MONDAY, NOVEMBER 14

American Heart Association. life is why

SCIENTIFIC SESSIONS 2016

DailyNews

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AHA, Amazon Web Services join forces to fight heart disease using the cloud

Researchers and clinicians in the growing field of customizing heart disease and stroke treatments for each patient will soon join together to access and analyze more of what they need most — massive amounts of information.

The American Heart Association and Amazon Web Services announced Sunday the creation of the AHA Precision Medicine Platform, a cloud-based marketplace for sharing the data that scientists use as fuel in the fight against cardiovascular disease, the No. 1 killer in the world.

"We are changing the way research is done and believe the Precision Medicine Platform is what's needed to establish a new paradigm for scientific collaboration," said AHA CEO Nancy Brown.

The Precision Medicine Platform is going to be a game-changer for researchers, added Eric D. Peterson, MD, MPH, FAHA, FACC executive director of the Duke Clinical Research Institute in Durham, North Carolina, which oversees the world's oldest and largest cardiovascular database.

Here's how the Platform will work:

- It starts with accumulating rich and diverse data sets. The AWS cloud will host a secure database filled with health information gathered from clinical research trials, long-running epidemiologic studies, clinical registries, co-hort studies and wearable devices and other personal technology. Researchers from around the world are submitting their data. A prerequisite for all data is that all participant personal identification information is removed.
- Next comes finding solutions. Using AWS tools, researchers and clinicians will be able to sift through the treasure trove of data to discover new patterns and new solutions to unsolved problems. For instance, researchers can quickly select data on individuals, groups or populations according to their risk of cardiovascular and hypothesized response to treatment.
- Ultimately, there will be results and solutions — and they could be life-changing and lifesaving for millions of people.

AHA CEO Nancy Brown

By aggregating, integrating and analyzing these large pools of data, the acceleration factor for scientists could uncover underlying factors that cause cardiovascular diseases, define new targets for therapy or identify biomarkers that can be used as diagnostic and research tools. An idea could turn into a breakthrough faster than before. It's all part of working toward the ultimate goal of precision cardiovascular medicine: preventing and or treating diseases based on each person's unique genetics, environment and lifestyle.

Joseph C. Wu, MD, PhD, director of the Stanford Cardiovascular Institute in Stanford, California, said he's glad to be part of a project that breaks scientists out of their usual environment of working in silos and rarely sharing methods and materials.

"The Precision Medicine Platform is like everybody is invited to the same party; all the data, tools and researchers are under one roof," Wu said.

The AHA launched its Institute for Precision Cardiovascular Medicine in 2014, committing $30 million over five years while seeking $100 million to keep it going. The Institute is the only organization dedicated exclusively to advancing precision medicine for heart disease, stroke and other cardiovascular care.

Earlier this year, the AHA announced a nearly $5 million initiative in partnership with AWS to fund more than a dozen data research

AHA/AWS INITIATIVE continued on page 13

AHA President recalls scientific journey, effort to save others from his father's plight

AHA President Steven R. Houser, PhD, FAHA

Over his first 25 years in cardiology research, American Heart Association President Steven R. Houser, PhD, FAHA, contributed to the science that showed that the cardiac muscle cells able to survive a heart attack become weakened and so worn out that heart failure sets in. many clinical trials showed that strengthening these myocytes put patients at risk of sudden death.

Then came what Houser calls "one of my scientific epiphanies." He concluded that the myocytes surviving a heart attack were indeed weak but it appeared to be an effect of heart failure rather than its cause. He believed the cause was that there were no longer enough myocytes to effectively pump blood throughout the body. And he was so committed to pursuing this new perspective that he dramatically refocused his laboratory at Temple University's Lewis Katz School of Medicine.

"Many colleagues questioned the wisdom of my decision, but I decided to go for it," Houser said Sunday during his Presidential Address at Scientific Sessions, the American Heart Association's flagship scientific event. "My goal was to learn things that could benefit patients and I felt that this was my best path forward."

AHA PRESIDENT continued on page 14

Ticagrelor, clopidogrel show equal benefit in PAD

PATIENTS WHO HAVE PERIPHERAL ARTERY DISEASE are likely to respond equally well to either ticagrelor or clopidogrel as monotherapy, according to results from the Examining Use of Ticagrelor in PAD (EUCLID) trial. EUCLID was the first of four studies presented during Sunday's Late Breaking Clinical Trials session.

The trial investigators reported that the two drugs produced nearly identical rates of cardiovascular death, myocardial infarction or ischemic stroke in patients who are symptomatic for PAD.

Prior trials had shown that clopidogrel is superior to aspirin for PAD, noted lead author Manesh Patel, MD, from the Duke Clinical Research Institute at Duke University Medical Center in Durham, North Carolina. And in patients with acute coronary syndrome, ticagrelor is superior to clopidogrel in reducing cardiovascular death, myocardial infarction or stroke. Many assumed that ticagrelor would be similarly superior to clopidogrel in PAD, Patel said.

"This trial shows us that we should exercise caution in extrapolating evidence from coronary artery disease patients and trials to peripheral artery disease," he said. "We need individual studies in PAD patients."

LATE BREAKING continued on page 14

Tuesday is "Sneaker Day" at Scientific Sessions. Everyone is encouraged to wear athletic shoes in recognition of the importance of regular physical activity.

TODAY AT SESSIONS

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

8 a.m.-6:15 p.m.
Frontiers in Science: Arrhythmia Research Summit
Rooms 255-257

9-10:15 a.m.
Precision Medicine 2016
Main Event I, Hall G

9:30-10:45 a.m.
Main Event Session: Pro-Con Debate on EMS Resuscitation Strategy
Great Hall A

10:45 a.m.-Noon
Late-Breaking Clinical Trials: Pioneering the Future of HeART Interventions
Main Event I, Hall G

10:45 a.m.-12:15 p.m.
Prehypertension: Unmet Needs
Rooms 215-216

12:30-1:30 p.m.
Nobel Laureate Lecture: Membrane Fusion in the Cell
Main Event II, Hall F

1:30-2:45 p.m.
Main Event Session: Epidemiology in Cardiac Arrest and Trauma
The Great Hall A

2-3:15 p.m.
Life's Sort of Simple 7: Implementing Ideal CV Health Through the Lifespan
Main Event I, Hall G

2-4 p.m.
ABIM Learning Session: Advanced Heart Failure and Transplant Cardiology, 2016 Update
Room 342

2-4:30 p.m.
Frontiers in Science: Vascular Disease Summit
Rooms 206-207

3:45-5 p.m.
What is the Role of PCSK9 Inhibitors in CV Prevention?
Main Event I, Hall G

5:30-6:45 p.m.
Structural Heart Disease Interventions
Room 222

HEARTY HUMOR by Jonny Hawkins

"Your EKG reveals that you are a little off beat."

Session to explore research on CV health disparities

Several investigators on Monday will review the latest data on underlying determinants of social disparities in cardiovascular health. David Siscovick, MD, MPH, senior vice president for research at the New York Academy of Medicine, will moderate the session "Cardiovascular Health Disparities: Challenges and Opportunities in Basic, Clinical, and Population Science Research" from 3:45-5 p.m. in rooms 346-347.

HIGHLIGHTS FROM THE PROGRAM CHAIR

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

Frank W. Sellke, MD, FAHA

Today is Wear Red Day! Put on your red dress, red pants or anything red to recognize the American Heart Association's mission to raise awareness of heart disease in women.

We also have another outstanding day of programming, including moderated posters and oral presentations on the latest advances in basic, clinical and population science.

Today's Main Event programming includes sessions on:

- "Precision Medicine 2016" (9 a.m. in Main Event I, Hall G)
- "Changing Landscape of Acute Coronary Syndrome Care" (10:45 a.m. in Main Event II, Hall F)
- "Life's Sort of Simple 7: Implementing Ideal CV Health Through the Lifespan" (2 p.m. in Main Event I)
- "Frontiers in Heart Valve Disease" (2 p.m. in Main Event II)
- "What is the Role of PCSK9 Inhibitors in CV Prevention?" (3:45 p.m. in Main Event I)
- James E. Rothman, PhD, of Yale University, will present the Nobel Laureate Lecture at 12:30 p.m. in Main Event II.

Further, we have three outstanding Frontiers in Science programs: "Arrhythmia Research Summit" from 8 a.m.-6:15 p.m. in rooms 255-257; "Thrombosis Summit" from 8 a.m.-6:15 p.m. in room 217; and the "Vascular Disease Summit" from 2-4:30 p.m. in rooms 206-207.

The meeting's second Late-Breaking Clinical Trials session begins at 10:45 a.m. in Main Event I with "Pioneering the Future of HeART Interventions" (see description below). Two high-profile, game-changing trials presented in the session will be "Randomized Comparison of Single Versus Bilateral Internal Mammary Artery Grafting in 3102 Patients: Effects on Major Cardiovascular Outcomes After Five Years Follow-Up" and "FUTURE – The Functional Testing Underlying Coronary Revascularization (FUTURE) Study: A 'Real World' Comparison of Fractional Flow Reserve-Guided Management Versus Conventional Management in Multi Vessel Coronary Artery Disease Patients."

You won't want to miss these. You may be surprised by the results.

I encourage you to stop by one of our Clinical Science: Special Reports sessions: "Cell Therapy: Ready for Prime Time?" from 3:45-5 p.m. in Main Event II, featuring initial presentations of the latest cell therapy trials; or "Risk Reduction Strategies on a Global Stage" from 9-10:15 a.m. in Main Event II. See below for details on today's Clinical Science: Special Reports sessions.

