetes is a disease with very indolent and silent progression that is associated with comorbidities even before its diagnosis," Harada said. "Therefore, if we accurately identify individuals at risk earlier along the path to disease, we may intervene for at-risk populations in a timely way."

The findings came from 25,925 participants in the Women's Health Study.

In the study's preliminary results, the researchers reported that individuals with an LPIR score greater than 67 had twice the risk of diabetes compared to those with an LPIR score less than 30, and the risk increased linearly along the LPIR spectrum. LPIR scores range from zero, the most insulin sensitive, to 100, the most insulin resistant.

"It is quite impressive, the magnitude of LPIR association with diabetes in this relatively healthy population," Harada said. "Moreover, LPIR association with diabetes was larger than other traditional markers like triglycerides, HDL-c, BMI and high-sensitivity C-reactive protein."

Comparing LPIR Q4 (>67) versus Q1 (<30), the unadjusted hazard ratio (HR) was 11.08, which remained significant but attenuated to 2.22 (1.72 to 2.85) in the fully adjusted model that included BMI, lipids and HbA1c. In comparing fully adjusted standardized HRs for incident diabetes, the HR per standard deviation of LPIR was 1.42 (1.31 to 1.54), greater than the components of LPIR and other markers of diabetes.

It is significant that LPIR was associated with diabetes risk by a high magnitude in a population with a very good metabolic profile at baseline, and therefore at low risk of diabetes, Harada said.

The study's results align with recently published results from the Multi-Ethnic Study of Atherosclerosis (MESA), Harada said. However, he noted, the MESA study's population is six years older, and had higher BMI and shorter duration of follow-up. ▼

Nitric oxide delivery improves outcomes in pediatric cardiac surgery

Delivery of nitric oxide (NO) to the cardiopulmonary bypass (CPB) circuit for children undergoing cardiac surgery significantly reduces the incidence of low cardiac output syndrome (LCOS), use of extracorporeal membrane oxygenation (ECMO) and ICU length of stay by varying degrees, according to age group.

Those findings were presented Tuesday by Chris James, BSc, BM, BCh, MRCPCH, FFICM, FCICM, pediatric intensive care consultant at the Royal Children's Hospital in Melbourne, Australia. The research won the 2015 American Heart Association Outstanding Research Award in Pediatric Cardiology.

"Mortality rates are low following surgery for congenital heart disease in children, but morbidity is significant and frequently related to the presence of low cardiac output syndrome and a protracted length of stay in ICU," James said. "Our study is important, as we have described an intervention which was not associated with adverse effects and can significantly reduce low cardiac output syndrome as well as ICU length of stay, reducing the burden of morbidity."

Compared to children in the study who did not develop LCOS, children with LCOS had a greater renal replacement requirement (51 percent versus 16 percent), longer duration of mechanical ventilation (72 hours versus 18 hours), longer ICU length of stay (144 hours versus 46 hours) and longer hospital length of stay (17 days versus eight hours).

Children requiring cardiac surgery with CPB frequently develop LCOS, particularly when very young, James noted.

"Any intervention that reduces the incidence of LCOS has the potential to make a big difference in reducing the morbidity associated with pediatric cardiac surgery," James said.

A 2013 pilot study of 16 children in Texas showed that the delivery of NO to the CPB circuit shortened duration of mechanical ventilation and ICU stay. James said his research team hypothesized that administering NO to oxygenator gas flow during CPB would decrease the incidence of LCOS and affect subsequent clinical outcomes.

The team conducted a prospective, blinded, randomized controlled trial in congenital heart disease surgery. Randomization was stratified by age.

Chris James, BSc, BM, BCh, MRCPCH, FFICM, FCICM

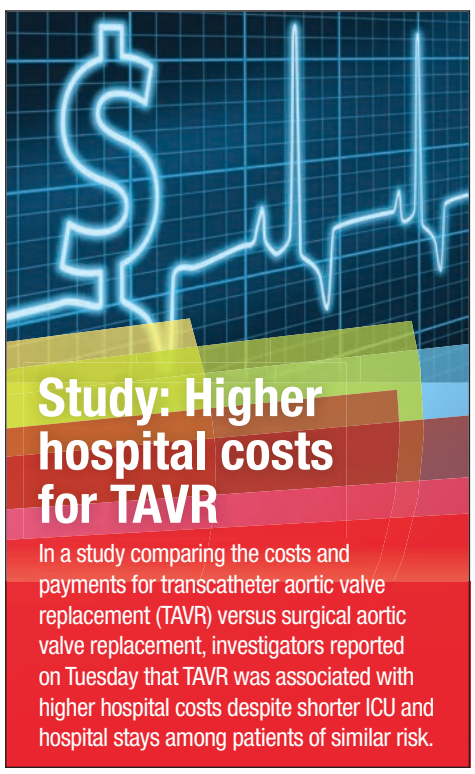
The children were randomized to receive oxygen alone (standard treatment) or 20 ppm gaseous NO and oxygen to the CPB gas administration line. Only the study perfusionist was aware of the allocation, and all equipment and devices were otherwise identical in each group. The cardiac surgeon and anesthetist remained blinded to patient allocation.

