

# DailyNews

## ORION trial results suggest potential for twice-yearly dosing with novel RNA interference agent

Inclisiran, a novel RNA interference agent, has the potential to significantly reduce low-density lipoprotein (LDL) cholesterol with two or three injections yearly, according to research presented during Tuesday's Late Breaking Clinical Trials session.

The Inclisiran Inhibits PCSK9 Synthesis by RNA Interference: Planned Interim Analysis of a Multi-center Randomized Controlled Dose-finding (ORION) Trial was one of five studies presented during the session.

Inclisiran shows a 50 percent reduction in LDL cholesterol with one dose and a reduction of 55 to 60 percent with two doses, said ORION lead author Kausik Ray, MD, MPhil, from Imperial College London in the United Kingdom. Inclisiran is a PCSK9 inhibitor with a four- to six-month duration of effect.

"The efficacy, safety and dosing profile we see here is likely to produce lasting reductions in LDL cholesterol," Ray said.



Kausik Ray, MD, MPhil

"Inclisiran has the potential to improve adherence and very favorably impact cardiovascular outcomes."

Antibody inhibition of PCSK9 can significantly reduce LDL cholesterol, but

requires injections every two to four weeks. The administrative and financial burden invites next-generation agents that are easier to administer, Ray said.

ORION researchers enrolled 501 patients into two study arms and 497 completed the study. The single-dose arm compared 200 mg, 300 mg and 500 mg doses of inclisiran to placebo. The two-dose arm compared two 100 mg, 200 mg and 300 mg doses of inclisiran to placebo.

The primary endpoint was the change in LDL cholesterol at 180 days. Secondary endpoints included LDL cholesterol at 90 days, PCSK9 levels, safety and tolerability. The data presented Tuesday came from a planned, 90-day interim analysis.

Treatment emergent adverse events were similar across all groups, Ray reported. The safety profile was very good. Nearly 6 percent of patients in the drug arms reported myalgia, but reports were not dose-related.

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## NON-CODING RNAs NEWEST FRONTIER IN CARDIOVASCULAR DISEASE

What has long been thought of as

"junk" in the human genome is actually a trove of potential therapeutic targets, according to Stefanie Dimmeler, PhD, who delivered the Paul Dudley White International Lecture on Tuesday.

Dimmeler, who is professor and director of the Institute of Cardiovascular Regeneration at the University of Frankfurt in Germany, said most of the RNAs coded within the genome play key roles in epigenetic regulation, transcriptional regulation, epithelial activity, atherosclerosis and much more.

"Humans have a very small number of genes, only about 23,000," she said. "About 3 percent of our DNA is transcribed into proteins and about 80 percent is transcribed into RNA. These noncoding RNAs appear to exert very precise controlling functions throughout the cardiovascular system and the rest of the body."

There are two basic types of noncoding RNAs. Small noncoding RNA have fewer than 200 nucleotides and are widely known as microRNAs (miRNAs). Long noncoding RNAs (lncRNAs) have more than 200 nucleotides.

There are more lncRNAs known than miRNAs — 30,000 compared to 2,000 — but more is known about miRNAs, Dimmeler said.

Most miRNAs are involved in translational repression and degradation of messenger RNA (mRNA), she explained. A single miRNA can target hundreds of mRNAs to exert broad effects on cell death, fibrosis, epicardial repair, angiogenesis, cardiomyocyte proliferation, cardiac reprogramming, endothelial function and more.

One of the most-studied miRNA, miR-92a, regulates angiogenesis and

NON-CODING RNAs continued on page 13



Stefanie Dimmeler, PhD

## Study links shorter telomere length to cardiovascular disease, hypertension, cancer

ABDULLAH SAID, A PhD STUDENT

in the department of cardiology, University Medical Center, Groningen in the Netherlands, presented data Tuesday at Scientific Sessions that showed support for a causal association between genetically determined shorter telomere length with overall cardiovascular disease, hypertension and common cancer development.

Previous research has shown an association between shorter telomere length and various age-associated cardiovascular conditions including coronary heart disease and heart failure, as well as high-grade glioma and other cancers.

"We believe that we add another piece of evidence that telomeres play a role in the development of cardiovascular and other age-associated disease and might not just be an innocent bystander or marker of biological ageing," Said reported. "Our data suggest common genetic variants explaining a proportion of shorter telomere length also are associated with an increased risk of developing cardiovascular disease and cancer."

Said and colleagues performed a Mendelian randomization with genetic risk score analyses using seven single nucleotide polymorphisms previously associated with telomere length. They studied whether telomere length was associated with cardiovascular disease, overall cancer or mortality in individuals from the UK Biobank population. The UK Biobank study is a United Kingdom-based prospective cohort study of 502,664 adults 40-70 years of age. Genetic data were available for 152,249 patients, of which 134,773 were eligible for statistical analyses. Patients in the analyses were 39-73 years of age.

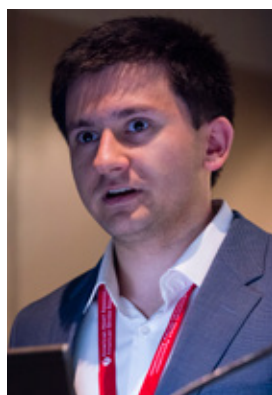
All analyses were adjusted for age, sex and principal components. The analyzed genetic variants associated with a shorter telomere length, per standard deviation shorter telomere

length, were associated with a 14 percent increased risk for overall cardiovascular disease (95 percent CI, 5 percent-23 percent;  $p=0.004$ ), a 16 percent increased risk for hypertension (95 percent CI, 7 percent-25 percent;  $p=0.002$ ) and a 37 percent increase risk for overall cancer (95 percent CI, 29 percent-45 percent;  $p<0.001$ ).

Said noted that the effect sizes in the study are small, making the clinical implications of the study limited.

"We required more than 130,000 individuals to draw our conclusions," Said explained. "However, they do provide us novel insights into biology,

and they enhance our understanding of the association of telomere length and the development of cardiovascular diseases and cancer as well. We believe our findings are indeed valuable to research in the fields of telomere length, cardiovascular disease and cancer." ▼



Abdullah Said



## 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](http://scientificsessions.org).

**9-10:15 a.m.**  
Trending Topics in Clinical Science  
Great Hall A

**9-10:15 a.m.**  
Trending Topics in Population Science  
Rivergate

**10:45 a.m.-Noon**  
Late-Breaking Clinical Trials: Guiding the Momentum to Effect HF Outcomes – Ironing Out the Wrinkles  
Great Hall A

**10:45-11:45 a.m.**  
Trending Topics in Basic Science  
Rivergate

### HEARTY HUMOR by Jonny Hawkins



"I was worried I may have strained my karate artery."

## CLAIMING CME/CE AT SCIENTIFIC SESSIONS

Healthcare professionals attending Scientific Sessions can claim and print CME/CE certificates when they have attended all of the sessions for the meeting.

- Sign in at [learn.heart.org](http://learn.heart.org) using your Lifelong Learning Center username and password. You can create an account if you don't have one.
- Find the activity you are registered for under the "Activities in Progress" tab in the left hand navigation.
- Resume the activity.
- Complete the evaluation.
- Claim your credit(s).

International attendees can obtain their attendance verification certificate at the registration center. For a full list of conference accreditation statements and credit hours, visit [scientificsessions.org](http://scientificsessions.org).

## ATTENDEE FEEDBACK

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

## HIGHLIGHTS FROM THE PROGRAM CHAIR

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

### It's the final day of Scientific

Sessions 2016 — without a doubt one of the best AHA meetings ever. And I'm happy to report that some of the best programming has been saved for last.