Today's joint sessions include:

- "Quality Improvement Strategies in Cardiology," with the Spanish Society of Cardiology (9 a.m. in Rivergate)
- "Alternative Treatment Strategies for Triple Vessel Disease," with Heart and Health Foundation of Turkey (9 a.m. in rooms 218-219)
- "Nurses Role in Prevention and Management of High Blood Pressure: A Global Perspective," with the Preventive Cardiovascular Nurses Association (10:45 a.m. in rooms 208-209)
- "Prehypertension: Unmet Needs," with the American Society of Hypertension (10:45 a.m. in rooms 215-216)
- "Novel Strategies in Vascular Surgery," with the European Society for Cardiovascular and Endovascular Surgery (3:45 p.m. in Rivergate)
- "Management of Atrial Fibrillation," with the Heart Rhythm Society (5:30 p.m. in rooms 211-213)
- "The Global Battle Against Cardiovascular Disease," with the World Heart Federation (5:30 p.m. in room 210)
- "Structural Heart Disease Interventions," with the Society for Cardiovascular Angiography and Interventions (5:30 p.m. in room 222)

Check the Final Program or Scientific Sessions Mobile Meeting Guide for the complete schedule of joint sessions.

Whether you're a cardiologist, basic scientist, surgeon, nurse, epidemiologist or other healthcare provider, Scientific Sessions has an outstanding selection of programs to learn the latest science, new clinical techniques and results of the latest clinical trials. ▼

Late-Breaking Clinical Trials II — LBCT.02 | 10:45 a.m.-Noon Monday | Main Event I

Pioneering the Future of HeART Interventions

TRIAL	DESCRIPTION
Randomized Comparison of Single Versus Bilateral Internal Mammary Artery Grafting in 3102 Patients: Effects on Major Cardiovascular Outcomes After Five Years Follow-Up	These are five-year results of the largest randomized trial of bilateral mammary artery coronary artery bypass grafting compared with standard single mammary artery grafting plus vein grafts in patients with multivessel coronary artery disease.
The FUnctional Testing Underlying Coronary Revascularization (FUTURE) Study: A "Real World" Comparison of Fractional Flow Reserve-Guided Management Versus Conventional Management in Multi Vessel Coronary Artery Disease Patients	The multicenter, randomized, controlled trial compared fractional flow reserve-guided therapeutic management to conventional therapeutic management in patients with multivessel coronary artery disease.
An OPen-label, Randomized, Controlled, Multicenter Study Exploring TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI)	The open-label, randomized, controlled, multicenter trial explored two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist strategy in patients with atrial fibrillation who undergo PCI.
Patients at Intermediate Surgical Risk Undergoing Isolated Interventional or Surgical Aortic Valve Replacement for Severe Symptomatic Aortic Valve Stenosis One Year Results From the German Aortic Valve Registry	The prospective, multicenter analysis compared the efficacy and outcomes of intermediate-risk patients receiving TAVI or conventional SAVR.

Clinical Science: Special Reports — CSSR.03 | 9-10:15 a.m. Monday | Main Event II, Hall F

Risk Reduction Strategies on a Global Stage

TRIAL	DESCRIPTION
A Comprehensive Lifestyle Intervention In Patients With Coronary Artery Disease: Main Results Of The Randomized Multicenter Response 2 Trial	The trial evaluated the effect of referral of patients with CAD to comprehensive lifestyle programs, using three established, community-based interventions, on top of usual care.
A Cluster Randomized Trial of a Comprehensive Approach for Hypertension Control in Low-income Patients in Argentina	The multilevel, comprehensive intervention program improved blood pressure control among low-income hypertensive patients.
A Randomized Trial of Community Health Action To Encourage Healthy Behaviors: The Grenada Heart Project – CHANGE Trial	The trial tested a community-based peer-support strategy to influence cardiovascular risk in low resource settings.
Large Scale Analysis of Lifetime Risk of Cardiovascular Disease in Europe and Population Attributable Risk of Cardiovascular Risk Factors. For the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Investigators	The study tested the single and aggregate effect of cardiovascular risk factors on CVD outcome in Europe and identified the population attributable risk of traditional and novel cardiovascular risk factors on a European level.

Clinical Science: Special Reports — CSSR.01 | 3:45-5 p.m. Monday | Main Event II

Cell Therapy: Ready for Prime Time?

TRIAL	DESCRIPTION
Administration of Autologous Bone Marrow Cells for Limb Salvage in Patients with Critical Limb Ischemia: Results of the Multicenter Phase III MOBILE Trial	The largest randomized, controlled, phase III clinical trial in the United States assessed the efficacy of autologous cell therapy to prevent major amputation in poor option critical limb ischemia patients.
Administration of ALDH Bright Cells to Patients with Intermittent Claudication: The NHLBI CCTRN PACE Trial	The trial assessed the safety and efficacy of autologous bone marrow-derived ALDH bright cells in patients with intermittent claudication.
Randomized Comparison of Allogeneic vs Autologous Mesenchymal Stem Cells in Patients with Non-Ischemic Dilated Cardiomyopathy – The POSEIDON-DCM Trial	The trial tested the safety and efficacy of allogeneic vs. autologous mesenchymal stem cells in patients with non-ischemic dilated cardiomyopathy.
The NHLBI TIME Trial: Role of Microvascular Obstruction in 2-Year Clinical and MRI Follow-up	The trial presented the long-term (two-year) follow-up of patients enrolled in the NHLBI TIME trial that examined the role of timing of stem cell delivery after STEMI.

My Research Legacy invites everyone to join in on cutting-edge research

There's a new, secure website where people can share their health data with researchers looking for new ways to treat and erase heart diseases and stroke.

The American Heart Association announced Sunday the launch of My Research Legacy, a network being built in conjunction with the Broad Institute of Harvard University and the Massachusetts Institute of Technology.

The premise is simple: Anyone can provide lifestyle, health and genetic data — all of it stripped of personal identification — and the network will crunch the numbers in search of previously unrecognized patterns. Once those patterns are recognized, scientists will explore them, thus expanding the quest to treat and beat cardiovascular diseases and stroke.

So without even leaving home, people can join research in the field of precision medicine — or, as it's often called, "personalized medicine," because its goal is to create a treatment plan that's unique to each patient.

While it may seem risky to build a program based on asking patients to provide their information, officials from the AHA and the Broad Institute believe the timing is right.

They pointed to studies showing that people are willing to give such data when they trust the organization collecting it. They also noted a shift toward patients becoming more involved in their health data, such as the popularity of wearable devices; in fact, some of the data being sought is the kind that's collected by fitness trackers.

And, considering that it only takes a few clicks to become part of this cutting-edge and potentially transformative work, organizers ultimately envision growing the network to 250,000 people.

"Patients *should* be a critical driving force in medical progress," said Eric S. Lander, PhD, president and founding director of the Broad Institute, a biomedical and genomic research center with one of the world's largest genome sequencing facilities.

Lander added that he believes the next major innovation in scientific research will not be powered by a new microscope or revolutionary therapy, but by gathering and interpreting data provided directly from patients.

"The intersection of digital technology and individuals' demand to control their own health data has created a new revolution in healthcare. Science is no longer a closed world," said Nancy Brown, CEO of the American Heart Association. "Through My Research Legacy, people have the opportunity to donate their data for the good of all and to play a direct role in accelerating discovery with the scientific community."

The AHA and the Broad Institute also announced plans for the first use of the network: a pilot study looking at 2,000 people who survived a heart attack, stroke, atrial fibrillation, aortic dissection or systolic heart failure suffered when they were between the ages of 21 and 50.

"Throughout history, far too many lives have been impacted before the age of 50 by cardiovascular diseases and stroke," Brown said. "Every one of these individuals are the inspiration for our work."

The pilot study will be led by Jane A. Leopold, MD, clinical director for the AHA Institute for Precision Cardiovascular Medicine and director of the Women's Interventional Cardiology Health Initiative at the Brigham and Woman's Hospital in Boston.

The pilot already has support from the Marfan Foundation, which will help recruit people younger than 50 who have suffered an aortic dissection.

Brown introduced both My Research Legacy and the pilot study during Sunday's Opening Session. She was joined onstage by several volunteers who shared their stories of heart disease disrupting their lives at a young age.

"They are serving as volunteer champions to represent the voice of the patient in research," Brown said. "These champions will share their story and data for the greater good and inspire others to do the same." ▼

CAREER PROGRESSION:
Barbara J. Fletcher, RN, MN, FAHA, FPCNA, FAAN

In her illustrious 45-year nursing career, Barbara J. Fletcher is especially proud of her tenure as chair of the AHA's Cardiovascular and Stroke Nursing Council's program committee from 1988-91.

"Through this committee, I believe I helped to propel nursing within the AHA," said Fletcher, clinical associate professor at the University of North Florida, Brooks College of Health, School of Nursing, in Jacksonville. "I think many viewed cardiovascular nursing differently after my years on the program committee."

Her work hasn't gone unnoticed. In 2009, Fletcher received the AHA National Award of Meritorious Achievement. She was honored again in 2013 for her efforts to increase nurse participation in the AHA's stroke-related activities.

Fletcher is the immediate past president of the Preventive Cardiovascular Nurses Association and has worked to prevent cardiovascular disease through research, teaching and volunteering her entire career.