Of the 198 children enrolled, there were no differences in patient characteristics, diagnoses or surgeries between groups.

Of the enrollees, 101 children received NO and had a significant reduction in LCOS, use of ECMO and a non-significant reduction in duration of ventilation compared to the 97 children who did not receive NO. ICU length of stay (48 hours versus 72 hours) and hospital length of stay was also improved in the NO cohort.

The reduction in LCOS was most pronounced in children less than six weeks of age and in children six weeks to two years, who also had significantly reduced ICU length of stay. LCOS occurred equally in the two cohorts in children older than two.

"As a result of our findings, our institution now administers NO during CPB for children undergoing heart surgery in which we consider the risk of developing LCOS to be high," James said. ▼



SCENES FROM SESSIONS

CELEBRATING RESEARCH

Some of the current and past American Heart Association research awardees gathered Monday. The AHA has funded $3.9 billion in research into heart disease, stroke and other cardiovascular diseases, more than any organization outside the federal government. The organization has funded 13 Nobel Prize winners and lifesaving research advancements such as the first artificial heart valve, cholesterol-inhibiting drugs, heart transplantation, and CPR techniques and guidelines.

LATE-BREAKING continued from page 1

developed predictive models for bleeding and ischemic events in patients who remained on DAPT 12 months following stent implantation, then combined them into a third model to predict the net treatment effect.

Risk factors include patient age, prior PCI or MI, stent diameter, MI at presentation, cigarette smoking, diabetes, vein graft PCI and other features. These factors were used to create a scoring system of 1 to 4. Patients with a score of less than two are more likely to bleed than see ischemic benefit, while patients with a score of two or higher are more likely to benefit from reduced ischemic events than bleed. The tool is available at www.daptstudy.org.

"The DAPT score is very similar to other clinical tools such as CH_2AD_2-VASC or HAS-BLED," noted James de Lemos, MD, professor of internal medicine at the University of Texas Southwestern Medical Center in Dallas. "This study demonstrates the value of standard clinical tools in providing personalized care."

In another presentation, researchers presented a quality-of-life analysis of the RIVER-PCI trial that echoed the study's primary outcome, finding that ranolazine had no significant effect on angina. The study is titled "Angina and Quality of Life following PCI with Incomplete Revascularization: Results from the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial."

Principal investigator E. Magnus Ohman, MBBS, professor of medicine at Duke University Medical Center, said the results indicate no incremental benefit from ranolazine.

"Most patients had angina going into RIVER-PCI and most were asymptomatic after their incomplete revascularization, with or without ranolazine," Ohman said. "We need more research into the relationship between patient-reported angina and ischemia-driven events."

John A. Spertus, MD, MPH, director of Health Outcomes Research at the Mid America Heart Institute in Kansas City, Missouri, said the trial suggests prophylactic use of ranolazine is not helpful to reduce angina after incomplete revascularization. He also noted that these patients require close follow-up for residual angina. Those with residual angina need additional treatment such as ranolazine, CTO PCI or other strategies, he said.

Results from "Long-Term Tolerability of Ticagrelor for Secondary Prevention: Insights from PEGASUS-TIMI 54 Trial" indicated that most patients who stop taking ticagrelor do so due to relatively minor side effects. Closer monitoring of these patients and better patient education and counseling could improve outcomes by improving adherence, noted Marc P. Bonaca, MD, MPH, an investigator in the TIMI study group and an associate physician in cardiovascular medicine at Brigham and Women's Hospital in Boston.

"We found that events which clinicians characterize as mild or moderate can drive discontinuation," Bonac said. "The majority of events leading to discontinuation are dyspnea and bleeding that require minimal or no intervention, not serious adverse events."

Noncompliance with ticagrelor — 22.5 percent at three years in the trial — is a serious problem, agreed discussant Marco Costa, MD, PhD, professor of medicine at University Hospitals, Case Medical Center, in Cleveland, Ohio. Discontinuation is likely even higher in clinical practice, he said.

"We tend to focus on the biological aspects of our drugs and ignore the human behavior elements," he said. "I call on our colleagues to pay more attention to these non-biological factors that lead to discontinuation."

Another study, "Clinical Outcomes of Intravascular Ultrasound Guided Everolimus-Eluting Stents Implantation in Long Coronary Lesions," found that intravascular ultrasound (IVUS) guidance provides better clinical outcomes than angiographic guidance for second-generation drug-eluting stents in patients with long coronary lesions. The trial followed 1,400 patients for 12 months.

"Among patients who require long coronary stents, IVUS guidance was associated with a significant 2.9 percent absolute reduction and a 48 percent relative reduction in the risk of MACE at one year," said lead author Myeong-Ki Hong, MD, PhD, professor of medicine at Severance Cardiovascular Hospital, Yonsei University College of Medicine, in Seoul, Korea.