We start with a Main Event session, our last Late-Breaking Clinical Trials session: "Guiding the Momentum to Effect HF Outcomes – Ironing Out the Wrinkles" (see description below). Five exceptional trials will be presented:

- "Transcatheter Interatrial Shunt Device Provides Sustained Clinical Benefit at One Year in Patients with Preserved or Mildly Reduced Ejection Fraction: The REDUCE LAP Heart Failure Trial." Will this be the answer for treating HFpEF?
- "ATHENA HF – Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure Trial"
- "Oral Iron Repletion effects ON Oxygen Up Take in Heart Failure (IRONOUT HF)"
- "Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure (EFFECT-HF): A Randomized, Controlled Study"
- "MOMENTUM 3 – Multicenter Study of MagLev Technology in Patients Undergoing Mechanical



Frank W. Sellke, MD, FAHA

Circulatory Support Therapy with HeartMate 3 — Primary Results of the Short Term (6 months) Cohort." This trial has the potential to change how we treat patients with end-stage heart failure.

These and other presentations this week will undoubtedly have long-lasting implications on treating our cardiovascular disease patients. The wide-ranging and cutting-edge clinical, population and basic science presentations are clearly what make AHA Scientific Sessions the premier cardiovascular meeting in the world.

cardiovascular meeting in the world.

Thank you, AHA staff and the Committee on Scientific Sessions Program, for your skills and hard work putting this meeting together.

Now, I turn over the Committee on Scientific Sessions Program chairmanship to the most capable Eric D. Peterson, MD, MPH, FAHA. I'm sure he'll do an exemplary job and improve the quality of the meeting yet again.

See you next year at Scientific Sessions 2017, Nov. 11-15, in Anaheim, California. ▼

### Late-Breaking Clinical Trials — LBCT.04

**10:45 a.m.-Noon Wednesday | Great Hall A**

Guiding the Momentum to Effect HF Outcomes – Ironing Out the Wrinkles

TRIAL	DESCRIPTION
Transcatheter Interatrial Shunt Device Provides Sustained Clinical Benefit at One Year in Patients with Preserved or Mildly Reduced Ejection Fraction: The REDUCE LAP Heart Failure Trial	The trial assessed the impact of the IASD in patients with HFpEF.
Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure (ATHENA-HF) Trial	The trial assessed the use of high-dose spironolactone vs. standard of care in patients with acute heart failure.
Oral Iron Repletion effects ON Oxygen Up Take in Heart Failure (IRONOUT HF)	The study of oral iron supplementation in patients with heart failure will evaluate improvement in functional capacity in these patients.
Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure (EFFECT-HF): A Randomized, Controlled Study	Multicenter, prospective, randomized, two-arm study assessed the impact of ferric carboxymaltose on exercise capacity in chronic heart failure patients with iron deficiency.
Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) – Primary Results of the Short Term (6 months) Cohort	The innovative trial compared HeartMate 3 to HeartMate II at 6 months for stroke-free (MRS >3) survival without pump replacement.

## WALKING CHALLENGE

Congratulations, Walking Challenge participants. You logged millions of steps at Scientific Sessions 2016. The top stepper is Shen Xiao, who logged 80,517 steps in the annual competition. Batoul El-Sayegh finished in second place with 74,737 steps, and Alex Junia came in third by logging 71,707 steps. Congratulations to the winners and thanks to all who participated!





## Neurologist, Framingham study pioneer delivers Distinguished Scientist Lecture

**T**he Framingham Heart Study has led not only to a better understanding of cardiovascular disease and its risk factors, but has provided valuable insight into the risk factors for stroke and dementia, a renowned neurologist said Tuesday.

Philip A. Wolf, MD, FAHA, made the comments during his Distinguished Scientist Lecture. The study, which launched in 1948, has followed multiple generations of residents from Framingham, Massachusetts.

“Mortality from stroke had been declining steadily at about 1 percent a year until the late 1970s, when (the decline) accelerated to about 7 percent per year, perhaps as a reflection of the advances in detection and attention to high blood pressure and other preventive measures,” said Wolf, the first neurologist to join the Framingham research team, in 1967, and the study’s principal investigator in 1989-2014.

Wolf credits the many studies and volumes of data generated from the Framingham population for much of what we know today about the risk factors for stroke, noting that the Framingham risk profile has been used for more than 25 years to estimate the probability of stroke.



Philip A. Wolf, MD, FAHA

Wolf was co-author of a landmark paper published in *JAMA* in 1970 that was among the first to clearly establish blood pressure as a risk factor for stroke.

“We showed that, as blood pressure increases, the cumulative risk of stroke increases,” he said. “That was important because it made it clear that prevention and the mediation of risk factors was the goal. Today, we believe we have the tools to prevent up to 75 percent of strokes.”

Wolf cited statistics from the Centers for Disease Control and Prevention, which estimates the number of initial strokes per year in the United States

at 610,000 — a number that could reach 1 million by 2050, according to an estimate from the National Institutes of Health. The risk of stroke or dementia is one in two for women and one in three for men, said Wolf, highlighting the need for more focused efforts on prevention and patient education.

Research has shown that many of the risk factors for stroke — hypertension, obesity, smoking, diabetes and physical inactivity — are also risk factors for cognitive decline and dementia.

“In a 1993 study, for example, we found that cognitive functioning was strikingly related to both age and level of systolic blood pressure,” Wolf said. “While early on in Framingham we focused a lot of attention on severe dementia, in more recent years that focus has shifted to detecting mild cognitive impairment and identifying people earlier in life who may be at risk and who may benefit from preventive efforts.”

In 1999, *The Washington Post* called the Framingham Heart Study one of the most important epidemiological studies and one of the top five medical accomplishments of the 20th century. ▼

## MEMBER SPOTLIGHT

**Tiny Jaarsma, RH, PhD, FAHA**

*Professor, University of Linköping, Sweden*



**How long have you been an AHA/ASA Professional Member?**

I joined the AHA in 1993 when I was a master's student in cardiovascular nursing in the Netherlands, just after my first AHA conference. During my career toward professorship, I continued my AHA membership to become a Premium Professional Member.

**Why did you join?**

I joined the AHA because I wanted to collaborate with scientists in my field, and I knew that the AHA unites a large number of excellent and dedicated nurse researchers in the area of cardiovascular care. At that time, I also was working as a staff member in the Netherlands Heart Foundation. I recognized that the AHA was a real example of how to work together with volunteers, professionals and scientists to improve care for cardiac patients.

**Are you involved in AHA councils?**

I am a fellow member of the Council on Cardiovascular and Stroke Nursing (CVSN) and of the Council on Quality of Care and Outcomes Research (QCOR). Our regional affiliate membership is a little different than members from the U.S. But even in my previous homeland, the Netherlands, and at my current location in Sweden, I am involved in national activities, either as a reviewer or on the advisory board for national grants or activities. I also try to be instrumental with the Council on Cardiovascular and Stroke Nursing and serve as a bridge to the members of the Council on Cardiovascular Nursing and allied professionals of the European Society of Cardiology whenever I can.

**What do you enjoy most about these roles?**

I feel at home in the AHA Council on Cardiovascular and Stroke Nursing. Working with colleagues in this council is always inspirational. A lot of my current research collaborations started at Scientific Sessions. I also enjoy bringing new colleagues or doctoral students to the AHA and introducing them to the activities in the councils. They are always very impressed.

**How else are you involved with the AHA?**

I was very honored to receive the Cardiovascular and Stroke Nursing Councils' Katharine A. Lembright Award in 2013. I have also been a member of a writing group of two scientific statements of the AHA that address sexual counseling and sexual activity in cardiac patients.

**Why is membership valuable to you?**

AHA membership gives me the opportunity to establish collaboration with an international perspective and to find mentors and mentees. For our European associations, the AHA is an inspiring example on how, for example, to mentor junior colleagues, how to support research careers or how to think really multidisciplinary on an equal level.

**What message would you convey to your colleagues about being an AHA member?**

I would ask them why they are not members yet and tell them to become a member as soon as possible. The AHA can really help you advance your career — and you meet great people. ▼

## CAREER PROGRESSION: Amy W. Pollak, MD

**Amy W. Pollak has put her heart and soul into raising awareness of women's heart disease and peripheral artery disease.**

She chairs the Go Red For Women Luncheon for the American Heart Association's First Coast Market in Jacksonville, Florida and the Peripheral Vascular Disease Council's Peripheral Arterial Disease in Women

working group, collaborating on an online continuing medical education program to increase provider awareness about PAD.