"I want to believe that in some small way I will have played a part in reaching this goal," she said.

To that end, she has conducted seminal studies on the effects of exercise in cardiac patients. She also has led several multidisciplinary research projects addressing cardiovascular risk factors.

Fletcher is a research nurse consultant specializing in cardiovascular disease at the Mayo Clinic in Jacksonville, Florida. She previously served as program director for the cardiac rehabilitation program at Georgia Baptist Medical Center in Atlanta, Georgia after a stint at Emory University in Atlanta, where she helped launch and coordinate the school's cardiac rehabilitation program.

"Nursing gives you so many opportunities — to teach, to do research and to practice nursing," she said. "There are so many facets of nursing. It fits a team approach. That gives you a lot of camaraderie and experiences you wouldn't get somewhere else."

Fletcher's AHA involvement began in 1975 as chair of the Council on Cardiovascular and Stroke Nursing Development Committee. Most recently, she traveled to China to foster relationships with cardiovascular nurses and develop connections between the AHA and Chinese hospitals.

"It was most educational and rewarding for me, and I hope for them as well," she said.

Fletcher credits the AHA for helping to launch her career. She's paying it forward by mentoring younger professionals in her AHA network and volunteering her time.

"The AHA gives you an avenue to begin to achieve your professional and academic goals, if not to solidify the achievement of the goals," she said. "For anybody on a career path, they need to belong to at least one or two professional organizations such as the AHA to fulfill their career goals." ▼

The AHA uses the tagline "Life Is Why" to answer the question: Why do we do our lifesaving work? We asked Fletcher the same question:

"I believe working with the American Heart Association over the years has put me in a better position to enhance the well-being of my community, both those very close and those farther away."

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MEMBER SPOTLIGHT

Raymond R. Townsend, MD
Professor of Medicine, Hypertension Program Director, Hospital of the University of Pennsylvania in Philadelphia

How long have you been an AHA/ASA Professional Member?
I joined in 1986.

Why did you join?
My primary area is high blood pressure, and the AHA was — and still is — the largest society with an interest in high blood pressure.

Are you involved in AHA councils?
I am actively involved with the Council on Hypertension (HTN). I also belong to the Council on Kidney in Cardiovascular Disease (KCVD). On the Hypertension Council, I have served in several capacities, including on the Program Committee and as an abstract grader, presenter and symposium organizer. I also served as a leader in the Hypertension Summer School and as past chair of the Professional Education and Publication Committee.

What do you enjoy most about these roles?
I enjoy the science of high blood pressure, the use of animal models, the gadgets that measure blood pressure and pulse waves, and thinking about how blood pressure affects different people in different ways. In some people it has no discernible effect, in some it's heart attack, in some heart failure, in some stroke, in some kidney disease and in others it's peripheral artery disease.

How else are you involved with the AHA?
I have worked on program committees for the AHA, run Hypertension Summer Schools, presented at AHA meetings, served on the National AHA Professional Education Committee — as well as on the Council on Hypertension's similar committee — and published in AHA journals, including *Hypertension, Circulation and Circulation: Heart Failure*. I have done screenings for AHA and fielded questions about high blood pressure and the role of the AHA from the media. I served in leadership roles within the Council on Hypertension for about a decade, stepping down in 2013 when I finished a stint chairing the Professional Education and Publication Committee. The most fun thing I ever did for the AHA was to co-chair the seventh and eighth Hypertension Summer Schools in 2010 and 2013.

Why is membership valuable to you?
AHA membership keeps me engaged in the society's activities, and I network with a number of people in the AHA. It gives me access to stroke statistics and AHA/ACCF guidelines, which I use in educational milieus since I do a fair amount of professional education in several societies each year.

What message would you convey to your colleagues about being an AHA member?
The AHA is genuinely engaged in aspects of care that are important to people. It has many leaders in many areas of cardiovascular health. It also has the web tools, national meetings, professional networks and momentum to help the careers of clinicians and investigators of all ages. ▼

The AHA uses the tagline "Life Is Why" to answer the question: Why do we do our lifesaving work? We asked Townsend the same question:

"Research improves healthcare is why."

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FDA commissioner calls for more information sharing

FDA Commissioner Robert M. Califf, MD, MACC, called on researchers, health systems, clinicians and patients to recognize that the future of medicine lies in information sharing during the annual Lewis A. Conner Memorial Lecture on Sunday.

"When I entered practice, the limiting factor in progress was technology," Califf said, emphasizing that health care needs a new paradigm for collecting, storing and using information. "In 2016, the limiting factor of progress is us."

Califf delivered his address — "Revolutionizing Cardiovascular Care Through Better Evidence" — during the Opening Session. Less than 15 percent of all clinical guidelines are based on strong evidence because the evidence simply isn't there. For example, the recent guidelines on opioid prescribing for chronic pain from the Centers for Disease Control and Prevention contain 12 specific recommendations, but none of them are supported by high-quality evidence, Califf said.

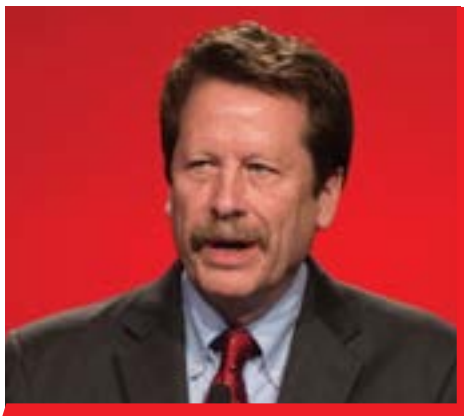
"We need to do a better job generating evidence and a better job of translating evidence into clinical practice," Califf said.

Key to optimizing evidence and moving it into clinical practice is creating a learning health system — a concept that isn't new or confined to heath care. The managed care industry has been promoting the idea of the learning health system for more than a decade.

The basic problem is that health care has traditionally separated evidence gathering research from routine practice, while sectors like commerce have long recognized the benefit of sharing information as widely as possible and embedding research in routine operations, Califf said.

The key to the success of Amazon, Google and other companies is the creation of a learning culture that values information sharing and implants research into everything they do. The idea of doing that as part of clinical practice is starting to take hold in health care.

Health systems nationally are already collecting and sharing data across their own networks, Califf said. With virtually all Americans in the healthcare system on electronic health records, collecting, sharing and analyzing data is easier than ever before, and federal agencies are moving in similar directions.



Robert M. Califf, MD, MACC

The Veterans Administration already has created a database of more than 500,000 veterans who have agreed to share their medical data and specimens for research. PCORNet, the National Patient-Centered Clinical Research Network, has enlisted about 145 million individuals who have agreed to participate in research and share both information and results.

"If we had an efficient data collection and sharing system, we would see greater than the 50 percent improvement we have already seen in cardiac outcomes," Califf said. "All we need is the cultural and ethical principle that promotes the sharing of information for the benefit of our patients and our clinical practices." ▼

Changes in LTPA impact AF risk

In an abstract poster session Sunday, researchers reported that changes in leisure-time physical activity (LTPA) are associated with a risk of incident atrial fibrillation (AF). The research suggests that people with persistently less LTPA in adult life have higher incident AF relative to those with persistently ideal activity.

To learn more about AF and the risk of intracranial hemorrhage during warfarin therapy, look for abstract 16593 during Monday's abstract rapid-fire oral presentation at 12:30 p.m. in the Science & Technology Hall, Population Science Theater.

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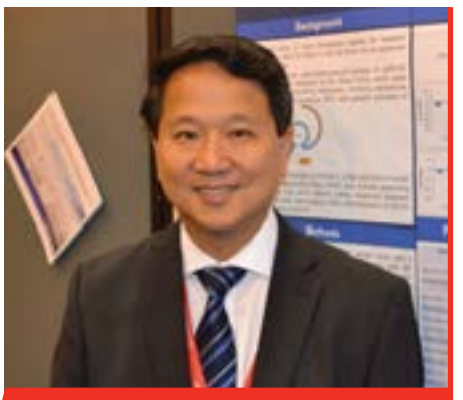
Lab-engineered peptide shows promise in treating resistant hypertension

The laboratory-engineered peptide ZD100 is effective at lowering blood pressure, improving renal function and suppressing aldosterone in resistant hypertension patients, according to Horng H. Chen, MD, of the Mayo Clinic in Rochester, Minnesota, who presented the findings during an abstract poster session on Sunday.

The AHA has defined resistant hypertension as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts.

"We know from a number of epidemiological studies that these patients are at high risk of developing kidney failure, coronary artery disease and heart failure. Currently there is no proven therapy for resistant hypertension," Chen said. "We've also learned from these studies that resistant hypertension comprises about 12 percent of all hypertensive patients. That adds up to about 9 million people in the U.S. with resistant hypertension who have no FDA-approved therapy."


Horng H. Chen, MD

Building on previous studies that demonstrated the important role natriuretic peptides play in controlling blood pressure, Chen and his colleagues engineered a peptide known as ZD100, which they administered to hypertensive patients over the course of a two-part, first-in-human study.

In the first part of the study, the investigators used an open-label, sequential, single-ascending-dose methodology involving three cohorts. Each cohort included four patients with blood pressure greater than 140/90 mm Hg who were taking at least one antihypertensive medication. All subjects stopped taking antihypertensive agents for 14 days and received a single daily subcutaneous injection of ZD100. The three cohorts were dosed at 1, 2.5 and 5µg/kg, respectively.