"We know the benefit is probably not due to operator behavior," Costa said. "We need to better understand the mechanisms responsible." ▼

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Gene mutations may explain poor prognosis in HCM patients with severe right ventricular hypertrophy

Research from China suggests that double or multiple sarcomere gene mutations might be associated with hypertrophic cardiomyopathy (HCM) with severe right ventricular hypertrophy (SRVH), according to a study presented Tuesday at Scientific Sessions.

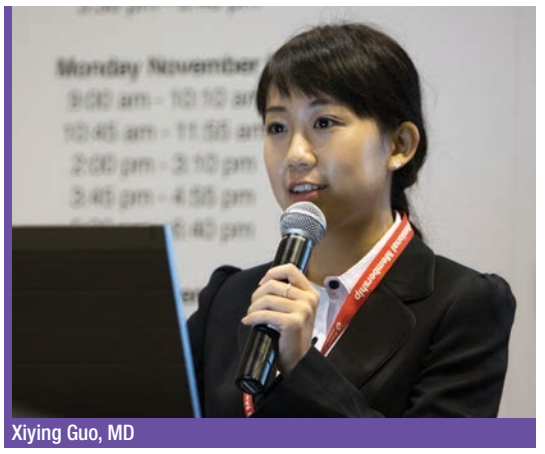
SRVH is a relatively rare subtype of HCM in which myocardial hypertrophy primarily affects the right ventricle. HCM is characterized by its great heterogeneity, including genotype and phenotype heterogeneity, which is a challenge for clinical practice, said Xiying Guo, MD, of the Key Laboratory of Clinical Trial Research in Cardiovascular Drugs, Ministry of Health, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing.

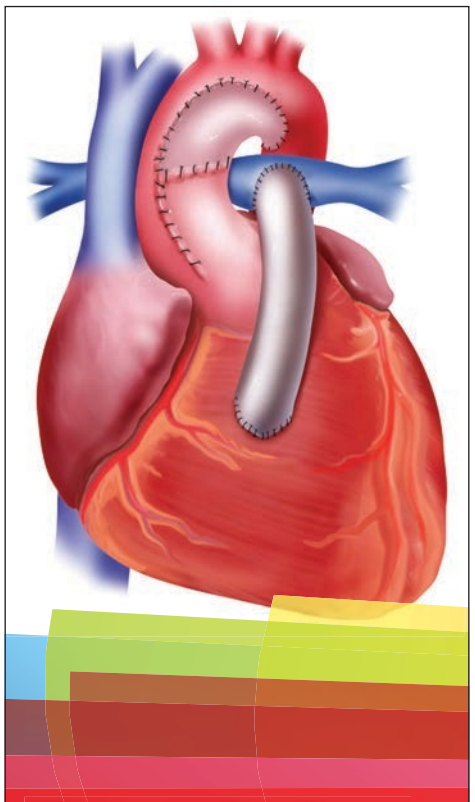
"Our study explored the prevalence, anatomic, clinical and relatively poor prognostic characteristics of SRVH, which have not been described well in the literature," Guo said. "Moreover, we used the newest whole-genome sequencing techniques to describe the genetic background of patients with SRVH and hope to explain the heterogeneity of HCM from a genetic aspect."

The researchers performed a retrospective cohort study of 2,415 HCM patients. Patients with HCM with a maximum right ventricular wall thickness of at least 10 mm, either with or without a pressure gradient at the RV outflow tract (RVOT) exceeding 25 mm Hg, were enrolled. Researchers identified 43 patients (1.6 percent) with SRVH and 12 of them demonstrated isolated RVOT obstruction. Deep (30X) whole-genome sequencing was performed in 11 patients using the Illumina HiSeq X ten platform.

The whole-genome sequencing results identified at least one variant in a specific sarcomere gene in 10 patients (90.9 percent), of which the MYH7 mutation was the most common (n=6, 54.5 percent). Ten novel locations were detected, and double or multiple mutations involving HCM genes were detected in eight patients (73 percent). All patients exhibited either double or multiple mutations, either in arrhythmogenic right ventricular, dilated cardiomyopathy or ion-channel disease genes.

"These findings prove patients with HCM with SRVH have a relatively poor prognosis in clinical practice." Guo said. "This might be a new risk factor for cardiovascular mortality or SCD." ▼


Xiying Guo, MD



Six-year findings of the SVR trial

During an oral abstract session Tuesday, researchers presented the most recent findings from the Single Ventricle Reconstruction (SVR) trial. They reported that six-year transplantation-free survival was an absolute 4.8 percent higher for patients who received the Norwood procedure with right ventricle-to-pulmonary artery shunt versus the modified Blalock-Taussig shunt group.