“It's been rewarding to do community outreach events and partner with other individuals who are committed to increasing awareness about women's heart disease and stroke,” said Pollak, who directs the Mayo Clinic Jacksonville's Women's Heart Clinic and delivers dozens of talks throughout the year.

“One of the things I love about the AHA is the chance to collaborate with colleagues in many different subspecialties, including cardiology, radiology, vascular surgery and vascular medicine, with the shared goal of wanting to improve patient education, patient outcomes and do collaborative research,” she said.

Pollak, who has long wanted to be a doctor, said one moment catalyzed her decision to pursue cardiology. On the day in 1999 that she earned her undergraduate degree from the University of Virginia in Charlottesville, her grandmother had a heart attack. She had reported symptoms of atypical angina to her primary care doctor, but the signs were ignored.



**The AHA uses the tagline “Life Is Why” to answer the question: Why do we do our lifesaving work? We asked Pollak the same question:**

“**Family is why.** My grandmother had a heart attack the day I graduated from college. This made a profound impact on my decision to be a cardiologist and focus on women's heart disease. Living heart-healthy lives and having symptoms of possible heart disease evaluated and treated are incredibly important steps to take so that we can all live longer, healthier lives with our loved ones.”



“That opened my eyes to how much work there is to be done to prevent heart attack and stroke in women, as well the importance of educating patients and providers on the symptoms of heart disease for women,” said Pollak, who has been an AHA Premium Professional Member since 2012.

“Cardiology is a field where there are always new studies, and opportunities to answer important clinical questions and collaborate with colleagues to help improve patients' lives,” she said.

Following a four-year cardiology fellowship at the University of Virginia that included advanced cardiac imaging training, Pollak joined the staff there before moving to the Mayo Clinic in Rochester, Minnesota. Two years ago, she transferred to the clinic in Jacksonville, where she performs cardiac imaging with magnetic resonance imaging, computerized tomography scans and echocardiograms.

Living in Jacksonville has given her ample opportunity to get involved with the local AHA chapter, as well as with the AHA nationally.

“The AHA provides a really fertile ground for collaboration with colleagues,

particularly in terms of developing innovative clinical practices, educational programs and collaborative research initiatives,” she said. “The career mentorship through colleagues I've met through AHA and the PVD Council has been invaluable in shaping my career progression. In particular, Dr. Alan Hirsch, Dr. Martha Gulati and Dr. Jere Fletcher have been wonderful mentors. The AHA connects us all in the work that we do through the PVD Council and collaborating councils.”

Pollak thrives on the diversity of her job and finds the combination of patient care, education, research and patient advocacy rewarding. In the coming years, she wants to continue building on the progress she's already made.

“I want to continue to develop some of my research interests of women with microvascular angina and also with peripheral artery disease,” she said. “I also want to continue to develop innovative practice patterns for our outpatient cardiology practice at the Mayo Clinic in Jacksonville, and be a speaker who can be effective at engaging CME talks.” ▼



# Study: Cardiogenic shock AMI mortality has decreased when adjusted for changing PCI population

**R**isk-adjusted, in-hospital mortality has declined in recent years among patients with cardiogenic shock after acute myocardial infarction (CS-AMI) when taking into account an increase in the number of extreme-risk patients undergoing percutaneous coronary intervention (PCI), according to the results of a retrospective study presented Tuesday at Scientific Sessions.

"Presentation after cardiac arrest is an extreme risk marker in patients with CS-AMI and some mechanism to account for this group is essential to accurately assess mortality trends in this population," said Udhay Krishnan, MD, of the Division of Cardiology at Weill Cornell Medical College, New York Presbyterian

Hospital-Cornell Medical Center in New York. "These results help reconcile the discordance between studies which showed a decline in mortality for the entire CS-AMI population and studies which showed a null effect on mortality for the PCI-only population."

According to Krishnan, many observational studies have reported a decline in mortality in patients with CS-AMI, a trend attributed to the increasing use of early revascularization. However, other contemporary studies that have focused specifically on patients with cardiogenic shock treated with early PCI have found no improvement in mortality over time.

Krishnan and colleagues hypothesized that sicker patients with CS-AMI with more

comorbidities and high clinical acuity were now presenting to the catheterization lab when compared with earlier years, and that certain extreme risk traits may not be properly adjusted for using current mortality models.

With this study, the researchers looked at 59,118 patients with CS-AMI who underwent PCI within 24 hours of hospitalization taken from the 2005-2012 Nationwide Inpatient Sample database. In an unadjusted analysis, there was no change in in-hospital mortality between 2005-2006 and 2011-2012 (30 percent versus 27.8 percent, respectively). There was an increase in the proportion of patients with three or more Elixhauser comorbidities (28.5 percent versus 51.5 percent, respectively) and

comorbidity scores of 5 or greater (37.2 percent versus 48.2 percent, respectively).

To better characterize what they considered "extreme risk" patients, such as those with higher clinical acuity on admission, the researchers examined a subgroup of patients whose presentation within the first 24 hours was complicated by cardiac arrest or the need for mechanical ventilation. They found that the population of patients that suffered from cardiac arrest or needed intubation on the first hospital day increased from 27.8 percent in 2005-2006 to 42.6 percent in 2011-2012. In a multivariable analysis that adjusted for these factors as well as clinical comorbidities, mortality rates in 2011-2012 had decreased significantly compared with 2005-2006 (OR=0.75; 95 percent CI, 0.65-0.85;  $p<.001$ ).

"Likely, as a result of broadened use of PCI, growing STEMI systems of care, improved pre-hospital survival and evolving practice guidelines that promote early revascularization, more patients with severe CS complicated by cardiac arrest are being selected for early PCI when compared to previous years," Krishnan said. "This 'migration' of extreme-risk patients into the cath lab over the years likely neutralizes much of the mortality benefit attributable to advances in contemporary invasive management when we restrict our viewpoint to a PCI-only sample."

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First Year in Review**

Monday, November 14, 2016,  
9:00 a.m. – 10:15 a.m.  
Room 345

## 2016 Poster Winners

Early career work is extremely important to the American Heart Association. The future of cardiovascular science is in the hands of these healthcare professionals and scientists, and the poster sessions include many examples of the important work being done by this group. Here's a look at the poster winners from Scientific Sessions 2016 — all of whom are early career professionals:

### Basic Science

Makoto Ariyoshi  
*Age Related Cardiac Dysfunction and Pancreatic-cell Function in Diabetes Were Improved by P53 Inhibition Through Parkin-mediated Mitophagy*



### Clinical Science

Jonathan Kopechek  
*Targeted Delivery of AntimiR-23a Using Ultrasound and Microbubbles Suppresses Cardiac Hypertrophy and Improves Cardiac Function In Vivo*



### Population Science

Brian O'Hartaigh  
*Achievement of Target Systolic Blood Pressure for Lowering the Risk of Major Adverse Cardiovascular Events: From the Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial*



### Population Science

Reshmy Jayaraman  
*Cardiac Arrest in Sports versus Sedentary Settings in Young Patients*



### Special Focus

Amit Shah  
*Association of Posttraumatic Stress Disorder with Repolarization Heterogeneity in Veteran Twins*



No Purchase Necessary. The giveaway is open to U.S. residents who complete two blood pressure monitoring readings at booth #2003 between Sunday, November 13 and Tuesday, November 15th at 3:30 p.m. The Prize consists of one (1) A&D home blood pressure monitor with a total approximate retail value of \$74.99. Three (3) prizes will be awarded to the Prize Winners. For full official rules, visit [www.hekahealth.com/aha-sessions-giveaway](http://www.hekahealth.com/aha-sessions-giveaway).



# SWEDEHEART: Recurrent MI twice as likely in non-culprit lesions

The risk of recurrent myocardial infarction (MI) originating from an untreated lesion — or non-culprit lesion — was more than twice as high as the risk of reinfarction from a previously treated lesion among patients with MI who underwent percutaneous coronary intervention (PCI), according to results of the SWEDEHEART study presented Tuesday at Scientific Sessions.

