Extended use of aspirin plus a second anti-clotting medication after coronary stent procedures reduced the likelihood of blood clots and heart attacks, according to research released on Sunday at American Heart Association’s Scientific Sessions 2014. The Dual Antiplatelet Therapy (DAPT) study falls within a class of research considered to provide the latest scientific breakthroughs in human trials that have the potential to significantly impact medical treatments. The trial began five years ago at the request of the U.S. Food and Drug Administration to address questions about the safety of aspirin plus an anti-clotting medication in patients who have received a coronary stent. “We know that dual antiplatelet therapy is essential for all patients receiving coronary stents to prevent blood clots within the stents and in patients with heart attack with or without stents can prevent a repeat heart attack. This study showed that the preventive benefit continues when the medication is taken for more than one year,” said Laura Mauri, MD, MSc, the study’s principal investigator and lead author.

People in the study who took aspirin and either clopidogrel (Plavix) or prasugrel (Efient) for 30 months after getting a stent had about half the risk of a new heart attack and about one-third the risk of developing blood clots inside their stents. That was compared to the placebo group that got both drugs for 12 months, then aspirin and a placebo for 18 additional months. “Overall the benefits of longer therapy were very consistent throughout the types of patients we studied,” said Mauri, an interventional cardiologist at Brigham and Women’s Hospital, associate professor of medicine at Harvard Medical School and chief scientific adviser at the Harvard Clinical Research Institute in Boston. Death from all causes was slightly higher in the extended medication group – by 0.5 percentage points – which was mostly related to trauma and cancer. “There was no significant difference in the occurrence of new cancers,” Mauri said. “In retrospect, there was an imbalance between the groups in the number of patients with known cancer before enrollment in the study. Interestingly, we did not see a higher rate of death from any cause in the bare-metal-stent-treated patients who continued these medications, although this was a smaller group.”

Moderate to severe bleeding was more common in the 30-month medication group than the placebo group, although fatal bleeding was rare in both groups. The extended treatment did not lower the rate of stroke or death. The international study lasted from August 2009 to June 2014 and evaluated 22,866 patients who received drug-eluting stents. Participants averaged 62 years old and about 25 percent were female. All received aspirin therapy plus a second anti-clotting drug. After 12 months, researchers randomly assigned 9,961 of those who had tolerated the dual treatment to 18 more months of the dual therapy or to the placebo group. Neither investigators nor patients knew who was receiving DAPT continued on page 14

Antman urges innovation to harness technology, big data

Scientific researchers and healthcare professionals must transform emerging technology and big data into innovative ways to help patients, American Heart Association President Elliott Antman, MD, FAHA, said Sunday during his Presidential Address at Scientific Sessions.

Antman cited several examples of groundbreaking science that are already putting technological and innovative advances to work in his address, “Saving and Improving Lives in the Information Age.” He also urged more innovation in the fight against heart disease and stroke — the two leading causes of death in the world. “We now have tools at our disposal that we could barely imagine only a few years ago,” said Antman, professor of medicine and associate dean for Clinical/Translational Research at Harvard Medical School and a senior physician in the Cardiovascular Division of the Brigham and Women’s Hospital in Boston. “New diagnostic and therapeutic options are being discovered at a pace unseen in human history,” he said. “We have an unprecedented opportunity to harness these advances to save and improve lives.”

First researchers announced for groundbreaking CVGPS project

The first funded researchers in the groundbreaking Cardiovascular Genome-Phenome Study were announced during Scientific Sessions on Sunday, with projects exploring a wide range of important topics including cardiovascular aging and death in diverse populations, interactions between genes and diet in blood vessel problems, and genetic signatures of tobacco exposure.

The Cardiovascular Genome-Phenome Study, also known as CVGPS, is designed to speed up the discovery of more personalized treatments and prevention for cardiovascular diseases and stroke — the leading causes of death in the world. CVGPS does this by enabling researchers for the first time to simultaneously access massive volumes of deeper-level data from multiple studies, including the famed Framingham Heart Study and Jackson Heart Study.

“These scientists are building the future on the power of the past and are following in the footsteps of the American Heart Association’s founders in a bold and novel way,” American Heart Association President Elliott Antman, MD, FAHA, said while announcing the winners during his Presidential Address.

Here is a brief look at the awardees and the projects they will lead starting Feb. 1:

- Ramy Arnaout, MD, DPhil, Beth Israel Deaconess Medical Center. His project is focusing on diversity in cardiovascular diseases, aging and death in a large multi-ethnic study cohort.
- Donna Arnett, PhD, MPH, BSN, University of Alabama at Birmingham. Her project will focus on the epigenetic determinants of...
If it’s Monday at Sessions, that must mean “Wear Red for Women!” One in three women will die of cardiovascular disease. As the AHA enters the second decade of Go Red! For Women, wearing red today will draw attention to the issue and show your support for combating heart disease in women. If you forgot to bring something red to wear, stop by the Heart Shop at the AHA HeartQuarters booth in the Science and Technology Hall. For my fellow male attendees, I recommend that you join Men Go Red. Now let’s turn our attention to the many scientific and networking opportunities at Sessions today. The Late-Breaking Clinical Trials session focuses on prevention and lipid-lowering. Colleagues from Japan will present the results of a randomized clinical trial comparing aspein with placebo among a group of elderly patients with cardiovascular risk factors. A group from Intermountain Health Care will present the results of a randomized clinical trial comparing the use of coronary CT screening with standard medical therapy in a group of diabetic patients. PCSK9 inhibitors are gaining much attention as the next strategies for LDL lowering beyond statin therapy. Also during today’s LBCT session, investigators will show data on a comparison of a PCSK9 inhibitor with ezetimibe for LDL lowering in a group of patients with statin intolerance. The final LBCT in the session is the IMPROVE-IT trial, a long-awaited RCT comparing simvastatin plus ezetimibe with simvastatin alone in a group of increased risk patients with a recent acute coronary syndrome. The trial will provide insights into the clinical benefits of lowering LDL beyond what we have typically sought with guideline-directed statin therapy, as well as the effects on clinical outcomes with LDL lowering with an agent other than statin therapy. It’s interesting that on Tuesday we’ll see the 20-year follow-up results from one of the early statin clinical outcomes trials, the West of Scotland Coronary Prevention Study.