2015 Poster Winners

Early career work is extremely important to the American Heart Association. The future of cardiovascular science is in the hands of these healthcare professionals and scientists, and the poster sessions include many examples of the important work being done by this group. Here's a look at the poster winners from Scientific Sessions 2015 — all of whom are early career professionals:

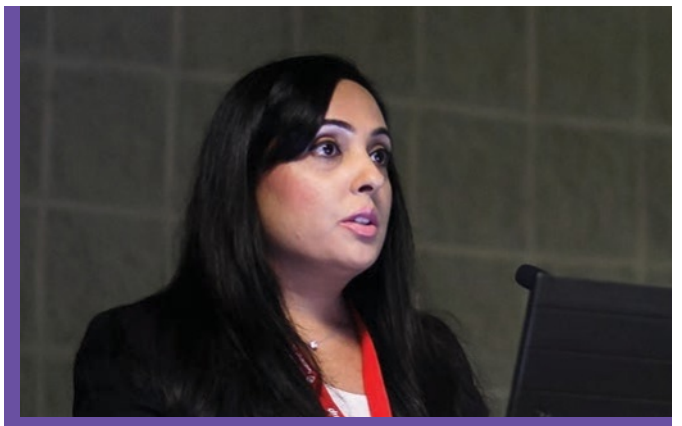
Basic Science
Toshiro Saito
Cardiac-specific Ablation of Ulk1, but not of Atg7, Attenuates Mitochondrial Autophagy in the Heart in Response to Energy Stress

Clinical Science
Shingo Kato
Left Ventricular Native T1 Time and the Risk of Arial-Fibrillation Recurrence After Pulmonary Vein Isolation in Patients With Paroxysmal Atrial Fibrillation

Population Science
Geng Zong
Frequent Consumption of Meals Prepared at Home and Risk of Type 2 Diabetes Among American Men and Women

Special Focus
Morten Smærup Olsen
Incidence of Epilepsy is Elevated in Children and Young Adults With Congenital Heart Defects Compared With the General Population: A Nationwide Cohort Study

Bystander CPR provided in nearly half of pediatric OHCA cases, study finds


Maryam Y. Naim, MD

According to research presented Tuesday at Scientific Sessions, nearly 50 percent of pediatric patients experiencing an out-of-hospital cardiac arrest (OHCA) receive bystander CPR and of those patients about 50 percent receive compressions-only CPR. The findings suggest increasing adherence to the 2010 AHA Guidelines for CPR and Emergency Cardiovascular Care (ECC), which emphasized compressions-only CPR as a viable alternative to conventional CPR when a rescuer is unwilling or unable to perform conventional CPR.

The study was presented by Maryam Y. Naim, MD, assistant professor of anesthesiology and critical care at the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia, from an analysis of the Cardiac Arrest Registry to Enhance Survival (CARES) database.

Nearly half of the patients in the study were infants (47 percent). Most arrests occurred at home (86 percent), were unwitnessed (75 percent) and had a non-shockable rhythm (93 percent).

Bystander cardiopulmonary resuscitation (BCPR) was provided in 49 percent of the cases, most commonly by a family member (71 percent). BCPR was more common for white children (60 percent) compared to black (42 percent) and Hispanic children (44 percent).

The finding that BCPR occurred in nearly half of the cases studied represented an improvement from previous research conducted 15 years ago. At that time, BCPR was performed in about 35 percent of pediatric OHCA cases, Naim said.

"In the last 15 years, there has been more education and awareness about bystander CPR," Naim said. "Children in schools are learning about bystander CPR. There is a lot in the news about compressions-only CPR, and there have been statewide campaigns, such as the one in Arizona. However, it's still just half of kids getting CPR, which is not good enough."

The study of 2,176 cardiac arrests included children who were 18 years of age or younger and who had non-traumatic OHCA from January 2013 through December 2014. The researchers defined neurologically favorable survival as a Cerebral Performance Category Scale of 1 or 2.

In a sub-group analysis, BCPR was associated with a higher rate of neurologically favorable survival for out-of-home arrests (34 percent versus 15 percent) and arrests presenting in a shockable rhythm (48 percent versus 32 percent).

It makes sense that BCPR resulted in better neurological outcomes for out-of-home arrests, Naim said, since there is a greater likelihood of more timely assistance and initiation of CPR when the incident occurs in public.

For infants, BCPR was not associated with survival (6.4 percent versus 6 percent) or neurologically favorable survival (5.2 percent versus 5 percent) — a finding with public policy implications, Naim noted.

"We have to find a way to prevent cardiac arrest in the population and perhaps monitor this population differently," she said.

As for the racial disparities in the administration of BCPR, Naim said that similar disparities have been observed in adult OHCA. It's an area ripe for further study and for potential educational intervention in minority communities, she added. ▼

CPAP therapy may improve PDD in patients with obstructive sleep apnea

Continuous positive airway pressure (CPAP) therapy for cardiovascular patients with obstructive sleep apnea has been shown to lower B-type natriuretic peptide (BNP) levels and has the potential to improve pre-clinical diastolic dysfunction (PDD), according to research presented Tuesday at Scientific Sessions.

The finding may represent the "missing link" between PDD and sleep-disordered breathing, according Sunao Kojima, MD, PhD, from the Department of Cardiovascular Medicine in the Graduate School of Medical Sciences at Kumamoto University in Japan.