"We found that all the patients tolerated the medication well and that, at the dose of 5 µg/kg, we saw a meaningful decrease in blood pressure with no serious adverse events," Chen said.

The second part of the study was a randomized, double-blind, placebo-controlled, multiple-ascending-dose design involving cohorts of five subjects each. All patients had "resistant-like" hypertension (BP>145/70 mm Hg) and were taking at least three medications, including a diuretic and ACE inhibitor or angiotensin receptor blocker.

All subjects continued their antihypertensive medications and each cohort received daily subcutaneous ZD100 injections over three days at doses of 0.5, 2.5, 3 and 5µg/kg, respectively. One patient in each cohort was given placebo.

Chen reported that the maximum tolerated dose of 5µg/kg resulted in a sustained decrease of blood pressure for 24 hours with each subcutaneous injection (max reduction systolic BP; ZD100: -26 ± 14 versus placebo: -1 ± 12 mm Hg). No significant adverse events were reported.

"With once-a-day subcutaneous injection at the dose of 5µg/kg given on top of their usual medications, we were able to decrease blood pressure over the whole 72-hour period," Chen said. "In addition to decreasing their blood pressure, we were also able to improve their kidney function and suppress aldosterone, which plays a key role in the pathophysiology of resistant hypertension."

The next step in the research, Chen said, is to study a larger group of patients with resistant hypertension to confirm the study's findings and determine the optimal dose of ZD100 patients with resistant hypertension. ▼

Join us for our Annual Awardee Group Photo at Scientific Sessions

- Monday, November 14, at 1:40 PM
- Main Event II, Level 3
- Participants will receive a special lapel pin!


AHA Research Awardees from Scientific Sessions 2015 in Orlando, Florida

Vesicle transport pioneer to deliver Nobel Laureate Lecture

James E. Rothman, PhD, who shared the 2013 Nobel Prize in Physiology or Medicine for his exploration of the core machinery and universal mechanisms of vesicle transport, will discuss his groundbreaking work and latest research during Monday's Nobel Laureate Lecture.

Rothman's one-hour lecture — "Membrane Fusion in the Cell" — begins at 12:30 p.m. in Main Event II, Hall F.

He is the Fergus F. Wallace Professor of Cell Biology and Professor of Chemistry, chair of cell biology and director of the Nanobiology Institute at the Yale School of Medicine in New Haven, Connecticut.

Rothman's discovery that the SNARE complex — proteins that drive and guide membrane fusion in the cell — helped cement the notion that every biological process is physical and chemical in nature.

Vesicles formed by successive budding from one membrane, fusion with the next membrane, budding and fusion carry specific cargoes from one compartment to another within cells, Rothman said. Related processes enable communication between cells in the body by releasing and receiving signals from hormones, growth factors and neurotransmitters. These intracellular communication processes are vital elements in endocrine physiology, exocrine physiology, cell division, cell growth, neuronal activity and contractility, including the muscular contractions that power the heart.

At its core, the cellular machinery that drives and controls the beating heart also drives and controls the release of insulin in the pancreas and a host of other physiologic and pathologic processes. One enduring question is how SNARE proteins adjust the processes they drive and control. Neurotransmitters are released within 200 millionths of a second at the neuromuscular junction, while the same molecular machinery releases insulin 1,000 times more slowly.

James E. Rothman, PhD

LECTURE PREVIEW

Nobel Laureate Lecture: Membrane Fusion in the Cell

12:30-1:30 p.m. Monday

Main Event II, Hall F

"How can you have the same machinery working at one speed here and 1,000 times faster or slower over there?" Rothman asked. "That's the scientific question we are addressing at the moment.

"There will be some linkage to disease, but not a lot because most people with diseases in this protein pathway are dead. On the other hand, the processes they help explain provide the concepts and the platform for understanding a wide variety of diseases, including cardiovascular disease." ▼

Likelihood of CPR training decreases with age, study finds

During an abstract oral presentation on Sunday, Audrey Blewer, MPH, a third-year PhD student in the department of epidemiology at the University of Pennsylvania in Philadelphia, presented the results of a study suggesting that older age is associated with a lower likelihood of CPR training.

The researchers administered a random-digit dial survey to a nationally representative adult sample and, using regression modeling, assessed demographics of individuals currently trained in CPR (<2 years) and those who had been trained at some point in time.

"Besides looking at overall CPR training prevalence, we wanted to see whether or not the disparities we see in bystander CPR rates translate to demographic disparities on an individual level, specifically the association between age and CPR training," Blewer said.

Of the 9,022 individuals who completed the survey, 65 percent had been trained in CPR at some point, while 18 percent reported being currently trained. A demographic assessment of the survey results indicated that, as age increased, the likelihood of being currently trained or ever trained decreased.

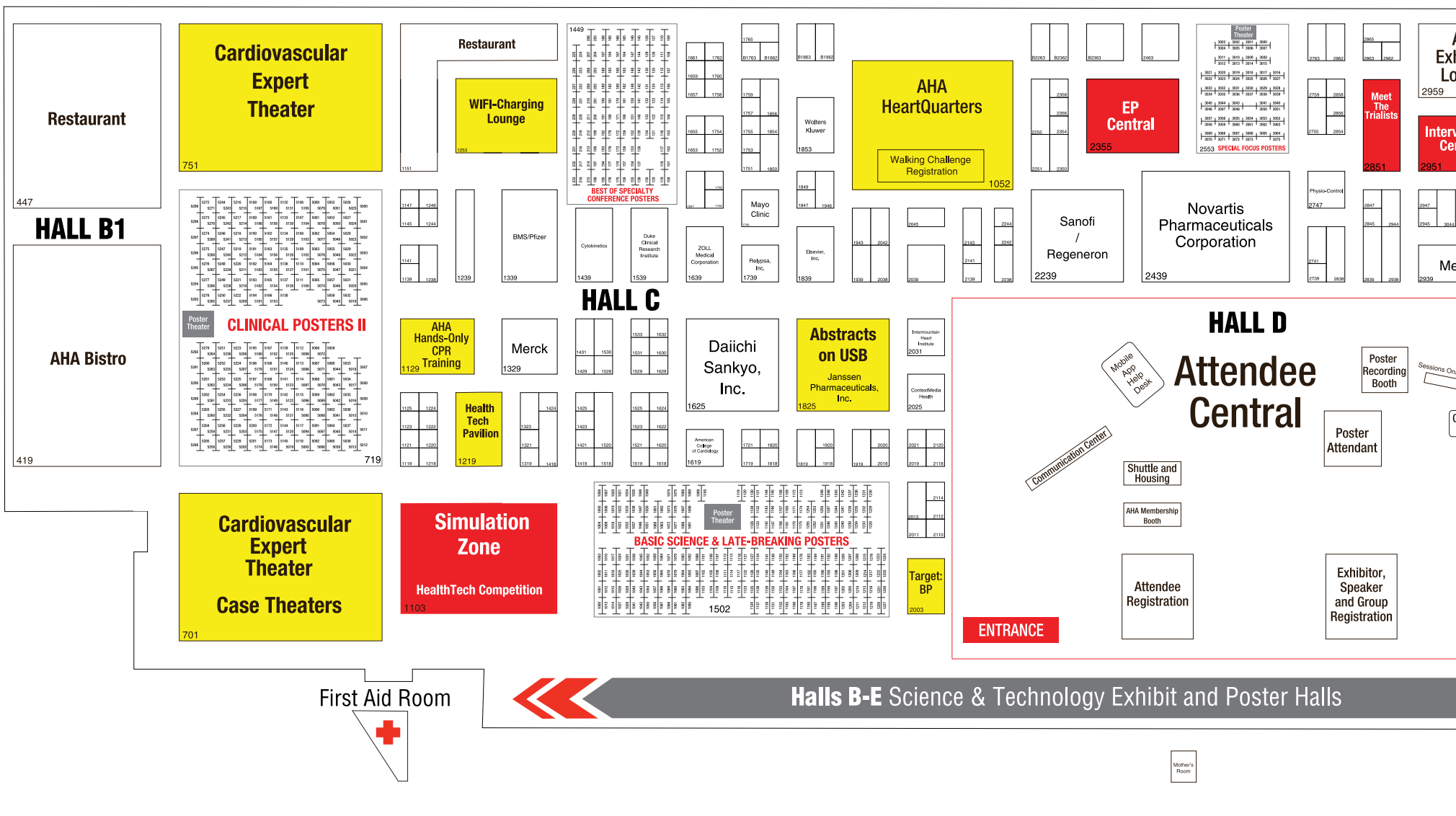
"This is significant because the majority of cardiac arrests in the U.S. occur among individuals who are 50 to 80 years of age, and it may be their similarly aged counterparts who would most likely be in the home with them, but who are less likely to have had CPR training," Blewer said. "This highlights an important mismatch and the importance of targeted CPR training to older individuals."

Blewer also reported that higher education and higher household income were associated with an increased likelihood of CPR training across all age groups. Future studies will focus on other demographic characteristics, such as race and socioeconomic status, as well as geographic associations, she said.

"Where you live — your neighborhood, your community — definitely can have an impact on a wide variety of health behaviors," Blewer said. ▼

2016 Scientific Sessions Exhibitors

Science & Technology Hall Hours		Lunch Break	
Monday	10 a.m.-4:30 p.m.	Monday	Noon-2 p.m.
Tuesday	10 a.m.-3 p.m.	Tuesday	Noon-2 p.m.