Despite improvements in the care of patients with MI and a reduced mortality in recent years, one in five patients in unselected MI cohorts experience a new ischemic event — recurrent MI, stroke or death — within the first year after an MI, according to researcher Christoph Varenhorst, MD, PhD, of Uppsala Clinical Research Center and the Department of Medical Sciences, Cardiology, at Uppsala University in Sweden.

“A better understanding of long-term disease progression and whether reinfarctions occur in previously treated (stented) lesions or in new or progressive lesions may have an impact on decisions on type and duration of medical treatment after an initial MI,” Varenhorst said in an interview prior to Scientific Sessions.

Varenhorst and colleagues conducted a prospective cohort study in 99,546 patients with first MI enrolled in the Swedish Web-

system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) between January 2006 and December 2014. A culprit lesion was identified in 41,789 patients who underwent angiography. Reinfarction occurred in 3,603 patients, 597 originated from the culprit lesion and 1,193 originated from a non-culprit lesion.

The cumulative event probability for reinfarction within eight years related to a



Christoph Varenhorst, MD, PhD

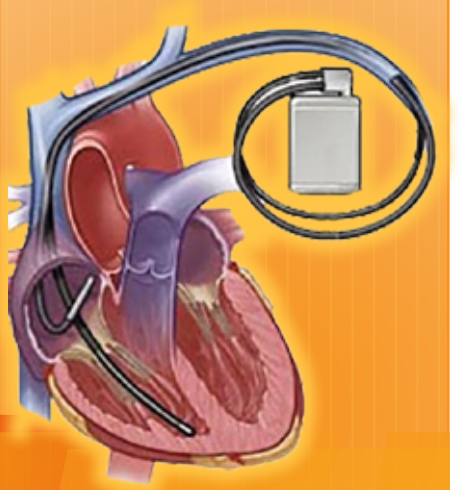
culprit lesion was 0.03 compared with 0.06 for a non-culprit lesion.

At index infarction, patients with subsequent culprit compared with non-culprit reinfarction were similar according to baseline characteristics including gender, age, infarction type, diabetic status, current smoking, hyperlipidemia and hypertension. However, the researchers did find that patients with culprit reinfarction were less likely to

have 3-vessel disease at index (12 percent versus 18 percent) compared to patients with non-culprit reinfarction. Procedural characteristics including number of stents, total stent length and mean stent diameter were similar between the two groups.

“Although patients undergo a successful PCI for the coronary stenosis believed to need revascularization, a substantial proportion of patients experience recurrent MIs that do not originate from the treated lesion,” Varenhorst said. “This insight highlights that secondary prevention post-MI is not only indicated to prevent the patient from stent-related adverse events, but maybe even more to prevent overall coronary disease progression.” ▼

### ICD therapy boosts mortality benefit even after EF improves



During an abstract oral session Tuesday, investigators reported that implantable cardioverter defibrillators (ICD) continue to offer mortality benefit after improvement in ejection fraction (EF) above 35 percent. The relative reduction in mortality for these patients was similar to patients whose EF remained 35 percent or less. However, patients' mortality risk with repeat EF greater than 35 percent was lower.

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## PARADIGM-HF: Sacubitril/valsartan reduced first, total events

### TREATING HEART FAILURE PATIENTS

with a combination of sacubitril/valsartan reduced both time to the first occurrence of heart failure hospitalization or cardiovascular death and the total number of events compared with

enalapril, according to results from the PARADIGM-HF trial presented Tuesday at Scientific Sessions.

Ulrik M. Mogensen, MD, PhD, of BHF Cardiovascular Research Centre at the University of Glasgow in the United Kingdom, said the results illustrate “that there was no loss of treatment efficacy and that sacubitril/valsartan has a sustained beneficial effect on morbidity and mortality.”

PARADIGM-HF included 4,212 patients with heart failure assigned to enalapril and 4,187 patients assigned to sacubitril/valsartan. The initial analysis included 2,031 first events (836 cardiovascular deaths). During the double-blind follow-up period (median of 27 months), a total of 3,181 cardiovascular deaths and heart failure hospitalizations occurred, including 1,251 cardiovascular deaths, a 57 percent increase.

When recurrent events were analyzed, sacubitril/valsartan compared with enalapril significantly reduced the rate by 21 percent (RR=0.79; 95 percent CI, 0.71-0.87;  $p<0.0001$ ) using a semi-parametric proportional rates model with robust variance estimator, or by 24 percent (RR=0.76; 95 percent CI, 0.67-0.85;  $p<0.0001$ ) using negative binomial regression.

“Because the relative risk reduction was similar for first and recurrent events, the absolute risk reduction was considerably larger when recurrent events were included,” Mogensen said. “The number of first heart failure hospitalizations prevented by treating 1,000 patients with sacubitril/valsartan instead of enalapril was 28, whereas, the total number (first and recurrent) of heart failure hospitalizations prevented was 53.”

According to Mogensen, analyses of recurrent events may give a better description of the total burden of heart failure on patients and healthcare systems, particularly as heart failure hospitalization is often repeated and is associated with poor subsequent survival. In addition, analysis of recurrent events assesses whether the treatment under investigation reduces the risk of second and subsequent outcomes, providing reassurance that there is no loss of treatment efficacy as the disease progresses. ▼



Ulrik M. Mogensen, MD, PhD

## Benzene exposure linked to risk of cardiovascular disease, hyperlipidemia

Exposure to benzene appears to put people at a greater risk for developing cardiovascular disease, according to an abstract presented Tuesday at Scientific Sessions.

Benzene is present in tobacco smoke, automobile exhaust and industrial emissions, and billions of people around the world are exposed to air pollutants like benzene and fine particulate in every breath, according to Wesley Abplanalp, PhD, of the Diabetes and Obesity Center at the University of Louisville in Kentucky.

“Given the rise of cardiovascular disease in regions transitioning into a more industrial environment, one suspects an environmental factor may be contributing to the increase in cardiovascular disease burden,” Abplanalp said. “It is imperative to understand the health effects of pollutants like benzene.”

Abplanalp and colleagues assessed benzene exposure by measuring urinary levels of the benzene metabolite trans,trans-muconic acid (t,t-MA) in 210 participants of the Louisville Healthy Heart Study with moderate to high cardiovascular disease risk. They used generalized linear models to assess any association between benzene exposure and cardiovascular disease injury and risk.

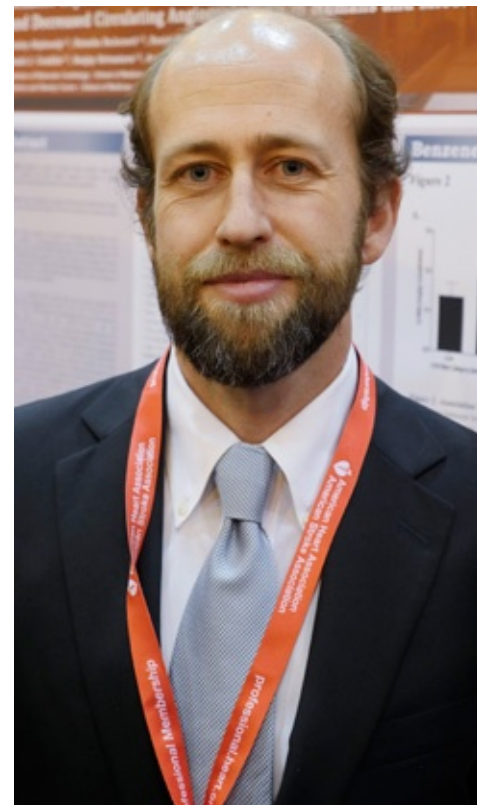
Levels of t,t-MA were inversely associated with circulating levels of angiogenic cells: CD31+/34+/45+, CD31+/34+/45+/AC133 and CD34+/45+/

AC133+. After adjusting the data for confounding, there was a 9 percent decrease in circulating levels of early (CD34+/45+/AC133+) and late (CD31+/34+/45+/AC133-) cells for every 0.1 mg t,t-MA per gram creatinine increase found in participants’ urine.