"Patients with cardiovascular disease should be screened for sleep-disordered breathing, and CPAP therapy should be performed in suitable patients for a better clinical outcome," said Kojima, adding that the study's findings are important because long-term mortality in heart failure patients with preserved ejection fraction (HFpEF) is similar to HF with reduced EF (HFrEF).

However, he said, guideline-based medications that have been shown to improve survival in HFrEF have not been successful in reducing mortality in HFpEF patients, possibly because the established treatments of HFpEF are limited compared with those of HFrEF.

In the study, Kojima and his research colleagues focused on ACC/AHA stage B HF patients with PDD and investigated whether they were associated with desaturation during the night. A spectrophotometry of oxygen saturation with a built-in memory device was performed in 857 consecutive electively hospitalized cardiovascular patients who were free of prevalent heart failure and with left ventricular ejection fraction less than 50 percent.

Patients were divided into PDD (n=240) and normal systolic-diastolic function (NSDF) (n=617) groups based on the mitral flow and mitral annulus early diastolic velocity ratio (E/E′) and BNP levels.

A logistic regression analysis revealed that PDD was associated with nocturnal minimum oxygen saturation independent of age and non-cardiac risks, such as hemoglobin and estimated glomerular filtration rate, Kojima said. A total of 220 patients suspected of obstructive sleep apnea (OSA) underwent polysomnography and a treatment of CPAP was introduced in 169 patients. The hazard ratio for PDD without CPAP therapy was 7.7 compared to 0.821 for PDD with CPAP. A treatment with CPAP for PDD also was shown to reduce BNP levels.

"CPAP therapy may contribute to the beneficial prognosis in OSA patients with diastolic dysfunction, possibly because continuation of CPAP therapy can produce a decrease of E/E′ and BNP levels, which seems to transform into normal LV systolic and diastolic function," Kojima said.

Preventive care before the development of HFpEF is essential, Kojima added. PDD is prevalent in patients with normal LV ejection fraction and cardiovascular specialists have to make efforts to detect OSA patients with LV diastolic dysfunction who are free from heart failure and introduce CPAP treatment in such patients, he said.▼

Digoxin appears to be beneficial in treating infants with single ventricle congenital heart disease

Digoxin use in infants with single ventricle congenital heart disease appears to be significantly associated with reduced interstage mortality, according to research presented Tuesday by Matt Oster, MD, MPH, director of the Children's Cardiac Outcomes Research Program at Sibley Heart Center in Atlanta.

Using digoxin, Oster said, is "the most effective treatment during the interstage period that has been shown in two separate multicenter trials to have this kind of potential impact on mortality."

The findings, he said, suggest that digoxin can be an important addition to current treatment modalities, which include close monitoring and the use of diuretics.

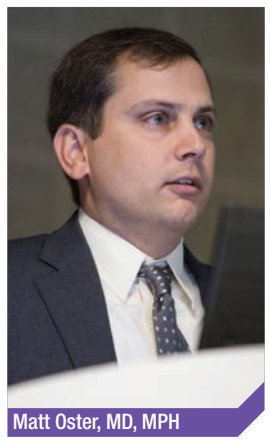
Oster noted that digoxin used to be a mainstay in the treatment of heart failure in children. However, in 1997, the Digitalis Investigation Group looked at the effect of digoxin in roughly 7,800 adult patients with heart failure and found no improvement in mortality. Because it's much more difficult to conduct those kinds of investigations in children and because single ventricle disease is much more rare than adult heart disease, Oster said many physicians extrapolated the results of that trial to children.

"So what we were left with was a small group of physicians who continued to use digoxin, and then many others who decided they were not going to use it," Oster said. "But it had never really been well-studied in this population, so this is an old drug that has been around for ages that may have some good benefit in this population."

Of the 330 infants studied, 102 (31 percent) were discharged home on digoxin. Interstage mortality for infants not on digoxin was 12.3 percent compared to 2.9 percent among those on digoxin, with a number-needed-to-treat of 11 patients to prevent one death during the interstage period, the time between discharge after the Norwood procedure and the Glenn procedure. The adjusted hazard ratio was 3.5 and there were no differences in complications between the two groups during the interstage period.

The researchers conducted a retrospective cohort study using the Pediatric Heart Network Single Ventricle Reconstruction Trial public use dataset from the National Heart, Lung, and Blood Institute at the National Institutes of Health.

The dataset includes information on infants with single right ventricle congenital heart disease, randomized to receive either a Blalock-Taussig shunt or right ventricle-to-pulmonary artery shunt during the Norwood procedure at 15 institutions in North America from 2005 to 2008.


Matt Oster, MD, MPH

Researchers used parametric survival models to compare the risk of interstage mortality between infants discharged to home on digoxin versus those discharged to home not on digoxin, adjusting for center volume, ascending aorta diameter, shunt type and socioeconomic status, Oster said. Further comparisons were made to the number of other adverse events in the two groups.

Oster said the trial was undertaken to try to replicate findings presented in March at the American College of Cardiology meeting.