In addition to the many clinical science offerings, today is also a celebration of basic science at Sessions, which is appropriate given the AHA’s longstanding funding support for basic science over the decades. At midday, Robert J. Lefkowitz, MD, from Duke University, will give the Nobel Laureate Lecture on the topic of “Seven Transmembrane Receptors.” Lefkowitz’s work, supported in his early years by Leducq International Grants, has had a profound impact on the understanding of many diseases and has led to the identification of many new drug targets. Robert will give the Nobel Laureate Lecture on the topic of “Seven Transmembrane Receptors.” Lefkowitz’s work, supported in his early years by Leducq International Grants, has had a profound impact on the understanding of many diseases and has led to the identification of many new drug targets.

Don’t miss today’s highlighted presentations and events. For a complete schedule, see the Final Program or view it online at scientificsessions.org.
Nobel Prize laureate to discuss 44-year career in research

The journey from initial research to Nobel Prize took 44 years for Robert J. Lefkowitz, MD. Along the way he learned plenty about G-protein-coupled receptors, for which he won the 2012 Nobel Prize in Chemistry. He also learned a lot about less scientific concepts, like faith, passion, perseverance and even failure.

“If you are going to do important things, you have to be bold. You have to be willing to take chances and you have to be willing to fail,” said Lefkowitz, who will discuss his journey during the annual Nobel Laureate Lecture at 12:30 p.m. Monday in S100ab. “I did plenty of failing on the way to Stockholm. It wasn’t that my basic premise was wrong, but I had no idea that the project I had taken on would be so extraordinarily difficult.”

Currently an investigator at the Howard Hughes Medical Institute and the James B. Duke Professor of Medicine at Duke University Medical Center in Durham, North Carolina, Lefkowitz shared the Nobel Prize with one-time trainee Brian Kobilka, MD, now professor of molecular and cellular physiology at Stanford School of Medicine in California.

Lefkowitz’s first National Institutes of Health research project was an attempt to demonstrate the existence of molecular receptors on the surface of cell membranes. Receptors are now recognized as components of molecular signaling pathways that regulate physiologic processes throughout the body. But in 1968, receptors were the speculative edge of conceptual research.

“There was more than a little controversy as to whether receptors even existed,” he said. “I was trying to demonstrate the reality of molecules that were thought to exist on cells to which hormones and drugs were believed to bind, thereby creating their mechanisms of actions. I set out to develop techniques that did not then exist to demonstrate the reality and the activity of molecules that had never been seen.”

Lefkowitz’s initial NIH fellowship project was to develop a technique that could directly demonstrate binding of radioactively labeled adrenocorticotropic hormone (ACTH) to a putative receptor in adrenal cell membranes. The next target was to identify and characterize plasma membrane receptors for epinephrine. Those initial successes marked a career shift from clinical medicine and cardiology to research.

Lefkowitz’s early work with alpha and beta adrenergic receptors and angiotensin receptors helped identify the mechanisms of action for beta blockers and angiotensin receptor blockers, spurring drug development in these two key classes of therapeutic agents. More recent research into G-protein-coupled receptors has led to the development of a new class of targeted therapies, now being tested in the clinic, that use biased ligands to selectively activate or inactivate specific elements within signaling networks to achieve more precise therapeutic activity.

Over the years, dozens, then hundreds and eventually about a thousand distinct transmembrane receptors have been identified, characterized and cloned. G-protein-coupled receptors have emerged as the most common drug targets in cardiovascular medicine and other fields.

“It’s easy to look back to see the research path that led from ACTH receptors to biased ligands, Lefkowitz noted, but it’s impossible to look forward to see where a particular research path might lead. It takes faith and the boldness to act on that faith.”

“Faith is belief in something in the absence of data to prove it,” he said. “There was so much indirect data supporting receptors that I had absolutely no doubt. However, if I knew then, at age 30, what I know now at age 71, I don’t think I would have had the guts to try. Good thing I didn’t know how difficult it was going to be!”

LEcTURER PREVIEW

Speaker: Robert J. Lefkowitz, MD
Title: Nobel Laureate Lecture: Seven Transmembrane Receptors
Time: 12:30–1:30 p.m. Monday
Location: S100ab

How long have you been an AHA/ASA Professional Member?
I joined the AHA in 1982.

Why did you join?
I joined because I was a nurse caring for patients in the coronary care unit and I wanted to be involved locally with the AHA’s medical education programs.

Are you involved in any AHA councils?
I’m a member of the Council on Cardiovascular Nursing and the Council on Clinical Cardiology.

What do you enjoy most about these roles?
Networking with colleagues around the world interested in cardiovascular research, teaching and practice.

How else are you involved with the AHA?
I’ve served on numerous committees and work groups at the local, affiliate and national levels for more than 30 years. In 1997, when I was chair of the Board of Directors for the San Francisco AHA, I led an initiative to place automated external defibrillators in public places, such as the San Francisco International Airport. Other AHA activities include grading abstracts and moderating sessions for Scientific Sessions; serving on the ECG and Arrhythmia Committee; and serving on research committees at the affiliate and national levels.

