TUESDAY, NOVEMBER 15

American Heart Association.
life is why

SCIENTIFIC SESSIONS 2016

DailyNews

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First projects in One Brave Idea initiative set to launch in January

One of the first studies in the $75 million research project seeking to wipe out coronary heart disease will target perhaps the most basic human experience: Eating.

Calum A. MacRae, MD, PhD

While generations of scientists have studied how the food people eat changes their bodies, it's never been done like this group plans to do.

Participants in the study will use an app to take a picture of their plate before and after every meal. The images will go into a database that will determine all sorts of crucial information. It's a lot more sophisticated — and, perhaps, more accurate — than the old-school way of asking people to write down what they ate.

"We can work out how many calories were consumed, what trace elements were ingested, how that affects the bacteria in your bowel and more," said lead investigator Calum A. MacRae, MD, PhD, chief of cardiovascular medicine at Brigham and Women's Hospital and associate professor at Harvard Medical School in Boston. "All those things can be brought together through the power of image analysis technologies combined with rigorous databases of food composition. So you just put the picture in your app, and the app would do everything else."

The study will be one of four studies launched Jan. 1, when the project known as One Brave Idea officially begins.

Funded by $25 million each from the American Heart Association, Verily (formerly Google Life Sciences) and pharmaceutical company AstraZeneca, One Brave Idea is all about conducting science in a new way to try wiping out coronary heart disease. Of the 17 million deaths per year from cardiovascular diseases, CHD accounts for about 7 million.

This mold-breaking project was announced last year at Scientific Sessions in Orlando, Florida. Within

ONE BRAVE IDEA continued on page 14

Study: No difference in single versus double mammary coronary bypass grafting

Patients who undergo coronary artery bypass graft (CABG) surgery can expect similar outcomes whether they receive a single internal mammary artery graft or a double graft, according to results from the Randomized Comparison of Single Versus Double Mammary Coronary Artery Bypass Grafting: 5 Year Outcomes of the Arterial Revascularization Trial (ART). ART was the first of four studies presented during Monday's Late Breaking Clinical Trials session.

David Taggart, MD

Grafting the left internal mammary artery is the established standard of care for CABG, said lead author David Taggart, MD, from the University of Oxford in the United Kingdom. Multiple observational studies suggest improved long-term outcomes and survival from double grafts versus single, which has led to double grafts in most CABG surgeries.

"We know that arterial grafts have better long-term patency than saphenous venous grafts, and logic says it is better to have two patent grafts than one over the long term," Taggart said, "We expect that bilateral internal mammary artery grafting will result in an absolute 5 percent reduction in 10-year mortality compared with single artery grafting."

Five-year data from ART do not meet that expectation.

In the study, all-cause mortality, cardiac death and myocardial infarction or stroke rates were nearly

LATE BREAKING continued on page 13

Cardiorespiratory fitness may predict risk of incident atrial fibrillation/flutter

THE BENEFITS OF REGULAR exercise in improving cardiovascular health are well recognized. However, the impact of changes in cardiorespiratory fitness on the incidence of atrial fibrillation/flutter is less clear.

The results of a study presented Monday at Scientific Sessions suggest that baseline cardiorespiratory fitness and improvements in cardiorespiratory fitness independently predict risk of incident atrial fibrillation/flutter. Nasir Hussain, MBBS, of the Mayo Clinic in Rochester, Minnesota, presented the research during an abstract oral session.

"Most of the prior studies assessing the relationship of exercise and cardiorespiratory fitness with atrial fibrillation utilized self-reported exercise history as a surrogate for cardiorespiratory fitness," Hussain said. "Self-reported exercise history, however, is subject to limitations such as recall bias and poor quantification of exercise intensity. In this study, we utilized functional aerobic capacity (FAC) as a practical and objective measure of cardiorespiratory fitness."

The study cohort included 3,178 patients who had undergone at least two clinically indicated treadmill exercise tests (TMET) between 1993 and 2010 at the Mayo Clinic Integrated Stress Center. The subjects were divided into fit (FAC≥100 percent), less fit (80 to 99 percent), and unfit (FAC<80 percent) cardiorespiratory fitness groups.

Nasir Hussain, MBBS

The patients were prospectively followed from the date of second exercise test until the end of January 2016 for occurrences of atrial fibrillation/flutter, which were ascertained through retrospective chart review. Proportional hazard regression modeling was used to assess the relationship of changes in FAC with outcome while adjusting for age, sex, baseline FAC, time between exercise tests, and cardiovascular risk factors at baseline and interval changes in risk factors.

During an overall median follow-up of 11 years, 422 patients (13.2 percent) developed incident atrial fibrillation/flutter. A 10 percent higher FAC at baseline was associated with 11 percent lower risk of incident atrial fibrillation/flutter. In addition, an interval increase of 10 percent in FAC decreased the risk of atrial fibrillation/flutter by 12 percent. The most significant improvements were seen in the less-fit (0.88 [0.79-0.98, p=.02]) and unfit (0.86 [0.78-0.96, p=.006]) groups.

"These findings demonstrate that both baseline and change in cardiorespiratory fitness independently predict risk of incident atrial fibrillation or flutter," Hussain said. "In the modern era, as primary prevention of various cardiovascular diseases is becoming a fathomable reality, our study adds to the armamentarium of tools available for patients and for physicians who believe in primary prevention." ▼

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.-3 p.m.
Cardiovascular Nursing Clinical Symposium: Day 2
Room 353

9 a.m.-6:45 p.m.
Frontiers in Science: Stem Cells Summit
Rooms 206-207

10:45 a.m.-Noon
Late-Breaking Clinical Trials: Insights from New Therapeutic Trials for Lipids
Main Event I, Hall G

12:30-1:30 p.m.
Distinguished Scientist Lecture: Contributions of Epidemiology to the Prevention of Stroke and Dementia
Main Event II, Hall F

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

2-2:30 p.m.
Paul Dudley White International Lecture: The Dark Genome: Function and Therapeutic Potential of Non-Coding RNA's in Cardiovascular Disease
Main Event I, Hall G

2-3:15 p.m.
Cardiology Practice in 2020: Sustainability, Quality, and Value
Rooms 260-262

3:15-4:30 p.m.
Main Event Session: Brain-directed Resuscitation
The Great Hall A

3:45-5 p.m.
Clinical Science: Special Reports
Main Event II, Hall F

5:30-6:45 p.m.
Hypertension: Is it Still a "Silent Killer" in South America?
Rooms 220-221

HEARTY HUMOR by Jonny Hawkins

"We did a major bypass so the way to your heart is not through your stomach."

The American Heart Association turned the New Orleans Ernest N. Morial Convention Center red on Monday in support of Go Red For Women, the AHA movement to raise awareness that heart disease is the No. 1 killer of women.

HIGHLIGHTS FROM THE PROGRAM CHAIR

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

Today is Sneaker Day! Put on your running shoes, tennis shoes or basketball shoes to show your support and acknowledge that exercise is a key factor in maintaining good cardiovascular health and preventing heart disease and stroke.

Frank W. Sellke, MD, FAHA

A highlight of the day's program is the Distinguished Scientist Lecture, presented by Harlan M. Krumholz, MD, of Yale School of Medicine, at 12:30 p.m. in Main Event II, Hall F. Stefanie Dimmeler, PhD, of Frankfurt, Germany, will then present the annual Paul Dudley White International Lecture at 2 p.m. in Main Event I, Hall G.

Today, we have our third Late-Breaking Clinical Trials session, titled "Insights from New Therapeutic Trials for Lipids," at 10:45 a.m.-noon in Main Event I. The session will include results from "Inhibition of PCSK9 Synthesis Via RNA Interference: 90 Day Data From Orion-1-a Multi-centre Phase-2 Randomized Controlled Trial" and "GLAGOV – Effect of Evolocumab on Progression of Coronary Atherosclerosis in Statin-Treated Patients: A Placebo-Controlled Intravascular Ultrasound Trial."

We also have two Clinical Science: Special Reports sessions today: "Precision Medicine on the Front Lines" (3:45-5 p.m. in Main Event II) and "Hi Impact EP Registries and Clinical Trials" (10:45 a.m.-noon in rooms 260-262). See below for details on today's Late-Breaking Clinical Trials and Clinical Science: Special Reports sessions.

Another highlight is "Frontiers in Science: Stem Cells Summit," a daylong program devoted to the latest in cell therapy at 9 a.m.-6:45 p.m. in rooms 206-207. Presenters will discuss the latest in stem cell biology, paracrine mediators of stem cell bioactivity, integrative models and translation, and results from clinical trials.

Today's Main Event sessions include:

- "Acute Pulmonary Embolism in 2016: The Challenge of Rapidly Shifting Paradigms" (9 a.m. in Main Event I)
- "Atrial Fibrillation — Innovating to Improve Outcomes" (9 a.m. in Main Event II)
- "From Precision to Population: Optimizing Outcomes in HF" (10:45 a.m. in Main Event II)
- "New Approaches to Repair The Damaged Cardiovascular System" (2 p.m. in Main Event I)
- "Maximizing PAD Outcomes in 2016" (2 p.m. in Main Event II)
- "Cardiology Practice in 2020: Sustainability, Quality, and Value" (2 p.m. in rooms 260-262)
- "Dilemmas at the Forefront of Stable Ischemic Heart Disease Management" (3:45 p.m. in Main Event I)

And don't miss today's Main Event with a new session format, "New and Future Treatments for Arrhythmias — TED-style Talks," at 3:45 p.m. in rooms 260-262.