"Having been trained to believe that digoxin was a drug that didn't do anything for heart failure in children, I felt that I needed to see this study replicated somewhere else before I would change my practice," Oster said. "And so when we found similar results in this population, I have subsequently become a believer, and I have changed my practice because of it." ▼

Study: SSC sheet transplantation is safe, feasible

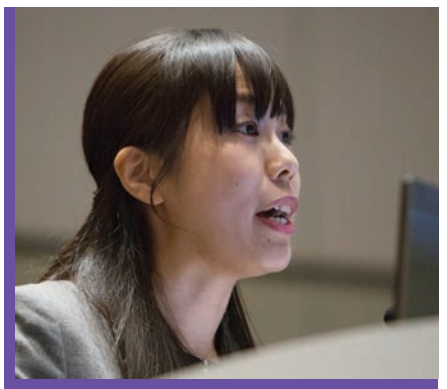
In an abstract presentation Tuesday, researchers reported that patients who received skeletal stem cell (SSC) sheet transplantation in the early stages of advanced heart failure gained functional recovery, including reduced LV wall stress. The researchers concluded that SSC sheet transplantation is safe and feasible.

Nanoparticle-mediated targeting offers therapeutic modality protecting against myocardial ischemia-reperfusion injury

Nanoparticle-mediated targeting of mitochondrial division inhibitor (Mdivi1) protects against myocardial ischemia-reperfusion (IR) injury through mechanisms independent of opening of the mitochondria permeability transition pore (mPTP), according to research presented Tuesday at Scientific Sessions.

The process works through the inhibition of mitochondria outer membrane permeabilization (MOMP)-induced mitochondrial injury via the inhibition of Drp1-mediated Bax translocation to mitochondria, said Ayako Ishikita, MD, a student in the department of cardiovascular medicine in the Graduate School of Medical Sciences at Kyushu University in Japan.

"There is an unmet need for a new therapy to reduce ischemia reperfusion injury," Ishikita said. "The most recent clinical trial targeting mitochondrial permeability transition pore failed to show clinical efficacy. Our study showed the efficacy of nanoparticulated Mdivi1 as a new therapeutic modality for myocardial IR injury targeting Drp1 and mitochondria outer membrane permeabilization."


Ayako Ishikita, MD

Ishikita and the research team hypothesized that nanoparticle-mediated targeting of Mdivi1 to myocardium would enhance the cardio protection by Mdivi1 against IR injury.

"It has been reported that Mdivi1 reduces infarct size only when it was administrated before the ischemia," Ishikita said. "Though that is an interesting finding, it is not a clinically feasible strategy to administer drugs before the onset of AMI."

Ishikita said her study indicates that the nanoparticle she and her research colleagues developed works as an excellent drug delivery system targeting ischemic hearts and that nanoparticle-mediated delivery of Mdivi1 is a clinically feasible strategy to prevent ischemia reperfusion injury.

She added that the Mdivi1-NP could be developed as a new drug to be administered during primary percutaneous coronary intervention for acute MI patients, which may limit myocardial infarct size and improve cardiac function and long-term prognosis.

The opening of the mPTP plays an important role in the pathogenesis of IR injury, she said.

However, an mPTP-opening inhibitor, cyclosporine, has not shown decisive therapeutic effects in animal studies or patients with acute myocardial infarction, Ishikita said.

Ishikita said the researchers formulated poly(lactic-co-glycolic acid) nanoparticles containing Mdivi1-NP.

In neonatal rat cardiomyocytes, nanoparticles were delivered to cytosol and mitochondria after the addition of H2O2 that mimics oxidative stress during IR.

Mdivi1-NP reduced H2O2-induced cardiomyocyte deaths more efficiently than Mdivi1 alone as indicated by a lower estimated EC50 (2.0 μM versus 25.0 μM) and greater maximal effects on cell survival (50.8 percent versus 45.1 percent).

In Langendorff-perfused murine hearts, treatment with Mdivi1-NP at the time of reperfusion reduced IR injury more effectively than Mdivi1 alone, Ishikita said.

"Drp1, a molecule that regulates mitochondrial division, was found to regulate Bax recruitment to the mitochondria to cause MOMP and cardiomyocyte death in the process of IR injury," she said. "Our Mdivi1-NP inhibited this mechanism and showed cardioprotective effect." ▼

GUIDELINE continued from page 1

Previous guidelines advised that PCI in a non-culprit artery should not be performed at the time of primary PCI in stable patients. That Class III recommendation was based on observational and registry studies. Four recent randomized controlled trials have examined the use of non-culprit PCI either at the time of primary PCI or as a planned, staged procedure.

"The literature now supports the recommendation that the performance of PCI in a non-infarct artery can be considered in selected patients with STEMI and multi-vessel disease (Class IIb)," O'Gara said. "Non-culprit PCI is not for every patient and clinical judgment is required, but in appropriate patients, it can be safe and effective."

This new recommendation largely reflects current clinical practice, O'Gara added. Up to 50 percent of STEMI patients have multi-vessel disease, presenting with an infarct in the culprit artery and high-grade disease in one or two additional vessels. Patients are typically stabilized following the index PCI, then returned to the cath lab for additional non-culprit artery PCI a few days later based on anatomy, renal function and other clinical factors. ▼

REPATHA™ (evolocumab)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

1. INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

REPATHA is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

1.2 Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

1.3 Limitations of Use

The effect of REPATHA on cardiovascular morbidity and mortality has not been determined.