Why is membership valuable to you?
The mission and goals of the AHA are in line with my interests. I enjoy the “cross fertilization” that the AHA fosters by bringing together scientists from multiple professions (physicians, nurses, dieticians, social, behavioral and basic scientists) who are all passionate about improving heart health and treating cardiovascular disease.

What message would you like to convey to your colleagues about being an AHA member?
AHA membership is valuable to keep abreast of new discoveries and treatments for the No. 1 killer of American men and women. Membership connects you to colleagues you would not normally meet or work with and provides opportunities to give back to the community, which is rewarding.
Conner lecturer Ingber envisions a future with more ‘biologically inspired engineering’

A

head lies a future where drug research can be done on three-dimensional models of human organs on microchips rather than in animals or cell cultures, according to Donald E. Ingber, MD, PhD. And nanotechnology will allow clinicians to use nanotherapeutic clot-busters that concentrate tPA at clot sites in narrowed blood vessels, said Ingber, this year’s Lewis A. Conner Memorial Lecturer.

That future is closer to reality, thanks to the work of Ingber’s lab at the Wyss Institute for Inspired Biological Engineering, which he founded, at Harvard University in Boston. Ingber is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children’s Hospital and professor of bioengineering at the Harvard School of Engineering and Applied Sciences.

In his lecture during Sunday’s Opening Session, Ingber described so-called “organs-on-chips.” These three-dimensional models of organs are made of clear silicon rubber. They’re about the size of a computer memory chip and are coated with human cells configured to mimic specific organ tissue. Biologically inspired engineering is a new scientific discipline that marries biological and engineering principles. The Wyss Institute works to identify the mechanisms that living organisms use to self-assemble from molecules and cells to develop advanced bioinspired devices and materials for healthcare and other applications.

“Medicine has been transformed over the past 30 years by applying engineering principles to solve medical problems, and that gave us stents and artificial hearts and pacemakers and so forth,” Ingber said. “But we feel we have actually uncovered enough about how nature builds, controls and manufactures that we are at a point where we can leverage biological principles to develop engineering innovations. This is what we call biologically inspired engineering.”

So far, Ingber and his colleagues have developed more than 10 different organs-on-chips, including a human breathing lung-on-a-chip, a small-airway-on-a-chip and a human gut-on-a-chip. They are working on a fully integrated human-body-on-a-chip. The Wyss Institute researchers are also using nanotechnology to model human diseases. For example, in research published in Science in 2010, they described a biomimetic microsystem that reconstructs the critical functional alveolar-capillary interface of the human lung. This bioinspired microdevice reproduces complex integrated organ-level responses to bacteria and inflammatory cytokines introduced into the alveolar space. In nanotoxicology studies, they demonstrated in the lung mimic that cyclic mechanical strain accentuates toxic and inflammatory responses of the lung to silica nanoparticles.

“Recently, we obtained cells from human patients with COPD and put them on normal and diseased bronchioles-on-a-chip and showed that COPD patients in vivo have decreased expression of TLR3 and TLR4 receptors,” Ingber said.

Currently it takes about 15 years and $500 million to develop a single drug, followed by clinical trials, he said.

“With a bioinspired engineering approach to drug development, you could literally develop iP5 (induced pluripotent stem) cells from genetic subpopulations, put them on chips and develop drugs in a focused program for a subpopulation, then have your clinical trials and accelerate the drug development process,” he said.

In another paper published in Science in 2012, Ingber and his colleagues described their work on the use of nanotechnology to target obstructed blood vessels. They used high-shear stress caused by vascular narrowing as a targeting mechanism — in the same way platelets do — to deliver tPA to obstructed blood vessels and were able to rapidly dissolve clots in mice, Ingber said.
Health technology competition debuts at Sessions today

The competition stems from the AHA Health Tech Forum in September that brought together more than 120 thought leaders from technology, medicine, academia, and venture capital to explore insights that could lead to new, more effective pathways to link technology innovation and healthcare.

“Health technology is important to improving patient outcomes,” said American Heart Association CEO Nancy Brown. “We can create a culture of health with technology at the center. We can leverage science and the AHA brand with our partners to provide solutions that can change the world.”

Collaboration is needed to bridge healthcare and technology, said Eric Peterson, MD, MPH, the Fred Cobb, MD, Distinguished Professor of Medicine and director of the Duke Clinical Research Institute at Duke University School of Medicine in Durham, North Carolina.

One of the most important things is the ability to bring together the technologists with clinicians who are delivering care every day,” she said. “When they work together, that’s where the best products are developed and implemented into routine clinical care.”

New tech tools can improve compliance, digital and social knowledge, tracking and monitoring patient status, office workflow and more. Adopting them depends on their benefits, incentives, integration into existing workflow, positive reports from early adopters and other factors. ▼
Collaborative program aimed at lowering blood pressure

I just may take a village to combat the nation’s high blood pressure problem. That’s why the American Heart Association is fostering collaboration between health-related groups with the Check. Change. Control.™ Leadership Community. The community comprises 35 organizations, including leaders from healthcare, pharmaceutical, device, retail and technology industries, along with key players in the community health. Participants interact on ideas, best practices development and collaborative initiatives through in-person meetings, webinars and online blogs, discussions and other resources. The collaborative forum lets members integrate multi-sector approaches to address high blood pressure issues.

BRILINTA® [ticagrelor] Tablets

WARNING: A BLOODING RISK and (b) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

See full prescribing information for complete boxed warning

A. BLEEDING RISK

• BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

• Do not start BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (see CONTRAINDICATIONS).

• Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to surgery (see WARNINGS AND PRECAUTIONS).

• Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angioplasty, percutaneous coronary intervention (PCI), CABG, or other surgery (see WARNINGS AND PRECAUTIONS).