American Heart Association®

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SCIENTIFIC SESSIONS 2016

Monday's Theater Demonstrations

Cardiovascular Expert Theater I

Booth 701

Noon-12:45 p.m.

PRALUENT® (alirocumab) Injection: Efficacy and Safety with Two Different Dosing Options

Sanofi Regeneron

1:15-2 p.m.

Repatha® (evolocumab): A Focused Clinical Review

Amgen

Cardiovascular Expert Theater II

Booth 3661

10:15-11 a.m.

Doctor, I'm Dizzy: Clinical Perspectives of Neurogenic Orthostatic Hypotension

Lundbeck

Noon-12:45 p.m.

Treatment Approaches for Hypertension

Allergan

1:15-2 p.m.

Moving Forward with Reverse, a Multi-Specialty Perspective

Boehringer Ingelheim

3:15-4 p.m.

The Balancing Act of AHF Care: A Focus on Treatment, Outcomes, and Economics

Novartis

Cardiovascular Expert Theater III

Booth 751

Noon-12:45 p.m.

From Particles to Plaque: Mechanisms and Measurement of Atherosclerosis

Amgen

1:15-2 p.m.

Addressing Treatment Priorities in Heart Failure

Novartis

HeartQuarters Theater

Booth 1052

10:15-10:45 a.m.

OSO PHD, Councils JP

11 a.m.-Noon

Mission: Lifeline STEMI Accreditation presentation

12:15-12:30 p.m.

CPR Simulation Training in the ED: Study Reveals Improved Clinical Chest Compression Fraction

Presenter: Michael Christopher Kurz, MD, MS, FACEP, FAHA, Associate Professor, Department of Emergency Medicine, University of Alabama at Birmingham

1:15-2 p.m.

Personal Stories in Research

Presenters: William C. Sessa, PhD, Yale University, AHA Merit Award Recipient; Ramy Arnaout, BS, DPhil, Harvard Medical School/Beth Israel Deaconess Medical Center; Miyong Kim, PhD, RN, University of Texas at Austin, School of Nursing

2:15-2:45 p.m.

Leadership Succession: How to Transition While Retaining Productivity, Building a Legacy and Promoting the Success of Others

Presenters: Lori Mosca, MD, MPH, PhD, New York-Presbyterian Hospital/Columbia University Medical Center; Marie-Pierre St-Onge, PhD, FAHA, Columbia University

Conventional bystander CPR associated with improved survival in pediatric OHCA patients

CONVENTIONAL BYSTANDER CPR (chest compressions with ventilations) is associated with improved overall survival and favorable neurological outcomes compared to compression-only CPR (CO-CPR) in pediatric out-of-hospital cardiac arrest (OHCA) patients, according to research presented Sunday at Scientific Sessions.

Maryam Y. Naim, MD

The study was presented by Maryam Y. Naim, MD, of the Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine, during an abstract oral presentation.

"In adults, compression-only CPR following out-of-hospital cardiac arrest has been shown to have similar outcomes to conventional CPR," Naim said. "Children, however, more commonly have respiratory arrests, so the AHA recommends conventional CPR for pediatric out-of-hospital cardiac arrest."

Naim and her colleagues performed an analysis of the Cardiac Arrest Registry to Enhance Survival (CARES) database, examining CPR characteristics and outcomes in children 18 and younger from January 2013 through December 2015. Outcomes in the study cohort included survival to hospital discharge and neurologically favorable survival (cerebral performance category 1 or 2).

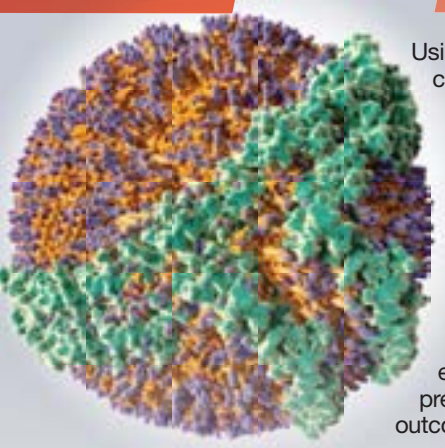
The researchers identified 1,411 cardiac arrest patients who received bystander CPR (BCPR). Of those, 49 percent (697) received conventional CPR and 51 percent (714) received compression-only CPR.

Infants were more likely to receive conventional CPR and children ages 1 to 18 were more likely to receive CO-CPR (53 percent versus 55 percent, p=0.0033), Naim said. Compared to white children (49 percent), Hispanic children (64 percent) and black children (56 percent) were more likely to receive CO-CPR compared to conventional CPR (p<0.0001).

Conventional CPR and compression-only CPR had higher rates of survival to hospital discharge compared to no bystander CPR (conventional, 17 percent; compression only, 14 percent;). There was no difference in the type of bystander CPR in gender, witnessed arrest status, arrest etiology, arrest location, arrest rhythm or AED use. On multivariable analysis, Naim said that conventional CPR was independently associated with overall survival to hospital discharge and neurologically favorable survival compared to CO-CPR.

"The most significant implications are that half of children who have out-of-hospital cardiac arrest are receiving compression-only CPR and that racial disparity exists in the provision of conventional CPR," Naim said. "While both conventional and compression-only CPR are associated with improved overall survival compared to no bystander CPR, only conventional CPR is associated with favorable neurological outcome. Increasing the provision of conventional CPR, especially in infants, may improve outcomes for children with out-of-hospital cardiac arrests." ▼

HDL and heart failure



Using a large cardiovascular cohort, researchers at Duke University characterized high-density lipoprotein (HDL) particle profiles to determine if they were independently associated to heart failure with preserved ejection fraction or predict adverse clinical outcomes.

The research will be presented during an abstract rapid-fire oral session at 12:20 p.m. Monday in the Science & Technology Hall, Clinical Science Theater II.

LVAD combined with pharmacologic therapy may reverse advanced heart failure

Interim results from the REmission from Stage D Heart Failure (RESTAGE-HF) study suggest that cardiac function can be improved and explantation rates increased with a combination of prolonged, optimized left ventricular assist device (LVAD) mechanical unloading and a standardized protocol of pharmacological therapy.

Emma J. Birks, MD, PhD

Findings from the study were presented during a Sunday poster session by Emma J. Birks, MD, PhD, of the University of Louisville School of Medicine in Kentucky.

"As the number of patients awaiting heart transplants far outweighs the number of donors available, we're seeing more heart pumps being implanted into people with advanced heart failure," Birks said. "We and others have previously observed that on the heart pump, sometimes the heart would shrink and the heart function would get a bit better. However, the rate at which the recovery actually happened was thought to be quite small."

Birks and her colleagues hypothesized that optimizing the heart pump to run faster, combined with enhanced drug therapy and regular testing of underlying myocardial function, could increase recovery and LVAD explantation rates by inducing reverse structural remodeling and reducing fibrosis.

To test the hypothesis, six centers in the United States were enrolled in the multicenter prospective non-randomized study consisting of HeartMate II LVAD support, with an aggressive pharmacological regimen and low-speed echocardiograms (6,000 rpm/6 mw) to regularly test cardiac function. The pharmacological regimen included daily doses of lisinopril (40 mg), spironolactone (25 mg), digoxin (125 mcg), losartan (150 mg) and coreg (25 mg) twice daily.

"Subjects at the participating centers include 40 patients with advanced heart failure due to nonischemic cardiomyopathy requiring LVAD implantation as a bridge to transplant or as destination therapy," Birks said. "We protocolized all patients to get the same medications to see how many patients would show sufficient improvement to have the pumps taken out, with a primary endpoint of sustained remission at 12 months."

Of the 13 patients who have undergone device explantation to date, duration of support was 344+182 days, EF pre-explant (measured with the pump at 6,000 rpm for 15 minutes) was 55+4 percent, EDD was 46+6 mm and ESD 34+3.2 mm, and PCWP was 9.2+6.4 mmHg. Prior to explant, there was no difference in Fick cardiac output/index with the pump on (4.97+1.1/2.43+0.4L/min/m2) or at 6,000 rpm (4.8+0.9/2.36+0.3L/min/m2).

"These early results suggest that advanced heart failure can be reversed and that you can avoid heart transplant in a lot of these patients, which saves a transplant for someone else," Birks said. "The next step, we hope, is for more centers to start doing this and then to see if we can potentially add other drugs to further optimize recovery and create a good platform to recover heart function." ▼

Study finds no evidence of 'obesity paradox' in HF-REF patients

In a study examining the relationship between anthropometric measures and event-free survival, researchers found no evidence of better outcomes among obese individuals in heart failure with reduced ejection fraction (HF-REF).

Ulrik M. Mogensen, MD, PhD

The study was presented Sunday by Ulrik M. Mogensen, MD, PhD, of the BHF Cardiovascular Research Centre at the University of Glasgow in the United Kingdom. Previous studies have suggested an "obesity paradox" in HF-REF, whereby patients with a high body mass index (BMI) had a better survival than those with a low BMI, contrary to observations in the general population.

The researchers used data from the PARADIGM-HF trial, in which 8,399 patients with a left ventricular ejection fraction (LVEF) of 40 percent or less and a New York Heart Association (NYHA) classification of II-IV were randomized to enalapril or sacubitril plus valsartan and followed for a median of 27 months. They examined the association between BMI at randomization and outcomes after multivariable adjustments using Cox proportional hazards models.