4. CONTRAINDICATIONS

REPATHA is contraindicated in patients with a history of a serious hypersensitivity reaction to REPATHA [*see Warnings and Precautions (5.1)*].

5. WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with REPATHA, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve.

6. ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the label:

- Allergic Reactions [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Primary Hyperlipidemia and in Patients with Heterozygous Familial Hypercholesterolemia

REPATHA is not indicated for use in patients without familial hypercholesterolemia or atherosclerotic CVD [*see Indications and Usage (1.1)*].

The data described below reflect exposure to REPATHA in 8 placebo-controlled trials that included 2651 patients treated with REPATHA, including 557 exposed for 6 months and 515 exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years, 49% of the population were women, 85% White, 6% Black, 8% Asians, and 2% other races.

Adverse Reactions in a 52-Week Controlled Trial

In a 52-week, double-blind, randomized, placebo-controlled trial (Study 2), 599 patients received 420 mg of REPATHA subcutaneously once monthly [*see Clinical Studies (14.1)*]. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% women, 80% White, 8% Black, 6% Asian, and 6% Hispanic. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in Study 2, are shown in Table 1. Adverse reactions led to discontinuation of treatment in 2.2% of REPATHA-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to REPATHA treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for REPATHA and placebo, respectively).

Table 1. Adverse Reactions Occurring in Greater than or Equal to 3% of REPATHA-treated Patients and More Frequently than with Placebo in Study 2

	Placebo (N=302) %	REPATHA (N=599) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reactions†	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

†includes erythema, pain, bruising

Adverse Reactions in Seven Pooled 12-Week Controlled Trials

In seven pooled 12-week, double-blind, randomized, placebo-controlled trials, 993 patients received 140 mg of REPATHA subcutaneously every 2 weeks and 1059 patients received 420 mg of REPATHA subcutaneously monthly. The mean age was 57 years (range: 18 to 80 years), 29% were older than 65 years, 49% women, 85% White, 5% Black, 9% Asian, and 5% Hispanic. Adverse reactions reported in at least 1% of REPATHA-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2.

Table 2. Adverse Reactions Occurring in Greater than 1% of REPATHA-treated Patients and More Frequently than with Placebo in Pooled 12-Week Studies

	Placebo (N=1224) %	REPATHA† (N=2052) %
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Nausea	1.2	1.8
Fatigue	1.0	1.6
Muscle spasms	1.2	1.3
Urinary tract infection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

†140 mg every 2 weeks and 420 mg once monthly combined

Adverse Reactions in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (Study 2) and seven 12-week trials. The mean and median exposure durations of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

Local Injection Site Reactions

Injection site reactions occurred in 3.2% and 3.0% of REPATHA-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in REPATHA-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

Allergic Reactions

Allergic reactions occurred in 5.1% and 4.7% of REPATHA-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for REPATHA and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

Neurocognitive Events

In placebo-controlled trials, neurocognitive events were reported in less than or equal to 0.2% in REPATHA-treated and placebo-treated patients.

Low LDL-C Levels

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1988 patients treated with REPATHA had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and REPATHA dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by REPATHA are unknown.

Musculoskeletal Events

Musculoskeletal adverse reactions were reported in 14.3% of REPATHA-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for REPATHA and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

Adverse Reactions in Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (Study 4), 33 patients received 420 mg of REPATHA subcutaneously once monthly [*see Clinical Studies (14.3)*]. The mean age was 31 years (range: 13 to 57 years), 49% were women, 90% White, 4% Asian, and 6% other. The adverse reactions that occurred in at least two (6.1%) REPATHA-treated patients, and more frequently than in placebo-treated patients, included:

- Upper respiratory tract infection (9.1% versus 6.3%)
- Influenza (9.1% versus 0%)
- Gastroenteritis (6.1% versus 0%)
- Nasopharyngitis (6.1% versus 0%)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of REPATHA has been evaluated using an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In a pool of placebo- and active-controlled clinical trials, 0.1% of patients treated with at least one dose of REPATHA tested positive for binding antibody development. Patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies; none of the patients tested positive for neutralizing antibodies.

There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of REPATHA, but the long-term consequences of continuing REPATHA treatment in the presence of anti-drug binding antibodies are unknown.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to REPATHA with the incidence of antibodies to other products may be misleading.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on use of REPATHA in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from organogenesis through parturition at dose exposures up to 12 times the exposure at the maximum recommended human dose of 420 mg every month. In a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with evolocumab in infant monkeys. Measurable evolocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placental barrier. FDA's experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In cynomolgus monkeys, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed during organogenesis to parturition at 50 mg/kg once every 2 weeks by the subcutaneous route at exposures 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. No test of humoral immunity in infant monkeys was conducted with evolocumab.