• If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of significant cardiovascular events (see WARNINGS AND PRECAUTIONS).

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

• Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided (see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES (14) in full prescribing information).

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a P2Y12 receptor inhibitor indicated to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the risk of a combined endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke. BRILINTA has been shown to reduce the risk of cardiovascular death, MI and stroke compared to clopidogrel in patients with ACS (see Clinical Studies (14) in full prescribing information).

Studies (14) in full Prescribing Information

Percutaneous Coronary Intervention (PCI)

In PLATO, a randomized trial of ACS patients treated with ticagrelor versus clopidogrel, ticagrelor was superior to clopidogrel with respect to the primary endpoint of cardiovascular death, MI, or stroke. In PLATO, ticagrelor had a beneficial effect on the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel in patients with ACS undergoing PCI (see Clinical Studies (14) in full prescribing information). BRILINTA is a P2Y12 receptor inhibitor indicated to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the risk of a combined endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke.
Gene network associated with cellular cholesterol metabolism linked to obesity, cardiovascular disease

Transcriptional analysis using purified monocytes from subjects in the Multi-Ethnic Study of Atherosclerosis (MESA) indicates that transcriptional activity of a network of genes associated with cholesterol metabolism may mediate obesity and cardiovascular diseases in asymptomatic individuals. Jiezhong Ding, MD, PhD, of the Wake Forest School of Medicine in Winston-Salem, North Carolina, presented the findings Sunday on a poster titled "Alterations of a Cellular Cholesterol Metabolism Network in a Molecular Feature of Obesity-Related Type 2 Diabetes and Cardiovascular Disease." In the study, monocytes were purified from blood drawn from the MESA subjects. The transcriptionomes from monocytes were quantified using Illumina HumanHT-12 v4 BeadChip.

Transcriptional analysis was undertaken for each individual and the data was then pooled and analyzed. Ding reported that 11 BMI-associated genes either showed an increase or were discovered as new transcripts. Of the genes related to sterol uptake, LDLR transcripts increased and MYLIP transcripts decreased. All sterol synthesis transcripts (SCD, FADS1, HMGCS1, FDM1, SQLE, FADS2, HMGCS2, and SREBF1) and APOB were increased. And transcripts (ABCA1 and ABCG1) of genes related to cholesterol efflux decreased. These results suggest an increase in intracellular cholesterol and is associated with an increase in obesity, Type 2 diabetes and coronary artery calcium. The study’s data was validated internally using mRNA sequencing. External validation was provided from monocyte expression data from 1,285 German men and women in the Gutenberg Heart Study. After confirming the study’s results provide a rationale for translating this as a systematic approach to modulate this sterol metabolism gene network, rather than individual genes, for optimizing the prevention and treatment of obesity-related Type 2 diabetes and CVD, Ding concluded. The MESA study was initiated in 1999 to investigate the prevalence, correlates and progression of subclinical CVD and risk factors that predict progression to CVD. It is a population-based study that includes 6,800 diverse men and women from six communities in the United States. This analysis was conducted in 1,264 subjects from the MESA cohort.

Absence of CAC reduces CV risk at 10 years

Patients with no coronary artery calcification (CAC) are less likely to experience a cardiovascular event after 10 years than patients with even minimal CAC scores, according to research presented Sunday at Scientific Sessions. Parag Joshi, MD, MPH, a John D. and Catherine T. MacArthur Fellow in Cardiovascular Prevention at the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease in Baltimore, presented 10-year follow-up data from the Multi-Ethnic Study of Atherosclerosis (MESA). The findings are consistent with five year data previously reported from the study.

In the 10-year analysis, Joshi and colleagues reported that 3,415 subjects with a CAC score of 0 experienced 2.9 CVD events per 1,000 person years. In comparison, those with at least a CAC score between 1 and 10 experienced 5.5 CVD events per 1,000 person years. The difference in event rates was significant and indicates that subjects with a CAC score between 1 and 10 were at an 86 percent higher risk for CV events after 10 years.

Smoking and hypertension were strong, independent risk factors for CV events in the entire cohort. However, subjects with no CAC score were at least three times more likely to experience a CV event across the entire group, and hypertension increased the likelihood of a CV event 10-fold among patients with a CAC score between 1 and 10.

The data suggests that absence of CAC can identify low risk across different subgroups, Joshi said. "Absence of CAC indicated low absolute prognostic risk regardless of other risk factors, including diabetes or family history of CHD," he said. "CAC (testing) is widely available at any center that provides computed tomography services." Joshi added that the absence of CAC has the potential to guide treatment options by reassuring physicians and patients of a low risk for future CV events.

"While most tests are used to classify patients as having a higher risk, it is important for patients and providers to have a test such as a CAC score that can reassure them that their risk is indeed low," he said. Further studies are needed to determine whether this information can be incorporated into management decisions, and to assess the cost-effectiveness of CAC testing within primary prevention settings.

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Restricting salt intake in Chinese adults — who are among the highest salt consumers worldwide — is associated with a significant reduction in their blood pressure, especially among those with hypertension, according to a meta-analysis presented Sunday at Scientific Sessions. Culturally tailored approaches such as salt-restriction spoons and salt substitution achieved similar effects.

Many local Chinese governments have provided 2-gram salt-restriction spoons to help educate citizens to consume less than 6 grams of salt per day.

Andrew E. Moran, MD, MPH, of Columbia University Medical Center in New York, did a poster presentation of the research, titled Effect of Dietary Salt Restriction on Blood Pressure in Chinese Adults: A Meta-Analysis. The study was a collaboration with Dong Zhao, MD, PhD, of the Institute of Heart, Lung, and Blood Vessel Diseases in Beijing, China.