Benzene exposure may increase cardiovascular risk in both smokers and non-smokers by inducing deficits in vascular repair and dyslipidemia, Abplanalp said.

Levels of t,t-MA were significantly higher in smokers and in people with hyperlipidemia ( $P<0.02$ ). In smokers, t,t-MA levels were associated with urinary metabolites of nicotine (cotinine) and acrolein (3-hydroxypropylmercapturic acid). Finally, the researchers found a positive association independent of smoking status between urinary t,t-MA and cardiovascular disease risk as measured by Framingham Risk Score.

After testing benzene exposure in humans, the researchers examined whether exposure to volatile benzene would induce cardiovascular injury in mice. Exposed mice have a 46 percent reduction ( $p=0.002$ ) in circulating angiogenic cells, induced cytopenias in neutrophils, lymphocytes, monocytes and platelets and a 23 percent increased plasma LDL:HDL ratio ( $p=0.004$ ) compared with mice who were not exposed.



Wesley Abplanalp, PhD

Data from the mice studies give “strong support to the human outcomes,” Abplanalp said.

“Breathing polluted air on a daily basis may put one at greater risk for the development of cardiovascular disease,” he said. “Therefore, improving a patient’s environment may help mitigate disease.” ▼

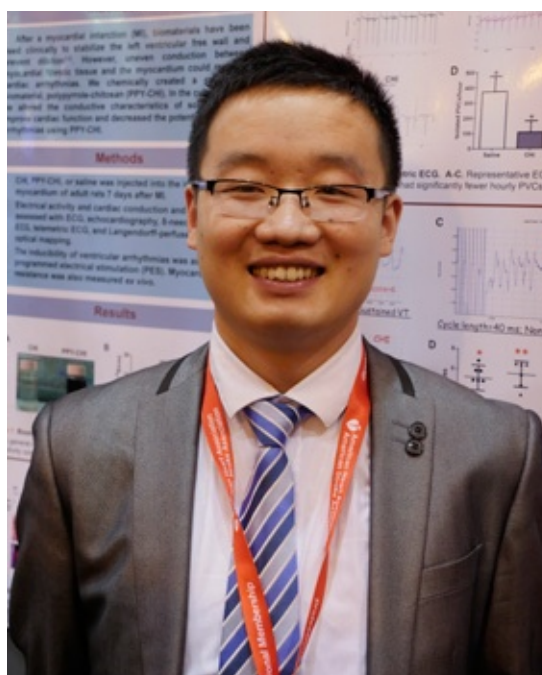
## Conductive biomaterial improves heart function after myocardial infarction, study finds

A new conductive biomaterial improved conduction problems in the heart, according to the results of a study presented Tuesday at Scientific Sessions.

Shen He, a post-doctoral fellow at the University of Toronto in Canada, reported that researchers chemically modified the hydrogel chitosan with the charge-carrying conductive polymer, polypyrrole (PPy), yielding a material with eightfold greater electrical conductivity than chitosan alone. Using this material in rats, they showed that chitosan-PPy (C-PPy) improved heart function by augmenting synchronized contraction and increased conduction velocity in infarct regions.

“After a heart attack, heart cells die and heart muscle tissue is replaced by fibrotic tissue,” He said. “While heart cells enable normal electrical conduction of the heart, fibrotic tissue does not, which results in delayed conduction. This new conductive biomaterial is biocompatible, and improved the conduction across the scar.”

In the study, the researchers injected chitosan alone, C-PPy or saline into the infarct regions of adult rats (eight



Shen He

rats per group) seven days after myocardial infarction. They assessed electrical activity, ventricular function and cardiac conduction with ECG, echocardiography, pressure-volume analysis and Langerdorff-perfused epicardial optical mapping.

Twelve weeks after the injection, the duration of QRS and QTc was greater in hearts treated with saline (15.9 and 169.0 ms, respectively) and chitosan

alone (15.2 and 181.9, respectively) compared with hearts treated with C-PPy (11.8 and 104.8;  $p<0.01$ ). According to the researchers, this suggests “less maladaptive ventricular remodeling and faster depolarizing and repolarizing conduction in the C-PPy group.”

Using optical mapping, He and colleagues showed that hearts treated with C-PPy had faster cross-scar conduction velocities measured on the epicardial surface compared with saline- or chitosan-treated hearts (62.5 versus 45.3 and 48.9 cm/second;  $p<0.05$ ).

“After introducing the conductive biomaterial into the damaged heart, we restored tissue conductivity, an important step to improve synchronous contraction,” He said.

Programmed electrical stimulation induced fewer ventricular arrhythmias in C-PPy-treated hearts compared with saline or chitosan-treated hearts ( $p<0.01$ ).

Finally, *ex vivo* C-PPy-treated tissue had lower myocardial tissue electrical resistance ( $p<0.05$ ) than the other two groups, and fractional shortening was enhanced in these hearts (33.7 percent versus 25.3 percent for saline and 28.2 percent for chitosan;  $p<0.01$ ).

Moving forward, He and colleagues will focus on translational research to evaluate the clinical applicability of this new biomaterial. ▼



# Community-based risk prediction score for sudden cardiac death developed, validated by researchers at University of North Carolina

Researchers have developed and validated a risk score that may help assess who in the general population is at risk for sudden cardiac death at a premature age.

Brittany Bogle, PhD, MPH, of the University of North Carolina Gillings School of Public Health in Chapel Hill, presented data on this community-based risk prediction score for sudden cardiac death on Tuesday at Scientific Sessions.

Bogle and colleagues derived their risk score using data from the Atherosclerosis Risk in Communities (ARIC) cohort, which includes 11,335 Caucasian men and women ages 45-64 at baseline. Sudden cardiac death was defined as death due to coronary heart disease within one hour of symptom onset.

During 10 years of follow-up, 95 participants had sudden cardiac death, 65 percent of which occurred in participants in the highest quintile of predicted risk. The researchers selected co-variables for the risk score model including age, sex, total cholesterol, lipid-lowering medication use, hypertension medication use, systolic and diastolic blood pressure, smoking status, diabetes and body mass index.

Bogle said that although the 95 participants are only a small percentage of the overall number of participants in the ARIC cohort,

participants had these factors ascertained at the first visit of the study when the average age of participants was 54.4 years and only followed for 10 years during the study.

“After 10 years of follow-up, the average age of participants who experienced sudden cardiac death was 64 years among ARIC participants and 69 among Framingham participants, and all deaths were prior to 75 years of age,” Bogle said. “Deaths prior to 75 years of age are



Brittany Bogle, PhD, MPH

considered premature, so this low rate for sudden cardiac death is not unexpectedly so, given the baseline age and follow-up period of the cohort.”

The risk score yielded very good discrimination in ARIC (c-index: 0.82; 95 percent CI, 0.78-0.85) and calibration plots indicated excellent calibration ( $\chi^2=5.3$ ;  $p=0.83$ ).

“We saw steep calibration curves when applying our risk score to the ARIC cohort,

indicating that there may be a high-risk segment of the general population that may be identified using our risk score,” Bogle said. “This subset may be targeted for therapies aimed at preventing sudden cardiac death.”

Next, the researchers validated the risk score among 5,626 Framingham Heart Study and Framingham Offspring Study participants 30-70 years of age. Again, the risk score yielded very good discrimination (c-index=0.82; 95 percent CI, 0.79-0.86), but calibration plots were poorer in Framingham ( $\chi^2=29.7$ ;  $p<0.001$ ). However, according to the researchers, a simple recalibration led to an excellent fit ( $\chi^2=2.1$ ;  $p=0.98$ ). ▼

## Lasting effects of pediatric heart transplant



Researchers used linked data from the Scientific Registry of Transplant Recipients and the U.S. Renal Data System to analyze the risk of developing end-stage renal disease (ESRD) following pediatric heart transplant. During a median follow-up of 4.5 years, 3.1 percent of the transplant patients developed ESRD. The actuarial risk of developing ESRD at five, 10 and 20 years after transplant was 0.3 percent, 3 percent and 16 percent, respectively. Of the various risk factors analyzed, African-American race, age 10-18 years at heart transplant, hypertension, diabetes, heart retransplant, graft failure, acute dialysis and infection were found to be significant on multivariate analysis, according to the researchers, who presented their findings Tuesday during an abstract oral session.