Today's joint sessions include:

- "Endocarditis: A Team Concept," with the European Society of Cardiology (9 a.m. in Rivergate)
- "Atrial Fibrillation: Global Perspective," with the Great Wall International Congress of Cardiology (10:45 a.m. in Rivergate)
- "Acute Type B Dissection," with the European Society of Cardiology (10:45 a.m. in rooms 220-221)
- "Heart Diseases in Subsaharan Africa: What is New?" with the Pan-African Congress of Cardiology (2 p.m. in Rivergate)
- "Recent Advances in Cardiovascular Genetics," with the Japanese Circulation Society (3:45 p.m. in Rivergate)
- "Hypertension: Is it Still a 'Silent Killer' in South America?" with the Sociedad Chilena de Cardiología (5:30 p.m. in rooms 220-221)

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

Today is the final day to visit the Exhibit Hall. Be sure to walk through the hall to find friends and colleagues, network and learn about the latest drug therapies and devices.

Finally, tonight's Council Dinners will take place at the Hilton New Orleans Riverside. Check the Final Program or Mobile Meeting Guide for times and locations.

With all that is offered, I'm sure you'll enjoy another great day at Scientific Sessions 2016! ▼

Late-Breaking Clinical Trials — LBCT.03 | 10:45 a.m.–Noon Tuesday | Main Event I, Hall G

Insights from New Therapeutic Trials for Lipids

TRIAL	DESCRIPTION
Inhibition of PCSK9 Synthesis Via RNA Interference: 90 Day Data From Orion-1-a Multi-centre Phase-2 Randomized Controlled Trial	The trial provides information on safety and efficacy of using RNA interference quarterly or biannually to target intracellular PCSK9 production as a means to lower LDL-C in a large patient cohort.
Effect of Evolocumab on Progression of Coronary Atherosclerosis in Statin-Treated Patients: A Placebo-Controlled Intravascular Ultrasound Trial	The trial is the first to assess the effects of a PCSK9 inhibitor on the regression or progression of coronary atherosclerosis as assessed by intravascular ultrasound.
The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Human ApoA-I, After Acute Myocardial Infarction – The ApoA-I Event Reduction in Ischemic Syndromes I (AEGIS-I) Trial	The phase 2b, multi-center, randomized, placebo-controlled, dose-ranging clinical trial evaluated the safety and tolerability of multiple administrations of two-dose arms of CSL1.
Ionis-angptl3-IRx, An Antisense Inhibitor To Angiopoietin-like Protein 3 [angptl3] Reduces Plasma Angptl3 And Lipids In Healthy Volunteers With Elevated Triglycerides	The trial evaluated antisense oligo against ANGPTL3 for its effect on lipid homeostasis.
Impact of Infusion of an ApoA-I HDL Mimetic on Regression of Coronary Atherosclerosis in Acute Coronary Syndrome Patients: The MILANO-PILOT Study	The trial evaluated whether infusions of a HDL mimetic-containing apia-I Milano would promote regression of coronary atherosclerosis in patients with ACS.

Clinical Science: Special Reports — CSSR.02 | 3:45–5 p.m. Tuesday Main Event II, Hall F

Precision Medicine on the Front Lines

TRIAL	DESCRIPTION
A Genome-wide Association Study (GWAS) Identifies Novel Loci Associated With Clinically Defined Statin-Associated Muscle Symptoms in a Double-Blind Cross-Over Re-challenge Trial	The trial identified genes associated with statin-associated muscle symptoms.
Incidence of Acute Myocardial Infarction in Patients With Genotyped Familial Hypercholesterolemia in Norway During 2001-2009	The trial reported the standard incidence ratio of myocardial infarction in FH.
A Loss-of-Function Variant in CETP Is Associated With Altered Lipid Metabolism but Not With Cardiovascular Disease Incidence in Chinese Adults	The large cohort study evaluated the effects of a loss-of-function variant in the CETP gene, mimicking pharmacological inhibition of CETP, on CVD risk in Chinese adults.
Prospective Clinical Implementation of CYP2C19-Genotype Guided Antiplatelet Therapy After PCI: a Multi-Site Investigation of MACE Outcomes in a Real-World Setting	The multi-site study determined the effect of clinical implementation of genotype-guided antiplatelet therapy on major adverse cardiovascular events after PCI.

Clinical Science: Special Reports — CSSR.04 | 10:45 a.m.–Noon Tuesday Rooms 260-262

Hi Impact EP Registries and Clinical Trials

TRIAL	DESCRIPTION
Atrial Substrate Modification With Aggressive Blood Pressure Control to Prevent Atrial Fibrillation (SMAC AF)	The trial examined the effects of aggressive blood pressure control on the incidence of recurrent atrial fibrillation.
Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor in Patients with Cardiovascular Risk Factors: ASSERT II	The trial examined the occurrence of sub-clinical AF in an elderly population as measured using an implantable monitor in patients at risk.
The San Francisco POstmortem Systematic InvesTigation of Sudden Cardiac Death (POST SCD) Study	The unique collaboration between cardiac electrophysiology and the county medical examiner precisely determined the burden and underlying causes of every incident of out-of-hospital sudden cardiac death in San Francisco via comprehensive autopsy.
Idarucizumab For Dabigatran Reversal: Updated Results Of The Re-verse Ad Study	The authors present updated results from the groundbreaking study that evaluated the safety and efficacy of idarucizumab as a specific reversal agent for dabigatran.

Membrane fusion vital to cell function

The human body is far simpler than some researchers recognize, according to James E. Rothman, PhD, who delivered the Nobel Laureate Lecture on Monday at Scientific Sessions.

A single mechanism — the fusion of intracellular vesicles to transport molecular cargoes inside, into and out of cells — underlies processes as seemingly different as cell division, hormonal secretion and muscle contraction, he explained.

"The machinery that controls the release of insulin in the pancreas is the same as the machinery that controls the release of neurotransmitters at the neuromuscular junction and the contraction of a heart muscle fiber," said Rothman, the Fergus F. Wallace Professor of Cell Biology, professor of chemistry, chair of cell biology and director of the Nanobiology Institute at the Yale School of Medicine in New Haven, Connecticut.

"If you disrupt the system in any way, cells can't grow and divide and function properly. You end up with one or more of a long list of debilitating and ultimately fatal diseases, including forms of cardiomyopathy."

Rothman shared the 2013 Nobel Prize in Physiology or Medicine for his exploration of the core machinery and universal mechanisms of vesicle transport. He discussed his work and the importance of foundational research during Monday's lecture.

James E. Rothman, PhD

"Vesicle transport is a choreographed program of secretory, biosynthetic and endocytic protein traffic that serves the cell's physiologic needs, propagates its internal organization and allows it to communicate with the outside world and receive nutrients and signals from it," he said.

Cells move proteins and other molecular cargoes by encapsulating them in vesicles that are 50-70 nanometers in diameter. The vesicles transport their contents by budding from one membrane and fusing to the next until the cargo reaches its final destination.

"Vesicles are ephemeral and absolutely vital," Rothman said. "If you have a strong mutation in one of the genes coding for this system, you die — you won't even survive long enough to be born."

Vesicle transport is one of the most basic concepts in medicine and biology. Cellular life from yeasts to flies to plants and humans use the same mechanism to transport molecular cargoes and regulate cellular architecture. Every human cell contains about 100,000 vesicles and each is designed to move a specific molecular cargo.

"It is this kind of foundational research that starts to understand the basis of life wherever it is found," Rothman said. "Foundational research provides the language by which clinical and translational researchers can frame their work. It is the foundational discoveries that lead to questions that could not otherwise be posed, such as cardiac contractility." ▼

CAREER PROGRESSION:
Jerrold H. Levy, MD, FAHA, FCCM

As a young man, Jerrold Levy aspired to be a research scientist.

But while working in a biochemistry lab as an undergraduate in the 1970s, his mentor suggested a career in medicine.

"Best advice I've ever gotten," said Levy, professor of anesthesiology, associate professor of surgery and co-director of the cardiothoracic ICU at Duke University Medical School in Durham, North Carolina. "What's great about medicine is that it's applied science in many ways."

After medical school at the University of Miami, Levy started in internal medicine and then trained as an anesthesiologist at Massachusetts General Hospital in Boston, where he was a fellow in respiratory ICU and cardiac anesthesiology. He worked alongside Warren Zapol, MD, (whose lab has made groundbreaking discoveries about the physiological and pathophysiological roles of nitric oxide) and managed some of the early extracorporeal membrane oxygenation in the 1980s.

Levy started with plans to become a hematologist and immunologist, but shifted to critical care in part because he was inspired by a series about acute respiratory failure in *The New England Journal of Medicine* written by three anesthesiologists with whom Levy trained.