Based on the researchers’ meta-analysis of salt restriction studies, a 10.9 gram reduction in salt intake was associated with a decrease in systolic blood pressure (SBP) of 6.3 mm Hg. In subjects with hypertension, a 9.5 gram reduction in salt intake was associated with an SBP reduction of 8.9 mm Hg. Change in SBP per gram of reduced salt intake was higher in subjects with hypertension: -0.94 mm Hg versus -0.58 mm Hg for all subjects. Similar trends were reported for diastolic blood pressure changes. Changes in blood pressure were approximately two times more in subjects with hypertension. For the same amount of salt-lowering, the change in blood pressure was substantially more for people with hypertension compared to those without hypertension.

Across the meta-analysis, the change in systolic blood pressure per gram of salt was slightly less in Chinese studies than in international studies pooled by other investigators. However, the expected blood pressure changes in all adults and hypertensive adults were generally consistent.

Moran and his colleagues also analyzed the effects of salt-lowering in studies that used two strategies tailored to China — substituting sodium with potassium and other minerals, and the use of salt-restriction spoons for home cooking. In data from three studies that included 1,517 subjects, only one study reported the effect of salt substitution in subjects with hypertension: a -4.2 mm Hg change of SBP and a -0.6 mm Hg change of DBP.

Four additional studies with 3,715 participants indicated that using a salt-restriction spoon is associated with a significant reduction in sodium, these studies did not report on blood pressure changes.

Lowering dietary salt has been promoted as a global “best buy” by the World Health Organization for reducing CVD mortality. Salt-lowering is a particularly important strategy in high salt-consuming countries like China, Moran said. It might lower blood pressure, especially in people with hypertension, and prevent cardiovascular disease, he added.
Study links low cardiovascular disease risk in youth with better functional status in older age

Low cardiovascular risk at a young age predicts better functional status in older age, according to a 32-year follow-up study presented Sunday in a poster session.

“Individuals with an ideal cardiovascular risk profile at a younger age have between 34 percent and 58 percent lower risk for functional disabilities in older age,” said Thanh-Huyen Vu, MD, PhD, who presented his poster “Ideal Cardiovascular Health in Younger Age and Functional Disability in Older Age — The Chicago Heart Association Detection Project in Industry (CHA) 32 Year Follow-up Health Survey.”

Researchers conducted baseline surveys of 39,565 high-risk adults in Chicago workplaces in 1967-73.

Data reported in the poster session was from a survey mailed in 2003 to surviving CHA participants who were 65 or older. At baseline, 348 of the 6,014 participants in the 2003 analysis had an ideal CVD risk profile; 1,500 had no risk factors; 2,467 had one risk factor; and 1,699 had at least two risk factors.

Participants were considered to have a low or ideal risk profile at baseline if they had all of these traits: total cholesterol less than 200 milligrams per deciliters untreated; no diabetes mellitus; nonsmoker; normal blood pressure (≤120/≤80 mmHg) untreated; and a body mass index of less than 25 kilograms per meter square.

Researchers determined risk at baseline by several factors: total cholesterol greater than 240 milligrams per deciliters or taking medications for high cholesterol; diabetes mellitus; smoker; blood pressure (≥140/≥90 mmHg) or on antihypertensive medication; and a body mass index of greater than 30 kilograms per meter square.

Adjusting for multiple traits, participants with:
- An ideal risk profile at baseline were at a 58 percent lower risk of functional disability in old age compared to participants with two or more risk factors.
- No risk factors at baseline were at a 48 percent lower risk for functional disability in old age.
- One risk factor at baseline was at a 37 percent lower risk for functional disability in old age.

Researchers measured functional disability with a validated 15-item questionnaire. Questions measuring activities of daily living (ADL) involved feeding, toileting, selecting proper attire, grooming, maintaining continence, dressing, bathing and walking. Additional questions measured instrumental activities of daily living (IADL), such as shopping, preparing meals, using communication devices, managing medications, managing finances, driving and doing housework.

“Having an ideal cardiovascular risk profile at a younger age is associated with the lowest functional disabilities in older age,” said Vu, in the Department of Preventive Medicine at Northwestern University’s Feinberg School of Medicine in Chicago. “An ideal risk profile at a young age may, therefore, be associated with a reduced loss of independence and improved quality of life in older age.”

Antman told the story of one of his own patients — a 67-year-old man who was referred for evaluation of heart palpitations — to illustrate technology’s lifesaving possibilities.

Antman prescribed a heart-rhythm monitoring device so the patient could take readings using an attachment to his smartphone case and email the results to Antman. He quickly diagnosed him with atrial fibrillation and formulated a treatment plan.

Atrial fibrillation, also known as AFib, greatly increases a patient’s risk for stroke and affects 33.5 million people worldwide. Antman, an expert in AFib, led the research team that last year published results of a study on the anticoagulant edoxaban’s effect on preventing stroke, as well as a larger analysis on the effectiveness of the three newer oral anticoagulants.

He detailed the history of such drugs to show that innovation is needed. Warfarin was essentially developed by chance, he said, while the development of alternative anticoagulants was costly and took many years.

“Obviously, we can’t rely on either method to find effective new therapies,” he said.

While looking ahead, Antman also looked back at some important history. The American Heart Association was founded 90 years ago by six cardiologists at the Drake Hotel in Chicago.

“They started this lifesaving organization just four miles away from where you’re sitting now,” he said. “Yet, it was worlds away when you consider what we can offer patients today.”

Using an electrocardiogram to illustrate his point, Antman compared a handheld device like the one he used to treat his patient to a bulky 28-pound wooden box that contained the ECG machine used by Paul Dudley White, one of the six founders of the American Heart Association.