Adjustment variables included age, sex, region, race, NYHA class, LVEF, heart rate, systolic pressure, glomerular filtration rate, diabetes, time since heart failure diagnosis, previous heart failure hospitalization, history of myocardial infarction, history of atrial fibrillation, history of stroke, log N-terminal pro brain natriuretic peptide (NT-proBNP) and randomized treatment (sacubitril/valsartan).

"We found that patients with a higher BMI were younger, more often female, had higher mean LVEF and systolic blood pressure, but higher NYHA class, more orthopnea, more fatigue, more edema, a shorter duration of HF and a lower NT-proBNP when compared to patients with normal BMI," Mogensen said.

When compared with patients who had a BMI of 18.5 to 24.9 in unadjusted analyses, subjects with a BMI ≥30 had lower risk of all-cause mortality (HR=0.75 [0.66-0.86], p<0.001), CV death (HR=0.73 [0.63-0.84], p<0.001), and a higher risk of HF hospitalization (HR=1.23 [1.06-1.42], p=0.007). In fully adjusted analyses, these numbers were (HR=0.95 [0.82-1.11], p=0.53), (HR=0.98 [0.83-1.16], p=0.85), (HR=1.31 [1.10-1.55], p=0.002), respectively. Waist circumference and waist-to-hip ratio was not independently associated with outcomes in the multivariable adjusted model.

"We did not find evidence of an obesity paradox when taking into account other prognostic variables, including levels of natriuretic peptides," Mogensen said. "This offers support to the idea that the obesity paradox may partly be explained by differences in baseline risk among patients with a high and a normal BMI. Obese patients tend to present at a younger age with a higher burden of symptoms, but less severe HF in terms of LVEF, and lower levels of natriuretic peptides. Adjusting for these differences seems to attenuate the better prognosis among obese patients." ▼

Updated PAD guidelines emphasize early detection

Highlights from the updated *Guideline for the Management of Patients with Peripheral Artery Disease* were presented Sunday at Scientific Sessions.

The updated guideline offers comprehensive recommendations across the spectrum of PAD, including asymptomatic patients and those with claudication or atypical leg symptoms, critical limb ischemia and acute limb ischemia. The updated guideline also offers new strategies and emphasizes existing ones.

"The writing committee wanted to ensure the document emphasized the importance of assessing patients at increased risk for PAD, including taking a comprehensive medical history and vascular exam to identify patients early," said Heather L. Gornik, MD, vice chair of the AHA's PAD Guidelines Writing Committee and medical director of the Cleveland Clinic's noninvasive vascular laboratory in Ohio. "We included a broad representation of disciplines involved in PAD patient care and research.

"We focus on the importance of medical therapy, including smoking cessation, antiplatelet agents and statins, blood pressure control and even simple things like promoting the flu shot," said Gornik, noting that she's particularly excited about the emphasis on supervised exercise for claudication. "These simple measures have the potential to prevent myocardial infarction, stroke and death in patients with PAD."

Mark A. Creager, MD, FAHA, past AHA president, said the guideline update — the first in nearly 10 years — is key to improving provider education and awareness about vascular disease, and will allow providers to manage their patients with evidence-based strategies.

"Vascular disease is very prevalent, and the risk of death is at least double for patients with PAD compared to patients who do not have PAD," said Creager, professor of medicine and surgery at Dartmouth Geisel School of Medicine in Hanover, New Hampshire. "Studies show physicians are unaware their patients have PAD about 50 percent of the time. So awareness is key."

Other recommendations in the guideline affect the most severe clinical manifestations of PAD.

"Critical limb ischemia causes non-healing lower extremity wounds and ischemic pain, and is a major risk factor for amputation," Gornik said. "The guideline considers acute limb ischemia (ALI) a medical emergency with recommendations for emergent assessment and triage of patients with ALI for revascularization procedures to restore blood flow to the limb."

During Sunday's session, experts discussed evidence gaps identified by the guideline writing committee, current PAD research and possible directions for future research.

"The AHA feels strongly that more attention needs to be paid to identifying patients with vascular disease because they are at such high risk for heart attack and stroke," Creager said. "They have impaired quality of life and are at risk for limb loss. We want to increase patient awareness and disseminate education to healthcare providers so they can provide effective and safe care to patients with PAD."

To read the full guideline, visit **circ.ahajournals.org**. ▼

Frontiers in Science: Vascular Disease Summit

For more information on vascular disease, you can attend the Vascular Disease Summit at 2-4:30 p.m. Monday in rooms 206-207. The program will feature investigators engaged in cutting-edge research in peripheral vascular disease. Speakers will present current research and participate in an in-depth discussion.

Gene expression profiling provides insight into antibody-mediated heart rejection

According to research presented Sunday at Scientific Sessions, antibody-mediated heart rejection (AMR) in transplant patients is driven by natural killer (NK) cell transcript burden, endothelial activation, macrophage burden and interferon gamma (IFNG) effects. The research also suggests that molecular intragraft measurements for these specific, pathogenesis-based transcripts classify AMR with great accuracy and correlate with the degree of injury and disease activity.

Results from this multinational study, which was performed in collaboration with the Alberta Transplant Applied Genomics Centre in Canada, were presented by Xavier Jouven, MD, PhD, of the Paris Cardiovascular Research Centre, France.

The investigators analyzed a large and extensively phenotyped multicenter cohort of heart transplant recipients with antibody-mediated rejection who were managed with a standardized clinical protocol. The phenotype included assessments of gene expression levels in endomyocardial biopsies, histological injury and immunologic monitoring.

The researchers prospectively monitored 617 heart transplant recipients referred from four French transplant centers between January 2006 and January 2011. They compared patients with antibody-mediated rejection to a matched control group of patients without antibody-mediated rejection. All patients were characterized using histopathology, immunostaining and circulating anti-HLA DSA at the time of biopsy, and also with systematic gene expression assessments of their allografts using microarrays.

Principal effector cells were evaluated by *in vitro* human cell cultures and an additional external validation cohort of heart recipients transplanted in Edmonton, Alberta, Canada, was also studied.

Among the 208 heart transplant patients included in the study (110 in the test cohort; 98 in the validation cohort), the researchers reported that antibody-mediated heart rejection showed a distinct pattern of injury characterized by endothelial activation with microcirculation inflammation by monocytes/macrophages and natural killer (NK) cells, as well as selective changes in endothelial/angiogenesis and NK-cell transcripts, including CD16A signaling and select IFNG-inducible genes. The molecular architecture and selective antibody-mediated rejection transcripts were highly conserved in the external validation cohort.

"This is the first study that approaches reading the endomyocardial biopsy specimen from a molecular standpoint and illustrates the clinical potential of a molecular microscope approach in heart transplant rejection," Jouven said. "The long-term objective of this study is to improve the current standards regarding rejection diagnosis, disease activity, disease stage, risk stratification and response to therapy in heart transplantation. The next step involves launching a prospective, multicenter study to confirm our results and to further test the clinical value of gene profiling." ▼

2016 Unofficial Satellite Events

MONDAY, NOV. 14

7-9 p.m.
Industry-supported Symposium
Achieving LDL-C Goal for all Patients in the Era of PCSK9 Inhibitors
Sponsored by AcademicCME
Supported by Amgen, Inc.
New Orleans Downtown Marriott at the Convention Center, Blaine Kern Ballroom, First Floor
Registration: 6:30 p.m.;
http://academiccme.com/LDL-C

7-9 p.m.
Industry-supported Symposium
The Foundational Role of IV Iron Repletion in Heart Failure and Associated Co-Morbid Conditions
Sponsored by CMEducation Resources
Supported by American Regent
Hilton New Orleans Riverside, Grand Ballroom C-D
Registration: www.Reg-IDA.com

7-9:15 p.m.
Industry-supported Symposium
Seeing Diabetes Through Heart Shaped Glasses: Multidisciplinary Perspectives on the Management of Comorbid Type 2 Diabetes and Cardiovascular Disease
Sponsored by Institute for Medical and Nursing Education, Inc
Supported by Boehringer Ingelheim Pharmaceuticals/Lilly USA
Hilton New Orleans Riverside, Salon A & B
Registration: www.caringfordiabetes.com/heart

7-9:30 p.m.
Industry-supported Symposium
Applying Guideline Recommended and Recent Evidence-based Therapies in the Treatment of Chronic Heart Failure
Sponsored by Paradigm Medical Communications
Supported by Novartis Pharmaceuticals Corporation
Hilton New Orleans Riverside, Napoleon Ballroom
Registration: www.paradigmmc.com/519

TUESDAY, NOV. 15

7-8:45 p.m.
Industry-supported Symposium
Evolving Perspectives on Intensive LDL-C Lowering and Plaque Regression: Potential Impact on Treatment Strategies
Sponsored by Amgen
Supported by PSL Group Services SARL
The Westin New Orleans Canal Place, Magnolia Ballroom (Third Floor)

7-9 p.m.
Industry-supported Symposium
Delving Deeper into the Complexities and Perplexities of Oral Anticoagulation
Sponsored by Paradigm Medical Communications, LLC
Supported by Paradigm Medical Communications, LLC
New Orleans Downtown Marriott at the Convention Center, Blaine Kern Ballroom (A-D)
Registration: 6:30 p.m.; www.paradigmmc.com/518

Summit brings precision medicine to clinical practice

The American Heart Association is launching a major effort to deploy precision medicine to cardiovascular clinical practice in its inaugural Precision Medicine Summit from 9 a.m.-5 p.m. Monday in rooms 260-262.