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

"A collaborative effort for improving patient care is why."

American Heart Association. life is why™

In 1983, he was recruited to Emory University School of Medicine in Atlanta to start a surgical ICU, and had an active hemostasis research lab.

"Our work focused on hemostatic therapies, evaluating thrombin signaling, understanding the coagulopathy of critical illness and extracorporeal circulation, as well as developing different anticoagulant and pro-coagulant strategies for the prevention and management of bleeding in critically ill patients," Levy said.

He spent 30 years at Emory Healthcare before being recruited to Duke in 2013. His research interests include anaphylactic shock, cardiovascular pharmacology and developing novel strategies to reduce bleeding.

"What I've been doing most recently is working closely with others to further develop and apply purified and recombinant strategies to treat bleeding, as well as reverse the direct oral anticoagulants," Levy said. "Developing therapies that have broad-scale implications is an important contribution."

Throughout his career, Levy has been actively involved in the AHA. He joined the Council on Cardiovascular Surgery and Anesthesia (CVSA) more than 20 years ago and is currently chair of the AHA's Membership and Communications Committee.

"It is a special privilege to be involved and active in the American Heart Association," he said. "It's been an amazing experience to see how cardiovascular medicine has evolved with a major focus over the years in hemostatic management with the evolution of novel anticoagulation agents. I am most appreciative to the American Heart Association for the opportunity to collaborate with so many outstanding colleagues and leaders in cardiovascular medicine." ▼

MEMBER SPOTLIGHT

Norrina Allen, PhD, FAHA
Assistant Professor, Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University in Chicago

How long have you been an AHA/ASA Professional Member?
I joined the AHA/ASA in 2005 as a doctoral student. During the past 11 years I have evolved from a trainee/early career member to a full professional member, and the AHA/ASA has become my scientific home.

Why did you join?
I joined to present my research in a forum that was supportive of new researchers and where I was surrounded by leading experts in the field. The AHA/ASA's commitment to mentorship and scientific excellence has made a major impact on my career development.

Are you involved in AHA councils?
I have been involved in several AHA councils, including the Stroke, Quality of Care and Outcomes (QCOR), and Epidemiology and Prevention (EPI) councils. Currently, I am a member of the Early Career Committees for QCOR and EPI, the Epidemiology and Prevention Leadership Committee and Scientific Sessions Planning Committee, among others. As an active member of multiple councils, I am excited to see a growing group of members whose interests and expertise span disciplines and ultimately bring the AHA together.

What do you enjoy most about these roles?
Having been involved with AHA for more than 10 years, I enjoy being able to share my experiences with others who are just starting their careers. Being involved with the AHA has been a tremendous asset to my professional development. I hope that others can take advantage of all the opportunities that the AHA has to offer.

How else are you involved with the AHA?
I am strongly committed to the AHA's mission to build healthier lives, free of cardiovascular diseases and stroke. I lead the population science project at Northwestern's Strategically Focused Prevention Research Center. Strategically Focused Research Networks are creating exciting new collaborative research groups and training the next generation of interdisciplinary researchers. I volunteer for the AHA at all levels, from our local Metropolitan Chicago Board to the Midwest Affiliate and up to the national level.

Why is membership valuable to you?
Being an AHA member means that I am part of a community of researchers, clinicians and advocates who are all devoted to improving the cardiovascular health of people in the U.S. and beyond. Each of us contributes to this shared mission in our unique way, and I feel proud to be part of the AHA.

What message would you convey to your colleagues about being an AHA member?
The AHA represents a commitment to mentorship, collaboration and scientific excellence. At each stage of my career I have benefited from being an AHA member through the support of other members, as well as by AHA staff and volunteers. I hope that I can be part of this legacy by contributing to the understanding of heart disease and stroke as well as serving as a mentor for the next generation of scientists. ▼

Quality of warfarin therapy connected to risk of intracranial hemorrhage in patients with atrial fibrillation

In patients with atrial fibrillation (AF), the quality of oral anticoagulation therapy with warfarin as measured by time in therapeutic range (TTR) is strongly associated with the risk of intracranial hemorrhage, according to a study presented Monday at Scientific Sessions.

Mika Lehto, MD, PhD, of Helsinki University Hospital in Finland, and his colleagues conducted an analysis of the FinWAF registry, which includes 54,568 unselected AF patients collected from other Finnish registries; 31,172 were prevalent warfarin users and 23,396 were new warfarin users. Crude incidence rates of intracranial hemorrhage (ICH) were correlated with TTR, as calculated using the Rosendaal method with a continuous calculation window of 60 days. Hazard ratios were adjusted for a variety of factors, including age, hypertension and previous stroke. The mean follow-up period was 3.2 years, during which time there were 1,558 ICH events.

Mika Lehto, MD, PhD

Using a TTR of 60 to 70 percent as a reference group, low TTR significantly increased the risk of ICH, while high TTR decreased it. Patients with a TTR <40 percent had the highest risk, with a HR of 2.11 (95 percent CI, 1.75-2.56; p<0.001); 618 of all the events in the study occurred in these low-TTR patients.

Those with a TTR between 40 and 50 percent also had a significantly increased ICH risk, with an HR of 1.32 (95 percent CI, 1.03-1.68; p=0.03). The 50 to 60 percent range was not significantly different from the reference group.

On the higher side, a TTR between 70 and 80 percent was not significantly different from the reference group, but patients with a TTR of >80 percent had an HR for ICH of 0.66 (95 percent CI, 0.54-0.80; p<0.001). Lehto said that though this patient group fared best, the annual rate of ICH was higher than expected. Still, he said, "we were surprised that the difference between the groups was so clear."

Along with TTR, several other factors were associated with an increased risk of ICH. These included hospitalization during the study period (HR, 1.67; p<0.001); age >70 years (HR, 1.60; p<0.001); male gender (HR, 1.63; p<0.001); hypertension (HR 1.13; p=0.03); and previous stroke (HR, 1.51; p<0.001). Patients under the age of 60, meanwhile, had a lower risk of ICH (HR, 0.61; p<0.001).

Lehto noted that the study is limited by the use of registry data, which lacked critical information like smoking status and use of aspirin. In spite of that limitation, the large number of patients and events makes the results convincing, he said. The study is the first time that a direct correlation between ICH and TTR has been demonstrated, he added.

"TTR should be continuously calculated. If it is greater than 80 percent, a patient is as safe as possible," Lehto said. "If it is low or decreasing, it is a red light — your patient is at high risk regarding ICH." ▼

Seeing double

Researchers studied male twins from the Vietnam Era Twin Registry and discovered that posttraumatic stress disorder is associated with increased microvolt T-wave alternans, a measure of repolarization heterogeneity that is associated with increased risk of sudden cardiac arrest. The study, which was presented during a poster session Monday, suggests that common genetic factors may predispose to both PTSD and repolarization heterogeneity.

Former Framingham PI to deliver Distinguished Scientist Lecture

Philip A. Wolf, MD, FAHA, who researched the epidemiology of stroke and dementia as principal investigator of the Framingham Heart Study from 1989 to 2014, will deliver this year's Distinguished Scientist Lecture at 12:30 p.m. Tuesday in Main Event II, Hall F. His lecture is titled "Contributions of Epidemiology to the Prevention of Stroke and Dementia."

Under the direction of the National Heart, Lung, and Blood Institute, the Framingham Heart Study was designed to identify factors that contribute to cardiovascular disease. The study began in 1948 with a cohort of 5,209 men and women ages 30-62 from Framingham, Massachusetts, who had not developed overt symptoms of cardiovascular disease or suffered a heart attack or stroke. The investigators have followed CVD development in three generations of participants.

Wolf was recruited to the study in 1967 as its first and, at the time, only neurologist. There were no laboratory tests to confirm a stroke diagnosis while patients were alive; the diagnosis rested on clinical evaluation of the patient during the acute event.

"Framingham was starting to see more and more strokes in their population and the study didn't have anybody who could opine that this was or was not a stroke," said Wolf, who has been a member of the AHA's Stroke and Epidemiology and Prevention councils and in 2006 received the AHA Distinguished Scientist Award. "I had just finished my training in neurology, was particularly interested in cerebrovascular disease and saw it as a great opportunity."

It didn't hurt that Wolf had trained in epidemiology and had worked on another cardiovascular epidemiology project. He was one of a handful of neuro-epidemiologists in the world.

Data from the Framingham Heart Study have been used to identify risk factors for cardiovascular diseases, including stroke, and particularly the importance of atrial fibrillation in people without valvular heart disease. The Framingham stroke risk profile has been used for 25 years to estimate the probability of stroke.

In recent years, it has become clear that many of the risk factors for stroke are also risk factors for cognitive decline and dementia. Hypertension, obesity, smoking, diabetes and physical inactivity increase the risk for later cognitive decline. While attention was initially focused on severe dementia, the focus of the study has shifted to mild cognitive impairment (MCI) and pre-MCI to identify people at risk who are most likely to benefit from preventive efforts earlier in life.