He also referenced the organization’s founders while making a major announcement — the first funded researchers in the groundbreaking Cardiovascular Genome-Phenome Study, also known as CVGPPS. The study is built on the big data of numerous studies, including the Framingham Heart Study and the Jackson Heart Study. (See full story, page 1.)

“They are building the future on the power of the past and are following in the footsteps of the American Heart Association’s founders in a bold and novel way,” he said.
Investing more funds in medical research is good for improving patient care—and it’s good for the economy. So why aren’t we doing more of it? That’s the question many scientists, patients and advocates are asking on Capitol Hill and across the country, but the reasons are complicated. The 2008 economic downturn had a negative effect on everyone’s funding, but experts believe investing in science is lagging behind other priorities and interests.

“The scientific organizations do not have the potent lobbies to persuade lawmakers,” said Gordon F. Tomaselli, MD, past president of the American Heart Association and director of the Division of Cardiology at Johns Hopkins University School of Medicine in Baltimore. “We spend 0.23 percent of our Gross Domestic Product on biomedical research. It’s not a low number; it’s an embarrassing number,” he said.

“That figure is dwarfed by other countries in Europe and Asia that are doing a much better job than us. It shows a dangerous lack of foresight in America because investing in research leads to innovation and ideas that get picked up by companies. It spurs the economy.”

The American Heart Association has invested more than $3.7 billion in cardiovascular disease research, including more than $100 million annually since 1996. In the 2012-2013 fiscal year, the AHA invested $121.6 million in research, the most since 2009. Only the federal government funds more.

The National Institutes of Health invests $30.1 billion annually in medical research, with more than 80 percent funding 50,000 competitive grants for more than 300,000 researchers. These cuts come after about a decade of flat funding for the NIH. And the NIH’s purchasing power is reported to be 25 percent less than what it was a decade ago.

The ongoing dwindling of federal support deters young people from pursuing careers in science, stymying innovation. The pipeline of drug and device development could slow down if stagnation continues.

“The government doesn’t know much about science or how to fund science,” Tomaselli said. “Should the NIH fund large-population, epidemiological studies or should the emphasis shift to more investigator-initiated research? Why not restructure the process to make it more streamlined so that studies are designed to move ideas into product development, to answer questions that are important and relevant? We don’t have that right now.”

Power of the patients’ voices
As part of the American Heart Association’s You’re the Cure campaign, in September, patients and advocates discussed with their state representatives and lawmakers in Washington, D.C., the importance of increasing medical research funding and the impact it has had on their own lives.

Tomaselli believes patients can persuade politicians.

“Lawmakers are more likely to listen to their constituents than special-interest groups,” Tomaselli said. “We all need to be advocates for this. The most effective message is a grassroots message. Scientists are often reticent to leave their labs and get out there, but they could join patients and tell Congress that medical research is important to them personally and it’s important to us as a society.”

More funding for scientific research needed in U.S.
MDCO-216 infusion induces lipid profile changes

MDCO-216, which is ApoA-1 Milano produced by a new and more efficient process, has been shown to change lipid parameters following a single infusion in healthy subjects and in patients with coronary artery disease (CAD). MDCO-216 infusion also resulted in a profound increase in cholesterol efflux, believed by some to be a key marker of high density lipoprotein (HDL) function, and to play a key role in the reverse cholesterol transport pathway.

David G. Kallend, MBBS, vice president and global medical director of The Medicines Company in Zurich, Switzerland, presented data from this Phase I study on Sunday on a poster titled “Single Infusion of MDCO-216 (ApoA-1 Milano/POPC) Induces Marked Changes on the Lipid Profile.”

In the study, a single infusion of MDCO-216 was shown to be safe and generally well-tolerated with no serious adverse events or deaths reported in either healthy volunteers or patients with stable CAD, Kallend said. In addition, no clinically relevant changes in safety laboratory parameters were observed after MDCO-216 infusion.

In the study, MDCO-216 was delivered as a two-hour infusion to 24 healthy volunteers divided into five cohorts, and 24 patients with CAD divided into four cohorts. Doses ranged from 5 to 40 milligrams per kilogram. Study subjects were followed for 30 days and returned regularly for safety assessments.

In the 40 milligrams-per-kilogram dose group, an 80 percent increase in ApoA-I (a combination of endogenous ApoA-I and exogenous ApoA) from baseline was reported. In healthy subjects, these increases returned to baseline by 24 hours. In patients with CAD, an additional decrease from baseline was observed from 24 hours until day 30 in the 30- and 40 milligrams-per-kilogram dose groups.

Elevation in triglyceride concentration was reported from the end of infusion until day seven. These increases were seen at all doses in healthy volunteers, but were more prominent at the 30 and 40 milligram per kilogram doses. In patients with stable CAD, triglyceride concentration increased two to three times above baseline levels.

Reduction from baseline in HDL-C levels was also reported. Reduction was most profound at the 30 and 40 milligrams per kilogram levels, and greater in stable CAD subjects compared with healthy volunteers.

Although low-density lipoprotein cholesterol (LDL-C) also decreased from the end of infusion until day 30 in the 30- and 40 milligrams per kilogram dose, the effect was not observed in the lower-dose groups or in the healthy volunteers.

At the end of MDCO-216 infusion, increased cholesterol efflux, which is believed to be associated with improved HDL function, was reported with doses at and above 20 milligrams per kilogram. A 13 percent increase in efflux per four hours was seen in both healthy subjects and in patients with stable CAD.

“In a previous imaging study, recombinant ApoA-1 Milano was shown by IVUS to produce significant regression in atherosclerosis,” Kallend said. “However, at this point, the development of ApoA-1 Milano was put on hold for nine years. With this new and improved production process, we hope to later demonstrate regression of atherosclerosis with MDCO-216 and ultimately continue clinical development with a large outcomes study.”
**Glycemic index not a good indicator to guide food choices, study suggests**

The glycemic index is not a good approach to guide food choices in the clinical setting, according to research presented Sunday at Scientific Sessions.