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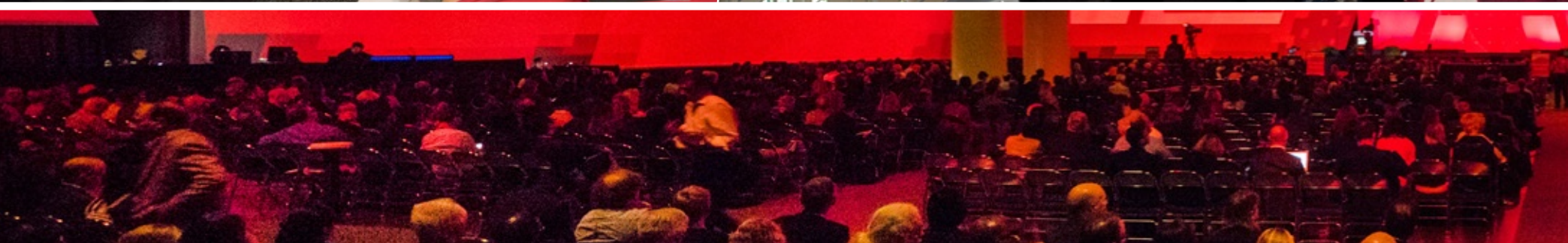
This event is not part of the official Scientific Sessions 2016 as planned by the AHA committee on Scientific Sessions Program.



## Health Tech Competition



Wellth, an app that offers incentives for healthy behavior change, took home the Judge's Choice Award in the third annual Health Tech Competition at Scientific Sessions. Twiage, a platform that delivers real-time data to hospitals in an effort to coordinate ambulance arrivals, earned the People's Choice Award. Twiage founder YiDing Yu, MD (left), and Wellth CEO Matt Loper accepted the awards. Congratulations to the winners and thanks to all the finalists: Arthur Health, CareAcademy, Cloud DX, Cor and Welbean.





# SCENES from Sessions



## Celebrating Research

Some of the current and past American Heart Association research awardees gathered Monday at Scientific Sessions. The AHA has funded more than \$4 billion in research into heart disease, stroke and other cardiovascular diseases, more than any organization outside the federal government. The organization has funded 13 Nobel Prize winners and lifesaving research advancements such as the first artificial heart valve, cholesterol-inhibiting drugs, heart transplantation, and CPR techniques and guidelines.



# New, presumed left bundle branch block with acute myocardial infarction identifies high-risk subset of patients

**P**atients with suspected acute myocardial infarction (AMI) and new or presumed left bundle branch block (LBBB) represent a small but high-risk group of patients with higher baseline cardiovascular risk, more preexisting comorbid conditions and worse clinical outcome, including a higher unadjusted in-hospital mortality rate compared with patients with ST-segment elevation (STE), according to data presented Tuesday at Scientific Sessions.

“However, after adjustment for their higher baseline cardiovascular risk profile, our results show that LBBB patients have the same adjusted risk of in-hospital



Juan F. Iglesias, MD

mortality than patients with ST-segment elevation,” said researcher Juan F. Iglesias, MD, of University Hospital in Lausanne, Switzerland. “Our results give support to the current recommendation that patients with clinical evidence of myocardial ischemia and new or presumed-new LBBB should continue to be managed as high-risk patients requiring aggressive management strategy in addition to standard medical therapy.”

Iglesias noted that it is still unclear whether this high-risk patient subset should be managed as a ST-segment elevation myocardial infarction (STEMI) equivalent and referred for emergency coronary angiography.

Current guidelines recommend that patients with symptoms suggestive of ongoing myocardial ischemia and new or presumed LBBB should be managed as STEMI equivalent and undergo an early reperfusion strategy, Iglesias said. However, he noted that “these recommendations are based on clinical studies performed more than 20 years ago, including patient populations that may differ notably from contemporary patient subsets.”

For this study, Iglesias and his colleagues analyzed data from a large, nationwide, multi-center registry of patients admitted with AMI in Switzerland. The study included 28,358 patients entered into the registry between 1997 and 2016; 92 percent of patients had STE and 8.2 percent had LBBB.

Patients with LBBB were older, had a higher cardiovascular risk profile, greater burden of pre-existing comorbidities, longer reperfusion delays, higher prevalence of cardiogenic shock and worse left ventricular systolic function, but also smaller AMI size.

The researchers adjusted data for age and gender and found that patients with LBBB were less likely to receive evidence-based antithrombotic therapies and undergo urgent coronary angiography (44.9 percent) or primary PCI (42.1 percent) compared to patients with STE.

Additionally, patients with LBBB had a higher rates of major adverse cardiovascular events (17.6 percent versus 8.2 percent), in-hospital mortality (16.2 percent versus 6.5 percent) and cardiogenic shock (11.6 percent versus 6.4 percent) compared with patients with STE.

A multi-variable analysis found that LBBB was associated with a similar risk for in-hospital mortality as STE (odds ratio=0.98; 95 percent CI, 0.83-1.15).

“Finally, trends from our large nationwide cohort of consecutive patients admitted for AMI between 1997 and 2016 in Switzerland demonstrate a dramatic reduction in rates of in-hospital mortality among patients with AMI over the last two decades, in a larger extent in LBBB than STE patients,” Iglesias said. ▼



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# Study: Blood telomere length predicts outcomes after AMI

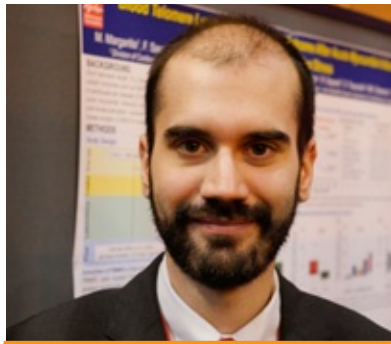
**S**horter telomere length in whole blood predicted all-cause mortality, cardiovascular-related death and new-onset acute coronary syndrome one year after percutaneous coronary intervention (PCI), and predicted the incidence of postoperative atrial fibrillation after coronary artery bypass grafting (CABG), according to the results of a study presented Tuesday at Scientific Sessions.

These findings were independent of chronological age and other conventional risk factors, suggesting that accelerated biological aging may be of particular importance to the development of cardiovascular disease.

“Based on our findings, we believe that telomere length measurement could potentially identify patients at greater risk following revascularization procedures,” said Marios Margaritis of the University of Oxford in the United Kingdom. “This could be used clinically by being incorporated into a risk prediction model, although considerably more research will need to be undertaken before this can happen.”

Margaritis and colleagues examined the role of blood telomere length as a biomarker in acute myocardial infarction in a cohort of 290 patients. They found the blood telomere length on admission was a strong predictor of cardiovascular mortality (HR=4.121; 95 percent CI, 1.39-12.22; p=0.011) during the first year post-AMI. This result was independent of chronological age and other predictors. However, telomere length was not related with new non-fatal acute coronary events (HR=1.561; 95 percent CI, 0.89-2.717; p=0.115).

The researchers proceeded to further investigate their findings in a second cohort: a group of 727 patients undergoing CABG in which they had access to human vascular tissue. In this group, they measured superoxide ( $O_2^-$ ) in peripheral blood mononuclear cells (PBMNCs) and conducted genotyping for genetic polymorphisms in the *CYBA* locus encoding for p22<sup>phox</sup> NADPH-oxidase subunit.



Marios Margaritis

Results showed that high oxidative stress caused accelerated telomere shortening in a tissue-specific manner in the cardiovascular system. Specifically, short blood telomere length was linked to high NADPH-stimulated  $O_2^-$  in PBMNCs. The effect of rs4673C+rs1049255G alleles was linked to high NADPH-stimulated  $O_2^-$  generation in PBMNCs and short blood telomere length, suggesting causal association.