Thomas P. Cappola, MD, ScM, chief of cardiovascular medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, and Carolyn Y. Ho, MD, associate professor and medical director of the Cardiovascular Genetics Center at Harvard Medical School in Boston, will co-chair the day-long program.

"Precision medicine is not about genomic medicine alone," Cappola said. "Precision medicine is about using all sorts of information to more precisely target care. We will hear from clinical cardiologists and cardiac surgeons using approaches like 3-D printing to customize surgical interventions, as well as from genome scientists and patients."

The White House and the National Institutes of Health identified precision medicine as a research priority in early 2015. The NIH rolled out a framework for the initiative in September 2015 and began creating an infrastructure to support a national research cohort. Then the cardiovascular community, including the AHA, responded with its initiatives.

Monday's summit will highlight the challenges and progress in expanding and implementing precision medicine. The AHA's Council on Functional Genomics and Translational Biology worked with other AHA councils to create the "meeting within a meeting," Cappola said.

Precision Medicine Summit

9 a.m.-5 p.m. Monday
Rooms 260-262

Presenters include: Robert M. Califf, MD, MACC, commissioner of the Food and Drug Administration; Gary Gibbons, MD, director of the National Heart, Lung, and Blood Institute; and Sharon Terry, patient advocate, president and CEO of Genetic Alliance and principal investigator of the Community-Engaged Network for All (part of the NIH Collaboratory Distributed Research Network).

AHA President Steven R. Houser, PhD, FAHA, senior associate dean of research and director of the Cardiovascular Research Center at Temple University in Philadelphia, will moderate the first series of lectures with Ivor Benjamin, MD, professor of medicine at the Medical College of Wisconsin in Milwaukee.

"If you want to be brought up to speed on precision cardiovascular medicine, this is where you will spend your Monday," Cappola said. "This summit will provide a broad introduction to a growing array of precision medicine tools. Our hope is this will accelerate their application in cardiovascular medicine." ▼

AHA/AWS INITIATIVE

continued from page 1

grants to power the Institute. The announcement of the Precision Medicine Platform builds on that relationship.

"Organizations from around the globe are already utilizing the AWS cloud to make their data open and available to the public," said Teresa Carlson, vice president, worldwide public sector, AWS, Inc. "We at AWS can offer our expertise at activating the immense computational and analytical power necessary to manage an information ecosystem of this magnitude."

The information will come from leading healthcare and research organizations such as Stanford Cardiovascular Institute, the Duke Clinical Research Institute and AstraZeneca.

Users will upload their data and will have access to information gathered by others. A give-and-take spirit of cooperation is expected to develop among the community of researchers.

Other early adopters include:

- Cedars Sinai Heart Institute, a Los Angeles-based facility with 16 centers and programs for heart patients.
- Dallas Heart Study, a multi-ethnic, population-based study of 6,101 adults run by the University of Texas Southwestern Medical Center.
- Intermountain Medical Center Heart Institute, a Utah-based nonprofit system of 22 hospitals and 185 clinics.
- International Stroke Genetics Consortium, more than 200 researchers from 50-plus nations working toward a better understanding of the genetic basis of stroke.

Data contributors agree to provide additional information as needed to requesters to uphold the depth and detail within the datasets. The AHA data technology committee assists with the governance policies with all data contributors.

Researchers will not be charged for accessing the data, but will be charged to use the powerful computing capabilities of the Platform using a pay-as-you-go plan based on consumption; similar to the AWS model used currently around the globe.

Organizations in the partnership are excited about the platform, and the endless possibilities that can stem from it.

"We owe this to the patient and the investigators who have helped us build this database," said Fouzia Laghrissi Thode, vice president, GPPS therapy area, cardiovascular & metabolism, AstraZeneca. "It's our way to give back to the academic community and scientific community what they have given to us." ▼

Studies explore dual antiplatelet therapy

The results of three studies looking at various aspects of dual antiplatelet therapy were presented Sunday at Scientific Sessions.

During an abstract oral session, Eric A. Secemsky, MD, MSc, of Massachusetts General Hospital, Harvard Medical School and the Baim Institute for Clinical Research in Boston, presented the results of a study demonstrating that patients with peripheral arterial disease (PAD) had similar ischemic benefit and bleeding risks with extended dual antiplatelet therapy after percutaneous coronary intervention (PCI) as patients without PAD.

The researchers found that patients with PAD had higher rates of ischemic events (6 percent versus 2.9 percent; p<0.01) and bleeding events (4.9 percent versus 1.7 percent; p<0.01) compared to those without PAD. Continued dual antiplatelet therapy for 30 months versus 12 months was associated with consistent reductions in MI/ST (with PAD: HR 0.63; without PAD: HR 0.53; 95 percent CI: 0.42, 0.66; interaction p=0.63) and increases in bleeding events (with PAD: HR 1.82; without PAD: HR 1.66; interaction p=0.81) for patients with compared to those without PAD.

"These findings suggest that there are comparable benefits and risks associated with 30 months of DAPT in patients with PAD relative to those without PAD," Secemsky said. "Importantly, PAD among patients undergoing coronary stenting is associated with a very poor prognosis, and this prognosis persists among patients even after they've survived one year without any event."

Another study presented Sunday suggests that extended-duration dual antiplatelet therapy with clopidogrel and aspirin does not impact mortality, but does reduce rates of myocardial infarction (MI) and stroke while increasing the rates of fatal and major non-fatal bleeding. These findings were presented during an abstract poster session by Sammy Elmariah, MD, MPH, of Massachusetts General Hospital, Harvard Medical School and the Baim Institute for Clinical Research.

Elmariah reported that, among 48,817 patients followed for a median of 546 days after randomization, dual antiplatelet therapy (N=24,411) and placebo (N=24,406) resulted in comparable all-cause, CV, non-CV and cancer-related mortality. Rates of ischemic events, including MI and stroke, were significantly lower for patients receiving continued clopidogrel therapy. While infrequent, fatal bleeding was more common with continued clopidogrel use, as was major non-fatal bleeding.

"Even relatively small effects of extended clopidogrel and aspirin therapy on mortality have relevance to millions of cardiovascular patients treated with these agents each year," Elmariah said. "It's reassuring that prolonged clopidogrel therapy does not adversely impact survival. However, more work is needed to develop methods to identify patients at increased risk of ischemic complications in whom prolonged dual antiplatelet therapy may be beneficial, and those at increased risk of bleeding in whom prolonged therapy may be detrimental."

Also on Sunday, Ada C. Stefanescu Schmidt, MD, of Massachusetts General Hospital, Harvard Medical School and the Baim Institute for Clinical Research, presented the results of an analysis from the DAPT study demonstrating that higher DAPT scores were associated with higher ischemic and lower bleeding rates within one year after coronary stenting in patients who were prescribed 12 months of dual antiplatelet therapy.

"We found that a little over 5 percent of patients had at least one interruption in thienopyridine in the first six months after PCI," Stefanescu Schmidt said. "Interruptions were more frequent in women and in patients who were more medically complex, and less common in patients who had a drug-eluting stent and index PCI done for a ST-elevation MI."

"Interruption of thienopyridine therapy in the first six months after PCI is associated with an increased risk of subsequent MI. In the first 12 months after PCI, the DAPT Score identified patients at elevated risk of ischemic events in the absence of elevated bleeding risk," Stefanescu Schmidt said. "The next steps are to further explore the reasons for interruption and discontinuation." ▼

LATE BREAKING continued from page 1

PRECISION trial

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial showed that celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, is not inferior to ibuprofen or naproxen in cardiovascular safety, according to lead author Steve Nissen, MD, from the Cleveland Clinic in Ohio.

"The highest event rates occurred in the ibuprofen arm and the lowest rates in the celecoxib group," Nissen said. "The time to major cardiovascular events was highest with ibuprofen and lowest with celecoxib, although the differences were not statistically significant. The time to death from cardiovascular causes was shortest with naproxen and longest with celecoxib. And the time to all-cause mortality was shortest with naproxen and longest with celecoxib, although these differences were not statistically significant."

Celecoxib was significantly safer in terms of serious gastrointestinal and renal events, Nissen reported. A post-hoc analysis showed celecoxib was significantly safer than either ibuprofen or naproxen for any adjudicated cardiovascular, GI or renal event.

The results raised questions about the trial design and execution. While PRECISION was designed to evaluate safety in patients at high cardiovascular risk, the majority of the 31,857 patients were low to intermediate risk, said former AHA President Elliott Antman, MD, senior physician at Brigham and Women's Hospital and associate dean for clinical and translational research at Harvard Medical School in Boston.

Antman also noted that nearly half of the patients in the trial were also taking aspirin and all trial participants were taking esomeprazole for gastric protection. Esomeprazole lowers gastric pH, which can reduce absorption of celecoxib.

"We don't have an answer on safety for high-risk populations and we don't know the effects of aspirin. And we don't know the effects of esomeprazole on celecoxib," Antman said.

HOPE-3 trial

Treating hypertension and elevated LDL cholesterol late in life does not slow cognitive or functional decline, according to results from the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial.

The HOPE-3 researchers reported the trial's cardiovascular outcomes — lowering blood pressure and statins both reduced cardiovascular events significantly — earlier this year, noted lead author Jackie Bosch, MD, from McMaster University in Hamilton, Ontario, Canada. The researchers used questionnaires at baseline and during follow-up to evaluate the effects of these interventions on cognitive and functional decline.