The variability in glycemic index was measured for white bread in 63 healthy subjects with fasting plasma glucose values less than 125 milligrams per deciliter in a study presented by Nirupa R. Matthan, PhD, assistant professor/scientist from the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston. A large variability in glycemic index values was reported in the same individual and among individuals, Matthan reported.

Matthan and her research colleagues recruited women and men from the greater Boston area between 18 and 85 with body mass index ranging from 18 kg/m² to 35 kg/m². The volunteers underwent a food challenge of white bread and glucose in random order three times each. Each set included either 500 milliliters of glucose solution or 104 grams of white bread included either 500 milliliters of glucose solution or 104 grams of white bread equivalent to 50 grams of carbohydrate and 500 milliliters of water.

The volunteers abstained from exercise and alcohol 72 hours before the food challenge, and they fasted for 12 hours. At each visit, arterialized venous blood was sampled at 15, 30, 45, 60, 90, 120, 150, 180, 210, 270 and 300 minutes. Glycemic index was calculated using a standardized area under the curve method.

The mean glycemic index for white bread was calculated at 62. Matthan and her colleagues determined that the variability in the glycemic index value among individuals was 25 percent for white bread. Variability within the same individual was 22 percent.

The researchers also showed that age, sex, BMI and body composition measured by dual-energy X-ray absorptiometry did not affect the glycemic index of white bread. However, baseline hemoglobin A1c (HbA1c) and insulin index explained 12 percent and 25 percent, respectively, of the variability in glycemic index among individuals. Glycemic index for white bread in individuals with HgA1c values greater than 5.7 was 57 compared to 66 for individuals with HgA1c at or less than 5.7.

“We typically rank foods based on their glycemic index. In this study, the wide variation in glycemic index for white bread suggests similar variations may exist for other foods,” Matthan said.

The study also suggests that glycemic control, even in healthy individuals, significantly contributes to the variability in glycemic response among individuals. The observation regarding HbA1c and insulin index is interesting and needs to be further assessed, as it may have clinical implications, Matthan noted.

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**CVGPS continued from page 1**

left ventricular structure and function in hypertensive African-Americans.

Christy Avery, PhD, MPH, University of North Carolina. Her project will focus on pharmacogenomics of risk factors for cardiac arrhythmias in global populations.

Susan Cheng, MD, Brigham & Women’s Hospital. Her project will focus on chronic inflammation, cardiovascular aging and longevity.

John Cole, MD, MS, University of Maryland, Baltimore. His project will focus on early-onset stroke and an extreme phenotype to identify rare variants in ischemic stroke.

Simin Liu, MD, MPH, ScD, Brown University. His project will focus on integrative genomics of gene-diet interactions in vascular outcomes across ethnicities.

George O’Connor, MD, MS, Boston University Medical Campus. His project will focus on transcriptomic and epigenetic signatures of tobacco exposure.

Marc Vidal, PhD, Dana-Farber Cancer Institute in Boston. His project will focus on integrated genetic, transcriptomic and epigenetic analysis of cardiovascular disease phenotypes.

CVGPS combines long-term population studies with the precision of molecular analysis at the individual level to characterize key distinctions within and between patient subgroups. These distinctions will point the way toward more precisely targeted, safer and more effective treatments based on a deeper understanding of individual risk profiles, therapeutic needs and other factors.

Joseph Loscalzo, MD, chair of the American Heart Association Science Oversight Group for CVGPS, has explained the goal of the project very simply:

“What we are trying to do with CVGPS is to speed up progress,” said Loscalzo, professor and chair of medicine at Harvard Medical School, physician-in-chief at Brigham and Women’s Hospital, Boston, and editor-in-chief of Circulation. “To use an analogy involving the speed of data delivery, we want to go from the days of the Pony Express to email.”

Researchers announced Sunday were awarded CVGPS Pathway Grants funded at $250,000 per year for two years. The funding is part of the $30 million over five years provided by the AHA, the nation’s largest funder of cardiovascular disease and stroke research outside the federal government.

The AHA is leading the CVGPS collaboration, along with the academic coordinating centers of the Framingham and Jackson studies: Boston University, the University of Mississippi Medical Center, Jackson State University and Tougaloo College. The project was inspired by the AHA’s long-term relationship with the National Heart, Lung, and Blood Institute.

Framingham is the nation’s largest and longest-running heart research program, with data extending from the original participants into a third generation. The Jackson Heart Study is the nation’s largest research study focused on African-Americans, who are at increased risk for heart attack and stroke compared to other ethnic and racial groups.

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**DAPT continued from page 1**

medication or placebo. There were more than 450 sites in the United States, Canada, Europe, Australia and New Zealand.

Prevention of heart attack and blood clots in stents with longer antiplatelet therapy was consistent in all patient groups, drug and stent types studied, Mauri noted, but “physicians should consider individual patient risks in prescribing dual anti-clotting therapy. In particular, the trial excluded patients with a history of major bleeding either before the stent procedure or within the first year of treatment.”

Guidelines recommend that patients take aspirin and a second anti-clotting medication to prevent clots. European guidelines recommend the treatment for six to 12 months; U.S. guidelines, for 12 months.

**TL-PAS: A Substudy of DAPT—More MI Seen After Stopping DAPT**

The variability in glycemic index was measured for white bread in 63 healthy subjects with fasting plasma glucose values less than 125 milligrams per deciliter in a study presented by Nirupa R. Matthan, PhD, assistant professor/scientist from the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston. A large variability in glycemic index values was reported in the same individual and among individuals, Matthan reported.