“We believe that our findings regarding the role of oxidative stress in telomere shortening could be used to identify new therapeutic approaches for cardioprotective treatments,” Margaritis said. “Despite the fact that antioxidant trials — vitamins, etc. — have failed to elicit a protective effect against CVD, more targeted treatments, such as statins through their pleiotropic effects, could be much more successful.”

Margaritis said that all currently available assays for measuring blood telomere length are for research use only.

“For telomere length to be used in everyday clinical practice, a user-friendly assay with high reproducibility would need to be developed,” he said. ▼

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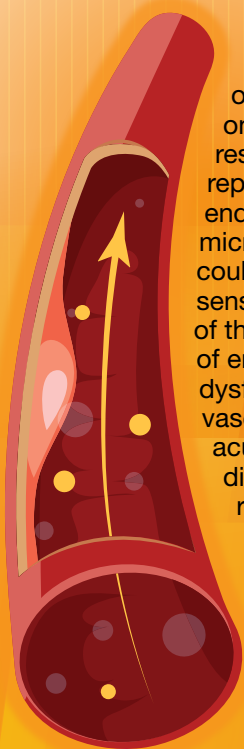
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## Mapping Kawasaki disease



In an abstract oral session on Tuesday, researchers reported that endothelial microparticles could serve as a sensitive marker of the severity of endothelial dysfunction and vasculitis in acute Kawasaki disease. The research also suggests that two microRNAs (hsa-miR-145-5p and hsa-miR-320a) may contribute to

regulation of gene expression of vasculitis and pathogenesis in acute Kawasaki disease.

#### References

- <sup>1</sup> Data from 2010 MarketScan® Commercial and Medicare databases from Truven Health Analytics, Inc. were used to characterize non-pacemaker and pacemaker cohorts and utilization or radiology services. Cohorts were matched based on age, gender and comorbidities.
- <sup>2</sup> Medtronic data on file 2015: ICD data from MarketScan® 2012 Commercial and Medicare Database, Truven Health Analytics.
- <sup>3</sup> Nazarian S, Reynolds MR, Ryan MP, Wolff SD, Mollenkopf SA, Turakhia MP. Utilization and likelihood of radiologic diagnostic imaging in patients with implantable cardiac defibrillators. *J Magn Reson Imaging*. January 2016;43(1):115-127.
- <sup>4</sup> Medtronic data on file 2015: CRT data from MarketScan® 2012 Commercial and Medicare Database, Truven Health Analytics.





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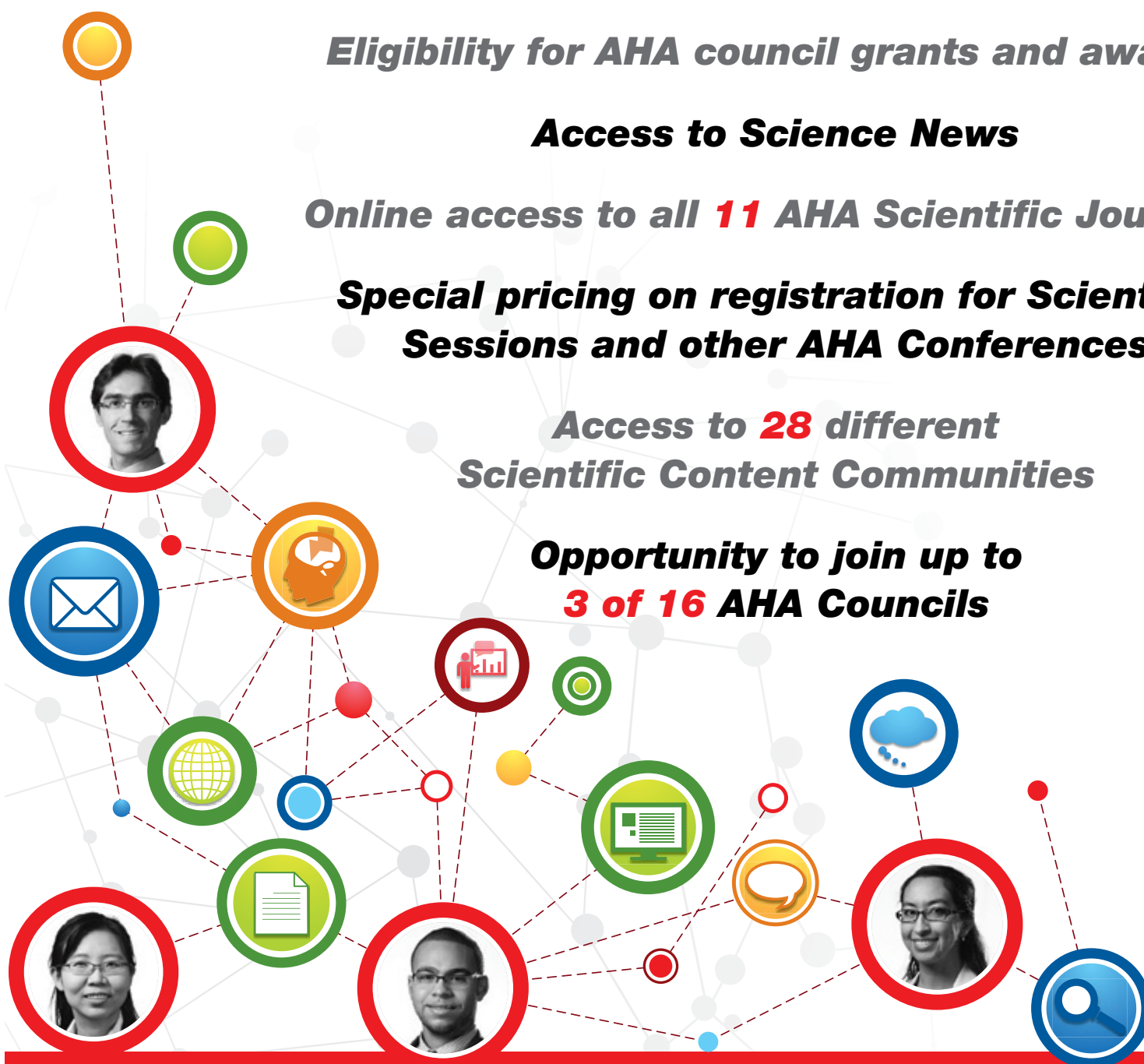
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## NON-CODING RNAs

continued from page 1

vessel patterning, but its biologic effects are far broader. Inhibiting miR-92a enhances neovascularization and recovery after ischemia, enhances tissue recovery after myocardial infarction and improves cardiac function after acute myocardial infarction.

In one study, inhibiting miR-92a reduced infarct size, improved global and regional cardiac function, reduced inflammation and augmented neovascularization, Dimmeler reported.

"Delivery is important," she said. "Intracoronary delivery via catheter appears to be more effective than intravenous delivery, with a 6.4-fold improved recovery for the intracoronary route."

Other studies show broad cardiovascular effects of miR-92a inhibition, with beneficial changes to endothelial cells, fibroblasts, cardiomyocytes and other cell types. About 50 targets for miR-92a inhibition have already been identified in different cardiovascular cells, Dimmeler said.

In addition to enhancing recovery from acute MI, miR-92a shows dramatic benefits in reducing hind limb ischemia, vasoprotection, protection against atherosclerosis and protection against metabolic syndrome while on a high-fat diet. All of these benefits accrue without any increase in tumor growth, Dimmeler said, suggesting a potential therapeutic role.

Preclinical studies have shown good efficacy at improving recovery following acute myocardial infarction with no liver or kidney toxicity up to a dose of 10 mg, and no treatment-related microscopic findings. The first in-human trials are slated to begin in late 2017.

"Work so far suggests that we need to work on improved delivery methods," Dimmeler said. "We have been looking at nanoparticle delivery, local delivery using a variety of devices, aptamers, vectors, light activation and ligands to stimulate receptor-mediated uptake."

Work in lncRNA is less advanced. Several lncRNA, including MALAT 1, have been linked to different stages in cardiovascular development from the pluripotent stem cell stage to differentiation into cardiac cell types. MALAT 1 is also present and active in mature organs. In endothelial cells, for example, the expression of MALAT 1 is regulated by hypoxia and laminar flow to modulate endothelial cell function and vessel growth.