8.2 Lactation

Risk Summary

There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REPATHA and any potential adverse effects on the breastfed infant from REPATHA or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies in adolescents with HoFH who require additional lowering of LDL-C were established based on data from a 12-week, placebo-controlled trial that included 10 adolescents (ages 13 to 17 years old) with HoFH [*see Clinical Studies (14.3)*]. In this trial, 7 adolescents received REPATHA 420 mg subcutaneously once monthly and 3 adolescents received placebo. The effect of REPATHA on LDL-C was generally similar to that observed among adult patients with HoFH. Including experience from open-label, uncontrolled studies, a total of 14 adolescents with HoFH have been treated with REPATHA, with a median exposure duration of 9 months. The safety profile of REPATHA in these adolescents was similar to that described for adult patients with HoFH.

The safety and effectiveness of REPATHA have not been established in pediatric patients with HoFH who are younger than 13 years old.

The safety and effectiveness of REPATHA have not been established in pediatric patients with primary hyperlipidemia or HeFH.

8.5 Geriatric Use

In controlled studies, 1420 patients treated with REPATHA were ≥ 65 years old and 171 were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is needed in patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic impairment [*see Clinical Pharmacology (12.3)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of evolocumab was evaluated in a lifetime study conducted in the hamster at dose levels of 10, 30, and 100 mg/kg administered every 2 weeks. There were no evolocumab-related tumors at the highest dose at systemic exposures up to 38- and 15-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. The mutagenic potential of evolocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

There were no adverse effects on fertility (including estrous cycling, sperm analysis, mating performance, and embryonic development) at the highest dose in a fertility and early embryonic developmental toxicology study in hamsters when evolocumab was subcutaneously administered at 10, 30, and 100 mg/kg every 2 weeks. The highest dose tested corresponds to systemic exposures up to 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. In addition, there were no adverse evolocumab-related effects on surrogate markers of fertility (reproductive organ histopathology, menstrual cycling, or sperm parameters) in a 6-month chronic toxicology study in sexually mature monkeys subcutaneously administered evolocumab at 3, 30, and 300 mg/kg once weekly. The highest dose tested corresponds to 744- and 300-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

13.2 Animal Toxicology and/or Pharmacology

During a 3-month toxicology study of 10 and 100 mg/kg once every 2 weeks evolocumab in combination with 5 mg/kg once daily rosuvastatin in adult monkeys, there were no effects of evolocumab on the humoral immune response to keyhole limpet hemocyanin (KLH) after 1 to 2 months exposure. The highest dose tested corresponds to exposures 54- and 21-fold higher than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. Similarly, there were no effects of evolocumab on the humoral immune response to KLH (after 3 to 4 months exposure) in a 6-month study in cynomolgus monkeys at dose levels up to 300 mg/kg once weekly evolocumab corresponding to exposures 744- and 300-fold greater than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

This Brief Summary is based on the REPATHA™ Prescribing Information v2, 09/15

AMGEN®

REPATHA™ (evolocumab)
Manufactured by: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License Number 1080
Patent: http://pat.amgen.com/repatha/

NOW APPROVED
REPATHA™

A NEW PCSK9 INHIBITOR FOR INTENSIVE, PREDICTABLE LDL-C REDUCTION

in adults with clinical ASCVD or HeFH on maximally tolerated statin therapy as an adjunct to diet[1]

Indication

- Repatha™ is a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor antibody indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol (LDL-C).
- Limitations of Use: The effect of Repatha™ on cardiovascular morbidity and mortality has not been determined.

Important Safety Information

- Contraindication: Repatha™ is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha™.
- Allergic reactions: Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients treated with Repatha™, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha™, treat according to the standard of care, and monitor until signs and symptoms resolve.
- Adverse Reactions: The most common adverse reactions (> 5% of Repatha™-treated patients and more common than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.
- In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2% of Repatha™-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to Repatha™ treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for Repatha™ and placebo, respectively).
- Adverse reactions from a pool of the 52-week trial and seven 12-week trials, included: Local injection site reactions that occurred in 3.2% and 3.0% of Repatha™-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in Repatha™-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

  Allergic reactions occurred in 5.1% and 4.7% of Repatha™-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for Repatha™ and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

  Neurocognitive events were reported in less than or equal to 0.2% in Repatha™-treated and placebo-treated patients.

  In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1,988 patients treated with Repatha™ had at least one LDL-C value < 25 mg/dL.

  Changes to background lipid-altering therapy were not made in response to low LDL-C values, and Repatha™ dosing was not modified or interrupted on this basis.

  Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by Repatha™ are unknown.

  Musculoskeletal adverse reactions were reported in 14.3% of Repatha™-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for Repatha™ and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).
- Immunogenicity: Repatha™ is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with Repatha™.

Please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. Repatha™ (evolocumab) Prescribing Information v2, Amgen. **2.** Data on file, Amgen;[1]; 2015. **3.** Data on file, Amgen;[2]; 2015.

AMGEN
Cardiovascular

Repatha™
(evolocumab) injection
140 mg/mL