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was non-significantly higher for patients on 30-month DAPT (2.4 percent vs 1.7 percent; p = 0.234) with patients on 30-month DAPT at a 40 percent greater risk for bleeding.

Withdrawal of prasugrel resulted in apparent loss of protection with an early increase in ischemic events, when stopped after 12 months, the difference was seen as early as 90 days after prasugrel withdrawal, concluded Garratt.

European Perspective: ISAR-SAFE and ITALIC Indicate a Shorter Course of DAPT Is Safer

With guidelines recommending a 12-month DAPT following stenting, European cardiologists typically advocate a shorter course of therapy to reduce risk of bleeding associated with DAPT following index procedure.

While the ISAR-SAFE and ITALIC studies may not have conclusively provided evidence in favor of a shorter course of DAPT, in the context of other studies, a shorter course of DAPT may indeed be safer for patients following the stenting.

“The results of the trial must be considered in view of its premature termination and lower than expected event rates,” said Stephanie Schulz-Schüpke, MD, Deutsches Herzzentrum München, Munich, Germany.

The ISAR-SAFE study objective was to show that after implantation of drug-eluting stent, six-month DAPT with aspirin and clopidogrel offers similar protection as 12-month DAPT. After stenting, patients were randomized to receive clopidogrel for six months or 12 months.

A planned, blinded interim analysis showed much lower than expected overall event rates. This, along with slow recruitment, induced the DSMB and the Steering Committee to terminate recruitment at a sample size of 4,000 patients, Schulz-Schüpke said.

At study termination, 1,997 and 2,003 patients received clopidogrel plus aspirin for six months and 12 months, respectively. The primary endpoint was the composite event rate for death, myocardial infarction (MI), stent thrombosis, stroke and major bleeding nine months after randomization.

Event rate for the primary endpoint was 1.5 percent for six-month versus 1.6 percent for 12-month clopidogrel therapy. With a hazard ratio of 0.91 for the primary endpoint of composite events, six-month was as effective as 12-month clopidogrel and aspirin therapy.

Major or minor bleed, although not significant, was higher for patients on 12-month versus six-month therapy (0.7 percent vs 0.3 percent). Individual event rates for six-month compared with 12-month clopidogrel therapy were also low and non-significant for death (0.4 vs 0.6 percent), MI (0.7 percent for each), stent thrombosis (0.3 vs 0.2 percent), stroke (0.4 vs 0.3 percent), and major bleeding (0.2 vs 0.3 percent).

Low event rate shows that the procedure is safer, but the trial was underpowered to determine whether it is significant, Schulz-Schüpke noted.

ITALIC was the second study to provide a European perspective. Presenting on behalf of the ITALIC Investigators, Martine Gilard, MD, PhD, department of cardiology, Brest University Hospital, reported that similar clinical outcomes were seen with six-month and 24-month therapy with clopidogrel and aspirin following at least one Xience V Des stenting procedure.

The single type of second-generation drug-eluting stents was used to minimize variation in efficiency and safety, Gilard said.

The ITALIC study enrolled 2,031 patients in 70 centers in Europe and the Middle East. Good aspirin responders (1,894 patients) were randomized to treatment for six months (926 patients) or 24 months (924 patients) of DAPT. Patients resistant to aspirin were excluded from the analysis.

After one year, composite event rate for death, MI, emergency target vessel revascularization (TVR), stroke, or major bleeding was similar: 1.6 percent for six-month DAPT and 1.5 percent for 24-month DAPT. For secondary endpoints in patients receiving six-month versus 24-month DAPT, respectively, event rates for all-cause mortality (0.9 vs 0.8 percent), death from CV events (0.5 vs 0.3 percent), MI (0.7 vs 0.4 percent), stroke (0.0 vs 0.4 percent), and TVR (0.2 vs 0.5 percent), were also not significant.

Although the trial was terminated early due to recruitment issues, Gilard noted that non-inferiority was established for six-month versus 12-month treatment. Rate of events was significantly lower (1.5 percent) than the expected 3 percent. Incidence of stent thrombosis and major bleeding were also low and not significant with six-month and 12-month DAPT.

Gilard concluded, “Although six-month DAPT was non-inferior to 24-month DAPT in good aspirin responders, larger trials are needed for confirming these observations.”

Low-dose DAPT Versus High-dose DAPT

Gilles Montalescot, MD, PhD, professor of cardiology, University of Paris VI, provided the much needed context to the four trials that seemingly contradicted each other and said the conclusions from these studies only suggest clinical guidance.

The trials highlighting DAPT usage beyond 12 months showed less MI, ST and death, but more bleeding. Those advocating DAPT of less than 12 months showed similar rates for early ST, MI and deaths, but less bleeding. Shorter course of therapy is safer, but longer course of therapy prevents secondary events such as MI, he said.

Although ISAR-SAFE and ITALIC were difficult to conduct and inconclusive on their own, the data aligned with five previous studies. In a meta-analysis, along with the other five studies, Montalescot concluded that a shorter course of DAPT significantly lowered bleeding events.

With respect to a longer course of DAPT following stenting, he indicated that in 1,000 patients with DAPT use for 30 months, one could expect to reduce 20 MI and nine ST events, and increase five deaths and 10 major bleeding events.

For patients at risk for bleeding (e.g., prior bleeding episodes, advanced age, need for surgery, need for anticoagulation therapy and comorbidities associated with risk), Montalescot suggested DAPT therapy for six months following stenting may be sufficient.

For patients at risk for ischemic events (e.g., patients with coronary artery disease, stenting, patients with first generation stents and prior ST), extended DAPT beyond 12 months is advocated.