LECTURE PREVIEW

Distinguished Scientist Lecture: Contributions of Epidemiology to the Prevention of Stroke and Dementia
12:30-1:30 p.m. Tuesday
Main Event II, Hall F

"The research tells us that if you control risk factors earlier — in midlife — not only will you prevent or delay cardiovascular disease, you will probably delay and reduce the burden of cognitive decline and dementia," Wolf said. "You won't abolish cognitive decline, but you can have a substantial impact on the brain beyond reducing the likelihood of stroke." ▼

Philip A. Wolf, MD, FAHA

2016 Unofficial Satellite Events

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

Angiography within 12 hours of hospital admission reduces 180-day ischemic risk in NSTEMI patients

Patients with high-risk non-ST segment-elevation myocardial infarction (NSTEMI) who undergo coronary angiography within the initial 12 hours after hospital admission have a lower risk of ischemic outcomes at 180 days than those undergoing angiography between 12 and 24 hours, or after 24 hours, according to a study presented Monday at Scientific Sessions.

Pierre Deharo, MD, a fellow in interventional cardiology at the Bristol Heart Institute in the United Kingdom, presented the study during an abstract oral session.

"It has been demonstrated that in high-risk patients, performing a coronary angiography and percutaneous coronary intervention, if necessary, within the first 24 hours reduced the risk of reinfarction or myocardial infarction, but we still do not know if further reduction of the delay may be beneficial," Deharo said.

Pierre Deharo, MD

The benefit of very early angiogram in high-risk STEMI can be explained, in part, by a reduction of ischemic events while patients are waiting for coronary angiography, Deharo said.

Early assessment also allows early risk stratification and optimal antithrombotic management, he added.

The study was a post-hoc analysis of the TAO trial, which randomized patients with moderate to high-risk NSTEMI and coronary angiography (CAG) within the first 72 hours after admission to heparin plus eptifibatide or otamixaban. The TAO trial found that otamixaban did not reduce the rate of ischemic events, but did increase bleeding.

In the post-hoc analysis, patients with a GRACE score above 140 undergoing CAG were stratified into three groups according to the timing of CAG measured from the first ECG performed on hospital admission: ≤12 hours, 12 to 24 hours, or >24 hours.

The analysis included 4,071 patients; 1,648 were in the ≤12-hour group (40.5 percent), 1,420 were in the 12 to 24-hour group (34.9 percent), and 1,003 were in the >24-hour group (24.6 percent). The primary outcome was a composite endpoint at 180 days, including all-cause death and MI.

Using the >24-hour group as a reference, the 12 to 24-hour group was not associated with any reduction in the primary endpoint. There were 189 events (13.46 percent) in the 12 to 24-hour group compared with 116 events in the >24-hour patients (14.46 percent), for an odds ratio of 0.95 (95% CI, 0.73-1.22).

The ≤12-hour group, however, did show a significant reduction in events compared to the >24-hour group. There were 180 events in the shorter-delay group (10.98 percent), for an OR of 0.73 (95 percent CI, 0.57-0.94; p<0.01).

The ≤12-hour group also had a better rate of ischemic outcomes at 180 days compared to the 12 to 24-hour group, with an OR of 0.79 (95 percent CI, 0.64-0.99; p=0.04).

"Our results support the fact that earlier is better, and it is likely that the first 12 hours represents the best window for intervention, while after 12 hours we are already late," Deharo said. "Our results suggest that the benefit of performing a coronary angiogram within the first 24 hours could be driven by the benefit of patients that actually had their CAG within the first 12 hours." ▼

Heart health: Bariatric surgery or lifestyle modification?

Using data from the Scandinavian Obesity Surgery Registry and a Swedish registry of people treated with a structured, intensive lifestyle program, researchers concluded that bariatric surgery is associated with nearly half the incidence of heart failure compared to intensive lifestyle modification. One year after intervention, the surgery patients lost an average of 41 pounds more than the lifestyle modification patients. The findings, which were presented Monday during an abstract poster session, suggest a causal effect of obesity on heart failure.

Paul Dudley White lecturer will discuss latest research, clinical potential of non-coding RNAs

Much of what has been thought of as junk DNA in the human genome has emerged as rich sources of gene regulation with enormous therapeutic potential, according to Stefanie Dimmeler, PhD, who will present the annual Paul Dudley White International Lecture on Tuesday.

Dimmeler will explore the latest research into the form, function and clinical utility of non-coding RNAs during her 30-minute lecture, "The Dark Genome: Function and Therapeutic Potential of Non-Coding RNAs in Cardiovascular Disease." Her lecture will open the session "New Approaches to Repair the Damaged Cardiovascular System," which begins at 2 p.m. in Main Event I, Hall G.

"Humans have a very small number of genes — only about 23,000," said Dimmeler, professor and director of the Institute of Cardiovascular Regeneration at the University of Frankfurt, Germany. "Only 3 percent of our DNA is transcribed into proteins, and about 80 percent is transcribed into RNA. This non-coding RNA appears to exert very precise controlling functions throughout the cardiovascular system and the rest of the body."

Non-coding RNA has been found to play key roles in epigenetic regulation, transcriptional regulation, epithelial activity and atherosclerosis, and is active throughout the cardiovascular system, Dimmeler said.

Why humans have relatively few genes remains a mystery, she noted. More primitive organisms such as plants can have nearly 40,000 genes. But what humans lack in gene numbers and complexity, they seem to make up in the complexity of gene expression mechanisms, Dimmeler explained. Many of these mechanisms appear to be mediated by non-coding RNA.

There are two primary types of non-coding RNA: short strands of fewer than 200 base pairs and long strands of 200 or more base pairs. Among the short strands, a class that plays crucial roles is known as microRNA, or miRNA.

MicroRNAs are better known and better studied than long non-coding RNAs. Researchers have identified several hundred microRNAs in the cardiovascular system, Dimmeler noted.

One of the best known is miRNA-92a, which was discovered and characterized by Dimmeler´s lab. In the cardiovascular system, this miRNA modulates endothelial cell function and recovery after myocardial infarction (MI). Knockout mice that lack the miRNA show better endothelial cell function and recovery following MI. As a surprise benefit, miRNA-92a knockout mice show reduced body weight after feeding on a high-fat diet compared to control mice.

"If you block this microRNA in obese mice, you have metabolic improvement," Dimmeler said. "We are not yet sure of the mechanism, but it may have something to do with the browning of white adipose tissue, so weight is reduced. It would be a nice add-on when we treat patients with myocardial infarction. Most of them have type 2 diabetes and are obese, so improvement of metabolic alterations and normalizing weight would be a very welcome side effect. We hope to develop this as a therapy."

Researchers have seen no signs of toxicity from either pharmacological inhibition or complete knockout of miRNA-92a in animal models, Dimmeler said. And while the mechanism of action is not fully clear, the research is moving toward a human trial in late 2017.

Less is known about long non-coding RNAs. Dimmeler's lab is working with several that appear to modify response to hypoxia and researchers are looking at cardiovascular effects.

"Their functions are quite complicated, so it takes some time to figure out at which levels these RNAs interfere with the processes they are controlling," Dimmeler said. "This is very new biology which has not been well explored yet. But everything we see says that there is a very good potential for therapeutic use in the future."