MALAT 1 also inhibits vascular inflammation, Dimmeler said. In mice, MALAT 1 can reduce the burden of atherosclerotic lesions and enhance the outcome of bone marrow transplantation. In humans, normal arteries have higher levels of MALAT 1 compared to atherosclerotic plaques and long-term survivors following bone marrow transplantation have higher levels of MALAT 1 compared to individuals who die sooner after transplantation.

How MALAT 1 and other lncRNAs function is not known, Dimmeler said. lncRNAs may function as sponges to hold and attract miRNAs to focus their activity in specific areas. Or lncRNAs may enhance miRNA stability to lengthen dwell time to improve function.

"We hope that by understanding the involvement of noncoding RNAs in cardiovascular disease, we may be able to target them to regulate cell function and treat cardiovascular and other diseases," Dimmeler said. ▼

## AHA bringing better BP care to people through local YMCAs

**G**ood news for some people who get their blood pressure checked at the YMCA: A doctor will see you soon.

All across the country, many people already take part in the Y's Blood Pressure Self-Monitoring Program. In 10 underserved communities, the American Heart Association will soon connect that program with local healthcare providers and offer other resources, such as Target: BP, the AHA's initiative to help people keep their blood pressure under control.

The AHA and YMCA of the USA are investing more than \$5 million — as well as specialists and other resources — into this pilot program, with the hope of expanding it by 2020. There's plenty of

room for growth considering the Y has 2,700 locations and a presence in 10,000 communities.

"The Y is one of the few community-based organizations with the ability to scale a program that takes healthcare out of the clinic and directly to the people who need it most," said Kevin Washington, president and CEO, YMCA of the USA. "Combining our reach with the American Heart Association's expertise will enable thousands of people, especially those in underserved communities, to get the resources and support they need to control their high-blood pressure."

In announcing the program at Scientific Sessions on Sunday, AHA CEO Nancy Brown said the aim is to "transform communities."

"High blood pressure is often referred to as 'The Silent Killer' — 87 million adults in the U.S. have it, but less than half have it under control," Brown said. "Extending care and services from the doctor's office to the patient's community holds promise to get blood pressure under control more quickly and effectively."

This pilot program will provide YMCA locations with the most up-to-date, science-based programs shown to produce better control of blood pressure. It also will loop in the YMCA's Diabetes Prevention Program.

The AHA also will support the Y's Healthy Heart Ambassadors, program leaders who are trained by the Y to help others to eat healthier, get physically active, understand the benefits of self-monitoring and learn how to properly take their own blood pressure. ▼



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**LATE BREAKING** continued from page 1

One dose of inclisiran lowered LDL cholesterol by 50 percent with levels gradually rising to a roughly 45 percent reduction at 150 days, Ray reported. Adding a second dose at day 90 pushed LDL cholesterol 60 percent below baseline. There was no significant difference in effect between the 300 mg and 500 mg doses.

**GLAGOV trial**

A second study, Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV), is the first trial to show regression in coronary plaque volume by intravascular ultrasound (IVUS), said lead author Steve Nissen, MD, of the Cleveland Clinic in Ohio.

The global trial compared statin monotherapy with statins plus evolocumab. A total of 846 patients completed the trial out of 968 who were originally randomized. Patients were treated for 18 months.

The trial showed surprisingly low LDL cholesterol levels — 29 mg/dL across the

entire cohort and 15 mg/dL in a subgroup of patients whose baseline LDL cholesterol was less than 70 mg/dL, Nissen reported. LDL cholesterol reductions were 59.8 percent for the statin-plus-evolocumab cohort and 58.3 percent for the low-baseline subgroup.

Atheroma volume declined by 5.8 mm<sup>3</sup>, or 1 percent, a clinically significant difference, Nissen said. In the statin-only arm, 47.3 percent of patients showed regression in atheroma volume compared to 64.3 percent regression in the statin-plus-evolocumab arm.

“We have never seen atheroma regression on this scale in any prior study,” Nissen said. “Safety looks very good, albeit this group is too small to call results definitive. We have clear evidence that going to lower levels of cholesterol is better.”

**AEGIS-I trial**

A trial testing the safety and tolerability of CSL112, a reconstituted, infusible, plasma-derived human ApoA-I, found a significant

increase in cholesterol efflux in patients after acute myocardial infarction.

CSL112 is human ApoA-I, the primary functional component of high-density lipoprotein (HDL) that supports the rapid removal of cholesterol from the macrophages present in arterial plaque. Cholesterol efflux is an independent predictor of cardiovascular risk and the first step in the transport of excess cholesterol by HDL to the liver for removal from the body.

The ApoA-I Event Reduction in Ischemic Syndromes I (AEGIS-I) trial compared low-dose and high-dose CSL112 to placebo in patients who had a spontaneous type 1 myo. myocardial infarction within the prior seven days. A total of 1,244 patients were followed for 112 days for clinically significant changes in hepatic and renal function. Cardiovascular events and efflux parameters were secondary endpoints.

Neither of the doses of CSL112 were inferior to placebo for renal or hepatic changes and adverse events were similar across the

three groups, reported lead author C. Michael Gibson, MD, from Beth Israel Deaconess Medical Center in Boston. The high-dose group showed a numerical advantage in time to first cardiovascular event, but the difference was not statistically significant.

“This material can cause plaques to de-lipidate and we believe it may have an effect on cardiac outcomes,” Gibson said. “We were grossly underpowered for outcomes (in this study), but we have a very strong basis to proceed to an adequately powered phase 3 trial.”

**ANGPTL3-LRx**

IONIS-ANGPTL3-LRx, an antisense inhibitor to angiopoietin-like protein 3 [ANGPTL3], reduces plasma ANGPTL3 and lipids in healthy volunteers with elevated triglycerides, according to lead study author Sotirios Tsimikas, MD, from the University of California, San Diego in La Jolla and Ionis Pharmaceuticals.

Using an antisense agent to block the translation of the ANGPTL3 protein is a novel approach to lipid control.

Preclinical data show that ANGPTL3 significantly reduces plasma cholesterol as well as plasma and liver triglycerides in mouse models, Tsimikas reported. The agent can also induce significant reduction in the progression of atherosclerosis.

The proof-of-concept trial had two arms — a single ascending dose arm using 20 mg, 40 mg or 80 mg of IONIS-ANGPTL3-LRx, and a multiple ascending dose arm using 10 mg, 20 mg, 40mg or 60 mg of IONIS-ANGPTL3-LRx for six weekly doses. Volunteers had elevated triglycerides but were otherwise healthy.

The agent reduced plasma levels of ANGPTL3 by up to 83 percent, with similar reductions in triglycerides (66 percent), apoC-III (68 percent), LDL cholesterol (35 percent), total cholesterol (36 percent), HDL cholesterol (25 percent) and non-HDL-cholesterol (40 percent).

“This was a very clean compound, with no injection site reactions, no flu-like symptoms and no dropouts,” Tsimikas said. “And there was a significant reduction in all atherogenic lipids. We think this will be a promising agent for development.”

**MILANO-PILOT**

In the final results of the MILANO-PILOT study, researchers found no signal for therapeutic activity for an HDL mimetic containing ApoA-I<sub>Milano</sub> and the sponsor elected to stop development of the trial agent, MDCO-216.

The pilot study, Effect of Infusion of ApoA-I<sub>Milano</sub> HDL Mimetic on Coronary Atherosclerosis in Acute Coronary Syndrome Patients, compared statin therapy to statins plus weekly MDCO-216 dosing over six weeks in 113 patients. The trial was designed to detect a signal for the regression of coronary atherosclerosis, said lead author Stephen Nicholls, MD, PhD, from South Australia Health and Medical Research Institute in Adelaide, Australia.

The primary endpoint was percent atheroma volume and there was no significant difference between the two arms.

“Most of the patients showed improvement in atheroma volume,” Nicholls said. “This demonstrates the efficacy of current guideline-based treatment and sets a very high bar for any future therapies.” ▼

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