Of the 12,705 participants who were randomized, 3,086 were 70 or older at baseline. Of this older cohort, 1,626 completed both the baseline and study-end questionnaire. The primary outcomes were the decline in processing speed and changes in function.

"There was no difference in mental processing speed, in executive function, in psychomotor speed or other cognitive or functional areas tested between the groups," Bosch said.

There was a trend for improvement in cognitive decline among patients with the highest baseline blood pressure and LDL cholesterol, but the results need to be replicated, Bosch added.

There was also a trend to improvement in cognitive and functional decline in patients who were followed for more than 5.5 years, she reported.

"We know that blood pressure effects begin in middle age," Bosch said. "We need to think about treating earlier and treating longer to affect cognitive function, especially for individuals at higher cardiovascular risk."

TRUE-AHF trial

Results from the Trial of Ularitide's Efficacy and Safety in Patients with Acute Heart Failure (TRUE-AHF) suggest that the standard model of AHF is incomplete, according to lead author Milton Packer, MD, from the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas.

"The trial was not a test of a specific agent; it was a test of a hypothesis of the mechanism of heart failure," Packer said. "We know that sodium retention and vasoconstriction lead to increased intravascular volume and acute ventricular distension that worsens heart failure events. The question was whether this myocardial congestion induces myocardial microinjuries that accelerate the rate of disease progression and increase long-term risk of cardiovascular death."

TRUE-AHF is the largest trial in AHF and the earliest to treatment — a mean of 6.1 hours after an unplanned hospitalization or emergency department visit for acutely decompensated heart failure. Patients were randomized to a 48-hour infusion of ularitide, a synthetic natriuretic peptide, or placebo, then followed for a mean of 15 months. Only one of the 2,157 patients randomized was lost to follow-up.

The trial found that ularitide had the anticipated effect of reducing blood pressure and markers of cardiac distension during infusion, which reduced the risk and number of in-hospital heart failure events, Packer reported. But the agent failed to reduce myocardial injury or change the natural history of AHF, including the long-term risk of cardiovascular death, he said.

"We can decongest a heart and decongest the intravascular space to improve short-term outcomes, but we cannot reduce AHF and long-term mortality," Packer said. "This changes the way we think about acute heart failure." ▼

AHA PRESIDENT continued from page 1

Houser described himself as "an old dog" when he left the comfort of a field where he'd thrived to join a new group of colleagues. It's been 10 years since the shift, and he remains fascinated by the quest.

"I strongly believe that – given the scientific intellect that's addressing this problem – new therapies that produce new cardiac tissue can be developed if we follow the data," he said.

Houser is so passionate about those last few words that they were part of the title of his speech: "Following The Data: My Journey to Help Patients With My Dad's Disease."

As for the personal side of it, he explained that during the address.

Houser was in his second year of working toward a Ph.D. at Temple's medical school, focused mainly on neurology, when his dad became ill.

Bob Houser was a hard-working, soft-spoken husband and father. He skipped work one day because of what he thought was a chest cold. About seven years later, doctors discovered that supposed cold actually had been a myocardial infarction, the technical term for a heart attack, and now he was in severe heart failure. He lived only about another year, dying at 51.

"During his decline, I began my education in cardiology," Steven Houser told the crowd. "I became hooked. I loved the field and, of course, I now felt a deep personal connection. I switched my thesis topic to a study of failing cardiac muscle. And I decided to devote my life's work to helping develop the knowledge needed to best treat patients with heart failure secondary to myocardial infarction."

Houser spoke fondly of his 25 years studying ways to make a failing heart stronger and to prevent lethal cardiac arrhythmias, calling it "an amazing period of new scientific discovery."

Houser also shared the tale of how he became an AHA volunteer.

It all started with an idea to study fundamental aspects of how cardiac muscle cells change during heart failure. He sought funding from the National Institutes of Health, but was rejected. So he tried again. And a third time.

"My score got worse with each resubmission," he said, laughing. "I was undeterred. I took my ideas to what was then the Philadelphia Chapter of the AHA and sought the equivalent of the current Scientist Development Grant. My grant was awarded on the first submission. I received the grand sum of $7,500."

Houser also gained the confidence to pitch another project to the NIH. It was accepted, and he's been funded by the federal agency ever since, receiving research grants totaling more than $25 million.

That early support from the AHA prompted Houser to learn more about the organization. Liking what he saw, he began taking on various roles. On July 1, he became the 80th President and the first Ph.D. Basic Scientist to hold the position.

Houser spoke about the three areas of emphasis for his tenure: scientific discovery, developing the next generation of cardiovascular scientists and prevention of cardiovascular diseases and stroke. He capped his address by urging colleagues to pursue each of these areas.

"Today, we have unprecedented opportunities to improve people's health," he said. "I urge you to find new ways to help someone live their life free of cardiovascular diseases and stroke. *Something* brought you to Scientific Sessions. Whatever that motivation is, let this meeting continue to stoke it, and to inspire you." ▼

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 v3, 07/16

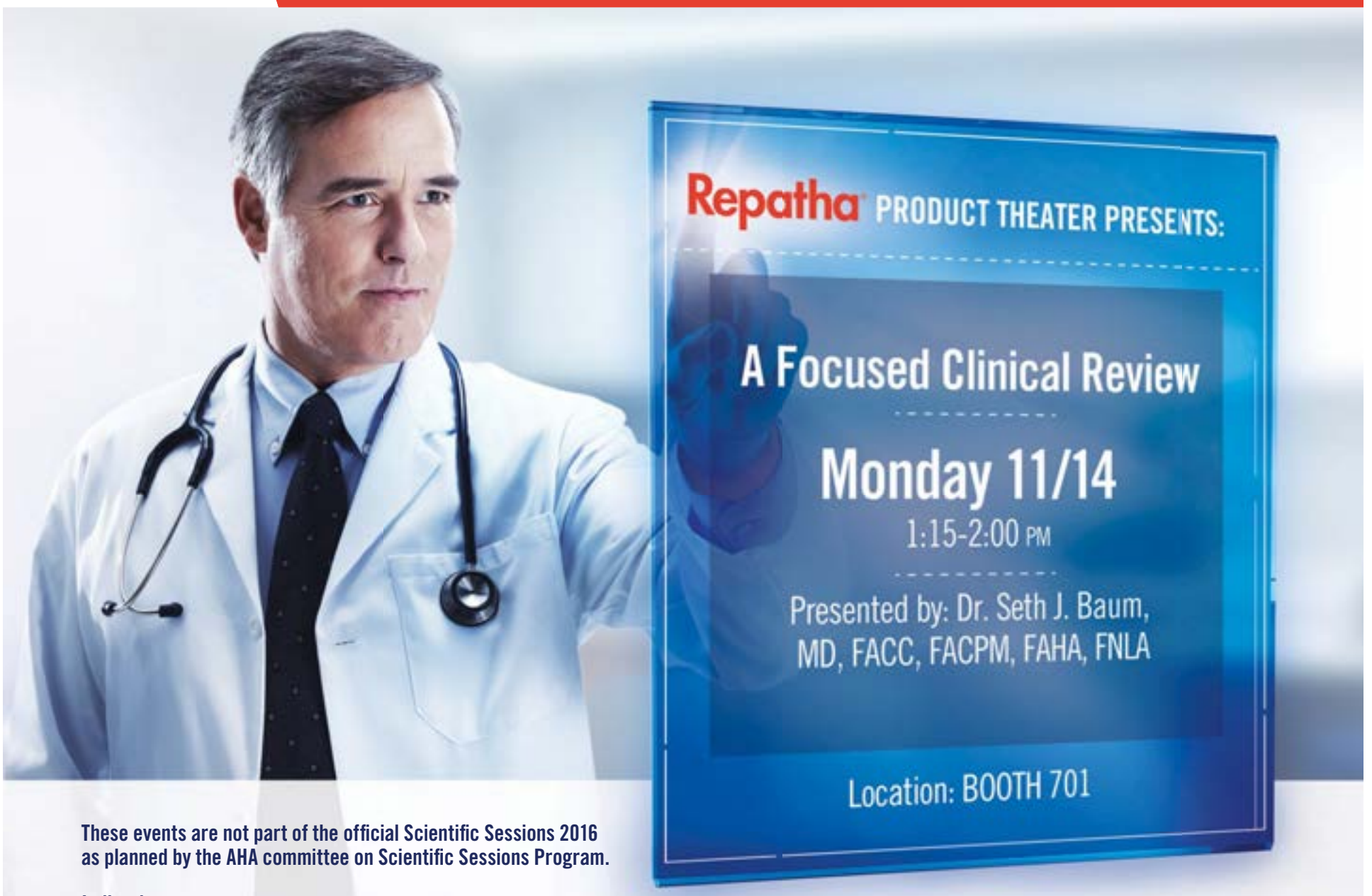
AMGEN®

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/

For adults with clinical ASCVD on maximally tolerated statin therapy as an adjunct to diet who require additional lowering of LDL-C[1]

REPATHA®

THE FIRST AND ONLY PCSK9 INHIBITOR WITH A SINGLE MONTHLY INJECTION[1]*



These events are not part of the official Scientific Sessions 2016 as planned by the AHA committee on Scientific Sessions Program.

Indication

- Repatha® is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- 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: Local 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 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 previous page.

*Administered subcutaneously.
ASCVD = atherosclerotic cardiovascular disease;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

AMGEN Cardiovascular

USA-145-033276 08-16

Repatha® (evolocumab) injection 140 mg/mL

BOOTH 3321