Stefanie Dimmeler, PhD

LECTURE PREVIEW

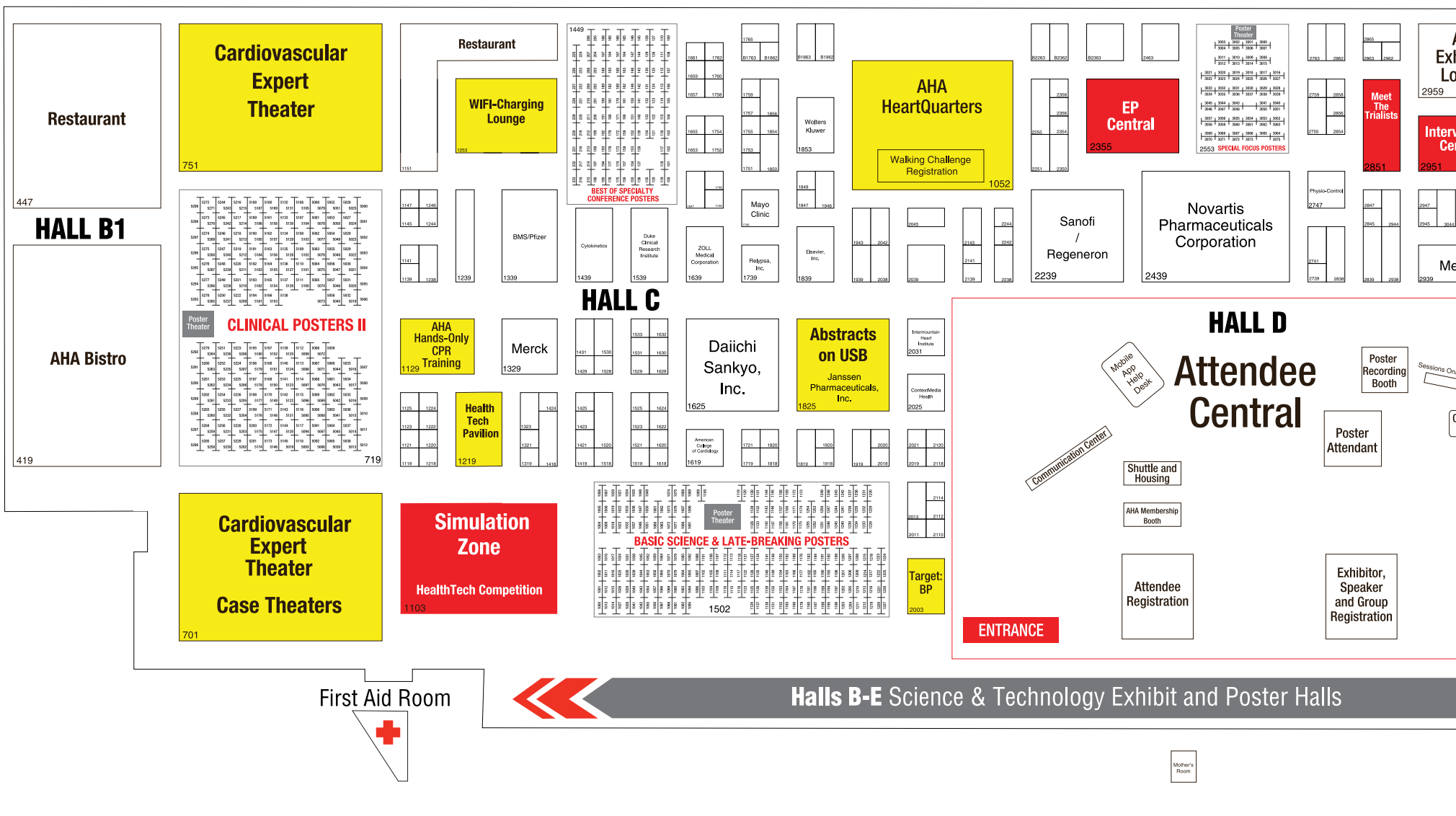
Paul Dudley White International Lecture: The Dark Genome: Function and Therapeutic Potential of Non-Coding RNAs in Cardiovascular Disease

2-2:30 p.m. Tuesday | Main Event I, Hall G

Dimmeler's lecture honors Paul Dudley White, who is widely regarded as the founder of preventive cardiology. White helped found the Boston Society for the Prevention and Relief of Heart Disease (now the Greater Boston Division of the American Heart Association). He joined forces with similar groups in New York City and Philadelphia, and in 1924, became one of the founders of the AHA. He served as AHA president in 1941. ▼

2016 Scientific Sessions Exhibitors

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



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Tuesday's Theater Demonstrations

Cardiovascular Expert Theater I

Booth 701

Noon-12:45 p.m.

Particles to Plaque: Mechanisms and Measurement of Atherosclerosis

Amgen, Inc.

1:15-2 p.m.

Dietary and Pharmacologic Management of Electrolyte Disorders in Heart Failure

Relypsa, Inc.

Cardiovascular Expert Theater II

Booth 3661

Noon-12:45 p.m.

The Diagnosis and Management of Atrial Fibrillation: Working Together to Reduce Stroke Risk in NVAF

Boehringer Ingelheim and Medtronic

1:15-2 p.m.

Roles of In-hospital Worsening Heart Failure and End Organ Damage in Long-term Outcomes

Novartis

Cardiovascular Expert Theater III

Booth 751

Noon-12:45 p.m.

Anticoagulation in Perspective

Daiichi Sankyo, Inc.

1:15-2 p.m.

Cardioprotection vs. Gastrotoxicity: Finding a Balance to Advance Secondary Prevention of Cardiovascular Events with Aspirin

Aralez Pharmaceuticals

HeartQuarters Theater

Booth 1052

10:15-11:15 a.m.

Abstract Submitters Reception

11:25 a.m.-Noon

***Hypertension* Journal CPC: A Case of Primary Aldosteronism with Discordant Hormonal and CT Findings**

Presenter: Laurence Amar, MD, PhD

12:15-12:45 p.m.

CME and CE credit for Scientific Sessions and more

12:45-1:15 p.m.

Research

1:15-2 p.m.

CRISPR – A Discovery and Its Complexities: What Should We Learn as Scientists?

Presenters: Jean McSweeney, PhD, RN, FAHA, FAAN, University of Arkansas for Medical Sciences; Kiran Musunuru, MD, PhD, MPH, FAHA, University of Pennsylvania

Gene editing fixes LQT syndrome abnormalities in stem cell model

ALLELE-SPECIFIC DISRUPTION using CRISPR-Cas9 gene editing techniques allowed researchers to "rescue" the electrophysiological abnormalities associated with an inherited type of long-QT syndrome (LQT) in a stem cell model, according to Yuta Yamamoto, DVM, of Kyoto University Graduate School of Medicine in Japan.

Yuta Yamamoto, DVM

Yamamoto presented the research on Monday at Scientific Sessions. The findings open a window into LQT and other inherited diseases with a dominant-negative mechanism.

Recent research has shown that mutations in the three distinct *CALM* genes are associated with severe early-onset LQT due to impaired inactivation of certain calcium channels. All three genes encode an identical calmodulin protein, and it is suspected that mutant calmodulin from one mutant allele could exert a dominant-negative effect over proteins from the other five alleles.

Yamamoto and his research colleagues used this rationale to test whether genome-editing techniques in a human induced pluripotent stem cell (iPSC) model could ameliorate the LQT associated with the abnormal allele.

Human iPSCs were generated from a patient with LQT known to carry a *CALM2*-N98S mutation. Guide RNA was designed to target the mutant allele sequence, and expression vectors were then transfected in the LQT-iPSCs. The iPSCs were then differentiated into cardiomyocytes, from which action potentials could be measured to assess electrophysiology of the cells.

The investigators created clones with the mutant alleles knocked out using the CRISPR-Cas9 gene editing system. The edited clones were confirmed using sequencing. The electrophysiological analysis of the resulting cardiomyocytes showed that the gene editing worked as planned: The decreased beating rate and prolonged action potential duration associated with LQT was rescued in the knockout cells ($p<0.05$). In fact, those electrophysiological parameters were similar to those seen in cardiomyocytes generated from a healthy volunteer.

"This study suggests that the iPSC-based disease model provides a powerful platform for studying the pathophysiological mechanisms of LQT," Yamamoto said.

Yamamoto added that while the CRISPR-Cas9 system works well in cell models, moving into clinical application poses a number of challenges. Improvements to the editing technique's specificity, efficiency and safety are needed, along with better *in vivo* delivery technologies, he said. Despite the challenges, the research group hopes to try this treatment in an *in vivo* model soon.

"Allele-specific ablation using the latest genome-editing technology is a promising therapeutic approach for inherited cardiac diseases caused by dominant-negative mechanism," Yamamoto said. ▼

Study: ICDs do not detect energy during gastrointestinal endoscopy, may not require deactivation

Implantable cardioverter defibrillators (ICDs) do not detect energy as ventricular arrhythmias during gastrointestinal endoscopy, and thus may not need to be deactivated during the procedures, according to a study presented on Monday at Scientific Sessions.

The study's results are in contrast to current recommendations, which suggest deactivating ICDs during all gastrointestinal endoscopic procedures.

"There was little or no previous evidence" for that recommendation, said lead author Catherine Wright, CCRN, MS, electrophysiology/cardiology APRN at the Joel E. Smilow Heart Institute at Bridgeport Hospital in Connecticut.

Wright and her research colleagues contacted three ICD manufacturers, none of which could provide data or studies to support deactivation of ICDs during gastrointestinal endoscopy. Still, published guidelines recommend the practice to prevent detection of energy as an arrhythmia and the resulting device discharge, and suggest that deactivation decisions should be made by anesthesia and electrophysiology specialists.

In the new study, patients with an ICD who were about to undergo a procedure had their devices reprogrammed to detect ventricular arrhythmias, but not to treat them. Instead, the detection would be stored in the device memory, which could be examined later and the device reactivated.

Catherine Wright, CCRN, MS

The study included 96 patients (79 men, 17 women). The mean age of the patients was 70.3 years. Patients underwent a total of 159 procedures, all non-emergent, including 65 upper GI and 94 lower GI procedures.

Intra-intestinal energy that could potentially be detected by an ICD was delivered during 33 of the procedures (21 percent). This occurred in a few scenarios, including the use of cautery to control bleeding and the use of "hot snare" forceps to remove polyps. The latter procedure was used in five upper GI procedures and 30 lower GI procedures. The ICDs did not detect a ventricular arrhythmia during any of the procedures.

"We were initially a little surprised" at the lack of any energy detection by the ICDs, Wright said, "given the concern that manufacturers had expressed. As we made more trips to the endoscopy suite, we became less and less surprised."

Wright noted that the study is limited by its relatively small size, but the fact that no energy detection occurred suggests that deactivation may not be necessary during gastrointestinal endoscopy. ▼

Social media could help sudden cardiac arrest patients get post-discharge support

A pilot observational analysis of social media use by sudden cardiac arrest survivors found a clear need for post-discharge support, according to Jane Xiao, MD, who conducted the study as an emergency medicine resident at William Beaumont Hospital in Royal Oak, Michigan. The findings from this study were presented during a Resuscitation Science Symposium abstract poster session on Monday.

"There is currently no unified channel or venue for cardiac arrest patients and their families to communicate," Xiao said in an interview prior to Scientific Sessions. "What I found was a lot of people looking for some kind of venue to talk about their experiences, to share their struggles. We need to provide them with a centralized resource, something that can be part of the standard discharge packet. Just providing a bit of structure and support can go a long way toward improving their recovery after they leave the hospital."

Xiao searched multiple social media platforms for public discussions by survivors of sudden cardiac arrest. Facebook was the most popular platform, with nearly three dozen discussion groups that had been active in the past year. The most common discussion themes included increasing public awareness of sudden cardiac arrest, asking for personal and medical advice, sharing feelings and celebrating re-birthdays.

Jane Xiao, MD

Twitter has a few hashtags relevant to sudden cardiac arrest awareness and advocacy, Xiao said. But other social media platforms, including Blogger, WordPress, YouTube, Instagram and Snapchat, had few meaningful public threads.

"Discussions would spring up, continue strongly for a short time and then taper off as individuals became overwhelmed," Xiao said. "We could gain important insights into what happens to our patients after discharge by taking a closer look at these groups. We have focused on the chain of survival and made important gains, but we have not focused on our patients' needs after they leave the hospital."

Not all patients are looking for professional support on social media platforms, she noted. When contacted directly, some survivors expressed surprise that anyone who had not experienced sudden cardiac arrest would be interested in the topic. Many preferred to keep their feelings private and limit their discussion to cardiac arrest survivors or their families. But some were willing to have an emergency medical physician join the discussion, especially if it improved awareness of sudden cardiac arrest.

"Providing patients with a common discharge toolbox, including online support resources, could be a good way to give them better answers and better support after discharge," Xiao said. "Healthcare providers also need guidance regarding which resources their patients need when going home. Having support from the American Heart Association behind that kind of post-discharge resource would be a real advantage." ▼

Summit to explore clinical utility of stem cells

Tuesday's Stem Cells Summit will unveil the new therapeutic frontier in clinical cardiology.

"There have been years of hype about stem cells and we are now beginning to get clinical trial results," said Eduardo Marbán, MD, PhD, director of the Cedars-Sinai Heart Institute in Los Angeles. "The time is very near when we will begin deciding if there is something viable."

The summit — part of the AHA's Frontiers in Science series — is 9 a.m.-6:45 p.m. in rooms 206-207. Attendees will be exposed to the full gamut of stem cell research as it applies to clinical cardiology.

"This program is a unique combination of exciting science, which is the whole Frontiers of Science concept," Marbán said. "But unlike most science programs, the day focuses on translating the basic science to patients."

The summit includes:

- The opening session on stem cell biology will explore how stem cells work and how the heart regenerates after injury. Expert presenters will discuss how the newborn heart can regenerate while the adult heart can't. Potential clinical applications include reprogramming fibroblasts into working heart cells.
- The second session on paracrine mediators of stem cell bioactivity will explore the growing realization that stem cells work largely by secreting soluble factors such as proteins and exosomes. These insights may soon lead to cell-free regeneration strategies, Marbán said.
- The next session will examine a variety of integrative models and translational research. The common thread is the difficult transition from a viable idea to realistic applications, such as tissue engineering, which is moving into early-stage clinical testing.
- Finally, presenters will discuss the tools, resources and constraints that affect clinical trials and the progression from animal to human studies. Results from the latest clinical trials will be reviewed, and timelines for approvals will likely be discussed.

"We will hear from investors and companies that are interested in ideas that can lead to widely available commercial products," Marbán said. "I expect some frank discussions of when some of these technologies might be publicly available and not just limited to clinical trials."

Eugene Braunwald, MD, chair of the TIMI Study Group and professor of cardiovascular medicine at Harvard Medical School in Boston, will cap the day with a special lecture examining whether stem cell therapy can become the next breakthrough in clinical cardiology.

Eduardo Marbán, MD, PhD

Frontiers in Science: Stem Cells Summit

9 a.m.-6:45 p.m. Tuesday
Rooms 206-207

"This will be one of the most exciting programs at Scientific Sessions 2016, with appeal to a broad swath of scientists, translational researchers, pharmaceutical and biotech company employees, clinical researchers and clinicians," Marbán said. "The entire program is tilted toward understanding how science can lead to real deliverables in terms of patient care." ▼

DailyNews

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Studies show improved surgical outcomes for patients with congenital heart disease

Three abstracts presented Monday at Scientific Sessions show improved survival and quality of life following heart-lung transplantation in adults with congenital heart disease, as well as in infants with surgical correction of Tetralogy of Fallot (TOF).

Clayton Smith, MD, a cardiology fellow at the Sibley Heart Center at Emory University in Atlanta, reported long-term outcomes after surgical repair of TOF for patients in the Pediatric Cardiac Care Consortium. In the study, 91.7 percent of patients achieved transplant-free survival at 20 years following all forms of surgical repair of TOF. Survival following simple repair of TOF was as high as 94.5 percent, but survival was lower for patients with more complex defects — between 75 and 80 percent, Smith reported.

"These are conservative estimates of the outcomes we can expect," Smith said. "The median follow-up so far is 19.4 years and we have good survival data from multiple centers going back nearly 30 years."

Simple TOF has no other associated lesions. More complex forms are associated with absent pulmonary valve (TOF-APV), complete atrioventricular canal (TOF-CCAVC) or pulmonary atresia (TOF-PA). Surgical repair is possible for all forms, but the new study confirms that more complex forms of TOF are associated with a higher risk of mortality.

Patients with a genetic defect also had a higher hazard of mortality compared to those without an identifiable genetic defect for both simple TOF, 4.1, and complex TOF, 1.82.

"There is also a difference in survival between patients that undergo an initial palliative shunt versus those who have an initial repair across the simple TOF, TOF-CCAVC and TOF-PA groups," Smith said. "The next questions focus around the factors that go into that survival. We want to assess long-term survival and whether the surgical center and surgical volume at that center play a role."

Clayton Smith, MD

In another study, which analyzed data from 15 years of a programmatic approach to TOF surgery, the findings suggest that the surgical approach to TOF may make a difference.

The surgical team at Stanford University has been using a detailed approach to attain complete repair of infants with TOF and major aortopulmonary collateral arteries (MAPCAs) since 1992. The approach emphasizes early and complete unifocalization and repair with the incorporation of all lung segments and extensive lobar and segmental surgical reconstruction.

"We had 458 patients, the largest cohort that has been published," said lead author Holly Bauser-Heaton, MD, PhD, in an interview prior to Scientific Sessions. "The five-year survival for all comers was 85 percent. If you look at patients who had complete repair, 92 percent were alive 10 years after surgery. These are the best outcomes that have been published to date."

Researchers conducted a retrospective analysis of all 458 patients who underwent surgical intervention for MAPCAs from January 2001 to January 2016 at Lucille Packard Children's Hospital at Stanford. Overall survival was better for patients whose first surgery was a complete repair compared to those who underwent palliation or revision, HR=0.46.

Patients with Alagille syndrome had a hazard ratio for mortality of 3.9 compared to children who did not have chromosomal abnormalities. Multivariate analysis showed that both the initial type of surgery and chromosomal abnormalities were associated with worse survival, Bauser-Heaton reported. Unifocalization to a shunt carried a hazard ratio of 2.5, deletion of chromosome 22q11 a hazard ratio of 2.8, and Alagille syndrome or other chromosomal abnormality had a hazard ratio of 6.2.

"Surgical skill is a large component of these results," said Bauser-Heaton, who is now assistant professor of cardiology at Emory University School of Medicine. "But even if you are not as skilled technically, following this kind of programmatic approach may give better survival and lower RV pressure, which is what we are looking for in these surgeries."

Another abstract presentation on Monday showed good outcomes for heart-lung transplantation in adults with congenital heart disease compared to pediatric transplantation. Earlier studies showed worse survival in pediatric heart-lung transplantation in the setting of congenital heart disease compared to transplantations for idiopathic pulmonary arterial hypertension.

"We find no difference in post heart-lung transplant survival in adult congenital heart disease patients compared to patients with a diagnosis of idiopathic pulmonary arterial hypertension," said lead author Asama M. Kahn, MD, a pediatric cardiology fellow at the Ann & Robert H. Lurie Children's Hospital of Chicago. "The adult congenital heart disease population continues to expand and diversify as more pediatric patients survive into adulthood. We must exercise caution when extrapolating pediatric data to adult congenital heart disease patients." ▼

LATE BREAKING continued from page 1

identical for bilateral and single grafts among the 3,102 patients randomized to the two treatment approaches. The only statistically significant differences were increased sternal wound complications and reconstructions in the bilateral graft group.

"We were surprised to see no real differences in outcomes at five years," Taggart said. "We attribute this to both groups being very good about following guidelines for aspirin, statins, beta blockers and ACE inhibitors or angiotensin receptor blockers."

FUTURE

The use of fractional flow reserve (FFR) testing does not improve clinical outcomes, according to results from the Functional Testing Underlying Revascularization (FUTURE) trial, which was halted early due to excess mortality in the FFR-guided arm compared to the angiographically guided arm.

"FFR is routinely used to guide (percutaneous coronary intervention) in patients with multi-vessel disease, but we didn't know whether we can use FFR to choose between different treatment strategies — PCI, CABG or medical treatment," said lead author Gilles Rioufol, MD, PhD, Hospices Civils de Lyon in France. "At least in the short term, FFR did not help."

Researchers randomized patients with multi-vessel disease to either FFR-guided or angio-guided selection of PCI, CABG or medical treatment. Patients in the open-label study were recruited at 31 centers across France. The goal was to detect a 30 percent relative risk reduction for major adverse cardiac events at one year in the FFR group.

At one year, the data safety monitoring board found a doubling of mortality — 4 percent versus 2 percent — in the FFR group compared to the angio group and recommended halting the study. Seventy-two percent of deaths were attributed to cardiovascular causes.

Trial sponsors and the steering committee stopped recruitment at 936 patients. All of the patients will be followed for at least a year, Rioufol said. The lack of success after more than half of the expected population has been recruited suggests that it would be futile to continue the trial, he said.

PIONEER AF-PCI

Low-dose rivaroxaban plus dual antiplatelet therapy (DAPT) is more effective in preventing bleeding in patients with atrial fibrillation who are undergoing intracoronary stenting compared to conventional triple therapy of a vitamin K antagonist plus a $P2Y_{12}$ inhibitor plus aspirin.

These results come from 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), and were published simultaneously in *The New England Journal of Medicine* on Monday.

Researchers randomized 2,100 patents to one of three regimens: rivaroxaban 15 mg plus a $P2Y_{12}$ inhibitor for 12 months; a "baby" dose of 2.5 mg rivaroxaban plus a $P2Y_{12}$ inhibitor and aspirin for one, six or 12 months at the treating physician's discretion; or a vitamin K antagonist plus a $P2Y_{12}$ inhibitor plus aspirin for one, six or 12 months at the physician's discretion. No patients were lost to follow-up.

C. Michael Gibson, MD

"The take-home message is that we saw very consistent bleeding reductions with both doses of rivaroxaban across all groups in the trial," said lead author C. Michael Gibson, MD, of Beth Israel Deaconess Medical Center in Boston. "You only have to treat 10 or 11 patients to avoid a significant bleed using either of these two strategies. And you only need to treat 10 to 15 patients to prevent a hospitalization."

GARY

One-year results from the German Aortic Valve Registry (GARY) indicate nearly double the mortality from transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) for patients at intermediate surgical risk with severe symptomatic aortic valve stenosis.

Researchers screened 49,660 patients enrolled in GARY between January 2011 and December 2013, and identified 5,997 patients who underwent isolated TAVI or SAVR. The final cohort included 1,596 SAVR patients and 4,101 TAVI patients at intermediate risk.

TAVI patients were significantly sicker than SAVR patients, said lead author Nicolas Werner, of Klinikum Ludwigshafen in Ludwigshafen, Germany. TAVI patients were older, predominately female, had higher symptom scores and more severe medical conditions.

The strongest predictors for TAVI were low calcium score, prior cardiac decompensation, coronary artery disease, pulmonary hypertension, lack of prior CABG and tricuspid valve regurgitation.

"TAVI is the recommended option for high-risk patients who are inoperable or at high surgical risk," Werner said. "But in this real-world population of intermediate-risk patients, we see clearly significant differences in all-cause mortality in favor of surgery. In clinical reality, TAVI patients were at significantly higher risk compared to SAVR patients." ▼

Peripheral artery disease in ACS patients raises three-year risk of adverse limb events

PATIENTS WITH PERIPHERAL ARTERY disease (PAD) and recent acute coronary syndrome (ACS) have significantly increased risk of major adverse limb events at three years, according to a study presented on Monday at Scientific Sessions.

Since few treatments are available specifically to prevent limb events, these results suggest that future trials should focus on this area to help prevent adverse outcomes, said Christina L. Fanola, MD, of Brigham and Women's Hospital and Harvard Medical School in Boston, who led the study.

The study was a post-hoc analysis of the SOLID-TIMI 52 randomized trial, which included 13,026 patients with recent (≤30 days) ACS and compared darapladib with placebo. At baseline, 1,088 of the trial patients (8.4 percent) had known concomitant PAD, while 11,921 (91.6 percent) had no known PAD. The median follow-up period was 2.5 years.

In PAD patients, major adverse limb events (MALE) were more frequent at three years than in patients with no known PAD (14 percent vs. 2.1 percent; HR, 6.4 [95 percent CI, 5.2-7.9]; p<0.001). Peripheral revascularization was required in 11.7 percent of PAD patients at three years and in 1.2 percent of patients with no PAD (HR, 9.8 [95 percent CI, 7.5-12.9]; p<0.001).

Acute limb ischemia occurred in 1.7 percent of PAD patients at three years compared with 0.3 percent of patients with no PAD (HR, 5.4 [95 percent CI, 2.7-10.6); p<0.001). Chronic critical limb ischemia was also more frequent in PAD patients, at 3.8 percent vs. 0.8 percent (HR, 5.9 [95 percent CI, 3.8-9.0]; p<0.001). New or worsening PAD occurred in 13.3 percent of those with PAD at baseline, and in 1.8 percent of those with no PAD at baseline (HR, 6.9 [95 percent CI, 5.4-8.9]; p<0.001).

After adjustment for the treatment arm of the trial, type of ACS, time from qualifying event and various baseline clinical factors, the increased risk in PAD patients remained clear. The study drug darapladib did not reduce MALE or any other outcome in PAD patients.

Fanola said the increased risk in PAD patients was not surprising, though the magnitude of the increase and the fact that the risk rose early in the study and remained elevated throughout follow-up did surprise the researchers. However, she noted that the post-hoc nature of the analysis limits its interpretation. Future clinical trials should consider adding adverse limb events to the adjudicated endpoints in order to obtain prospective data, she said.

Because PAD is relatively common in ACS patients, "clinicians should consider following these patients closely not only for recurrent cardiac ischemia, but also for progressive peripheral artery disease that may lead to limb ischemic events, a need for revascularization or even amputation," Fanola said. ▼

AVR associated with improved survival in moderate to severe AS

The results of a study presented Monday at Scientific Sessions suggest that aortic valve replacement (AVR) improves survival regardless of gradient, flow or aortic valve area (AVA) in moderate to severe aortic stenosis (AS).

Yujing Mo, MD, of Guangdong Cardiovascular Institute in China, reported findings from the study, which was conducted at the Cardiovascular Center, OLV-Clinic Aalst in Belgium.

The study population consisted of 506 consecutive patients (age 75±9y, 57.5 percent males) with moderate to severe aortic stenosis (AVA ≤ 1.5 cm^2) and preserved left ventricular ejection fraction (≥50 percent) defined at heart catheterization. Baseline Doppler-echocardiography data were available in 327 (65 percent) subjects. To account for measurement errors, echocardiography Doppler-derived stroke volume (SV) was replaced by the LVOT-independent SV calculated during the heart catheterization. Follow-up of all-cause death was obtained after a median of 6.6 years (IQR 3.4y-8.8y).

At catheterization, 62 (12 percent) patients had moderate AS (MAS) (AVA 1.20± 0.13 cm^2) while 119 (24 percent) and 325 (64 percent) had severe AS (AVA 0.67±0.18 cm^2, p<0.001) with a low (<40 mm Hg) (LG-SAS) and a high mean pressure gradient (HG-SAS), respectively. Significantly fewer patients with MAS and LG-SAS than HG-SAS underwent AVR (58.1 percent versus 59.7 percent versus 83.1 percent, p<0.001).

AVR was independently associated with a decrease in all-cause mortality in the severe AS groups (p<0.05) regardless of the PG, SV or AVA, and it tended to predict mortality in patients with MAS (p=0.075). In contrast, gradient pattern, SV or AVA were not predictors.

Yujing Mo, MD

Using Doppler-echocardiography, 271 patients had severe AS (AVA 0.69±0.17 cm^2, mean gradient 50±16 mm Hg). Post AVA recalculation, 109 (40 percent) patients showed AVA > 1.0 cm^2 while 162 (60 percent) patients remained with AVA ≤ 1.0 cm^2. During follow-up, significantly lower all-cause mortality was observed in the reclassified MAS group than in the persistent SAS group (p<0.05). However, AVR was associated with improved survival in both groups.

"In low-gradient severe AS, as well as classical high-gradient severe AS, we found that aortic valve replacement improves survival regardless of gradient, flow or aortic valve area," Mo said. "We believe this advocates for early AVR, but prospective and multicenter trials are needed to define the optimum therapeutic approach between early aortic valve replacement versus a watchful waiting strategy in these patients." ▼

Cardiosphere-derived cell exosomes help macrophages protect against ischemic injury

Cardiosphere-derived cell (CDC) exosomes are the primary contributor to CDC-mediated protection against ischemic injury, according to research presented Monday at Scientific Sessions.

The exosomes enhance macrophage capacity to scavenge cellular debris and reduce pro-inflammatory protein expression in cardiac macrophages, said Geoffrey de Couto, PhD, a project scientist at the Cedars-Sinai Heart Institute in Los Angeles, who led the new study.

"We believe these data reveal key insights into how CDCs and CDC exosomes [CDCexo] confer their functional effect *in vivo*," he added.

Previous research showed that CDCs are cardioprotective against ischemia/reperfusion injury when delivered within 30 minutes of reperfusion. Although CDCexo-mediated polarization of macrophages was thought to be behind this protection, the mechanism behind that effect was unclear.

In the new animal study, 45 minutes of ischemia were followed by 20 minutes of reperfusion. The subjects were then randomized to receive intracoronary infusion of either CDCexo or inert fibroblast exosomes (the control group).

After two days, the hearts that were treated with CDCexo showed significantly reduced infarct mass compared to those treated with the inert fibroblast exosomes (FBexo; 6.38 percent vs. 13.32 percent; p<0.05). The CDCexo-treated hearts also showed attenuated expression of pro-inflammatory genes, including *Nos2*, *Tnf* and *Il6*.

The researchers then tested the effect of CDCexo on macrophage efferocytosis, the process by which macrophages scavenge cellular debris from dying cells. Bone marrow-derived macrophages were primed toward M1, M2, M_{FBexo}, or M_{CDCexo}, and Dil-stained ventricular myocytes were UV-irradiated to produce apoptotic cells, which were were placed in culture with the various macrophages.

The M_{CDCexo} macrophages showed markedly enhanced uptake of the cell debris compared to the other macrophages (M1: 3.07 percent; M2: 18.4 percent; M_{FBexo}: 15.73 precent; M_{CDCexo}: 24.30 percent; p<0.05).

The enhanced efferocytosis was also tested *in vivo.* Dil-labeled M_{CDCexo} or M_{FBexo} macrophages were injected into the border zone. After two hours, the investigators isolated the cardiac macrophages and found that M_{CDCexo} macrophages had significantly greater uptake of eGFP than M_{FBexo} macrophages, confirming that the enhanced efferocytosis does occur *in vivo*.

The specific mechanism involved in the enhanced efferocytosis remains under investigation.

"Based on our current work, it appears that a specific payload within exosomes, which comprises an array of distinct small RNAs (e.g., microRNA, small non-coding RNA, etc.), targets the engulfment pathway," de Couto said. ▼

ONE BRAVE IDEA continued from page 1

a few months, 349 researchers from 22 countries submitted applications. MacRae was announced as the winner in October.

His premise is that all cases of coronary heart disease look similar once diagnosed, but every patient gets there in a different way. So he's searching for the earliest possible markers of the disease and he's looking for them in places where researchers traditionally haven't looked. That includes things like the shape of people's faces, the air they breathe and, of course, the food they eat.

"We've known for a long time that the disease can be detected in some forms in your teens," MacRae said. "Using biology and technology, we want to be able to detect the different forms before they converge."

Everything about the One Brave Idea project is unusual for the world of medical research — from the timeline that took it from concept-to-reality to the amount of funding for a single project. It's the largest single research investment in the AHA's 92-year history. Those unusual steps are part of the genesis of the project. That is, the brave idea behind the project was aiming to do things differently.

MacRae provided an overview of his plans Sunday. On Monday, he took part in a panel discussion with several members of the group overseeing his work: Robert Harrington, MD, FAHA, FACC, an AHA Board member; Greg Keenan, MD, vice president of medical affairs and U.S. head medical officer of AstraZeneca; and Jessica Mega, MD, MPD, chief medical officer of Verily.

"This is really such a fun journey," Mega said. "It just feels right."

The project will run for five years, with MacRae and his team tapping into the expertise of each of his funding organizations for support. For instance, on the food study, his team member Dr. Laszlo Barbasi, PhD, of Northeastern University in Boston, plans to use AHA resources to expand participation and they will rely on Verily for help translating the findings.

He expects the food study will start Jan. 1, which is when the whole project formally kicks off. He hopes the food study goes nationwide within a year and eventually believes it will expand to other countries.

"We know already that coronary heart disease is a growth abnormality of the blood vessels," he said. "So we're asking: Is there a detectable abnormality in other tissues? Does it change the way in which you interact with your nutrition? How do you distribute your nutrition around your body? How are you actually using the nutrition that comes in? Are there specific nutrients that drive the biology in a particular direction?"

There is one major caveat to this study, and to everything else One Brave Idea undertakes: It might be a dead end.

If early efforts indicate it's not a good use of resources, MacRae and the leadership group are willing to scrap it. This is another example of their new way of doing things, an approach the group often compares to having the culture of a start-up company.

"Traditionally, science takes a long time," Keenan said. "We're already demonstrating a need for speed here. It doesn't mean we're throwing out good methodology. We're just moving more quickly." ▼

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.

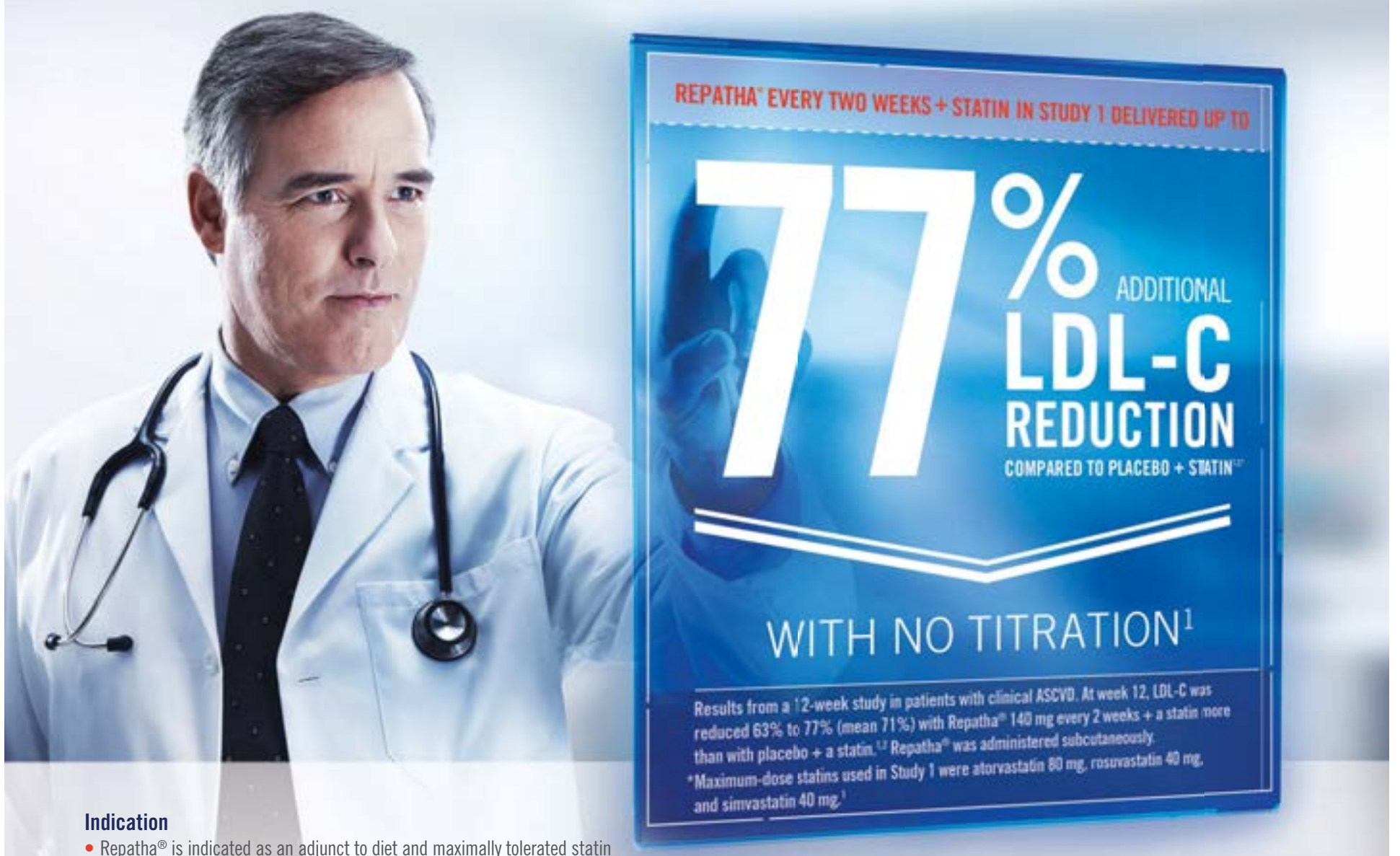
This Brief Summary is based on the REPATHA® Prescribing Information v3, 07/16

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[1]

REPATHA® MAXIMIZE EFFICACY FROM THE START



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.

ASCVD = atherosclerotic cardiovascular disease.

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

AMGEN® Cardiovascular

USA-145-037689 08-16

Repatha® (evolocumab) injection 140 mg/mL

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