American Heart Association. | SCIENTIFIC SESSIONS 2015

Tuesday, November 10

DailyNews

INSIDE

AHA, AMA announce joint program to improve blood pressure control

The American Heart Association and the American Medical Association announced a nationwide initiative yesterday to help healthcare providers and patients improve blood pressure control.

The initiative, Target: BP, encourages providers to reach blood pressure goals below 140/90 mm Hg for each patient with hypertension, based on individual needs and the most current AHA guidelines.

The program was announced on the same day that findings from the Systolic Blood Pressure Intervention Trial (SPRINT) were presented at Scientific Sessions. The SPRINT results refute the notion that higher blood pressure may be acceptable in some situations, said Willie E. Lawrence Jr., MD, FAHA, chief of cardiology at Research Medical Center in Kansas City, Missouri.

"Target: BP emphasizes our current recommendation of a blood pressure goal of less than 140/90 mm Hg," Lawrence said. "However, we note that the initial SPRINT data go beyond confirming this current recommendation and strongly suggest that in certain patient populations, more aggressive blood pressure control may be indicated."

For more information about the trial results, see article at top right.

"Improving blood pressure control in the United States will take a concerted effort, and Target: BP aims to support clinicians in that effort," Lawrence said. "Only about half of all Americans with high blood pressure are achieving recommended reduction goals."

In the Target: BP program, hospitals, medical practices, practitioners and health service organizations will join forces with the AHA and the AMA to raise awareness about

TARGET: BP continued on page 17

SPRINT trial supports intensive blood pressure management below 120 mm Hg

Targeting a lower systolic blood pressure than is recommended in most current guidelines could result in a substantial reduction in cardiovascular events and all-cause mortality compared to current standard care.

These findings come from the "Systolic Blood Pressure Intervention Trial" (SPRINT), which was presented during a Late-Breaking Clinical Trials session on Monday. The study was published simultaneously in the *New England Journal of Medicine*.

The AHA and other groups generally call for maintenance of systolic blood pressure below 140 mm Hg. SPRINT compared the current standard of care to intensive treatment to bring systolic blood pressure to below 120 mm Hg.

"We know there is a strong observational relationship between blood pressure and cardiovascular disease," said SPRINT Steering Committee Chair Paul K. Whelton, MB, MD, MSc, from Tulane University School of Public Health and Tropical Medicine in New Orleans. "To date, there is no evidence of a lower threshold. The real question for those of us in practice is how low should we go?"

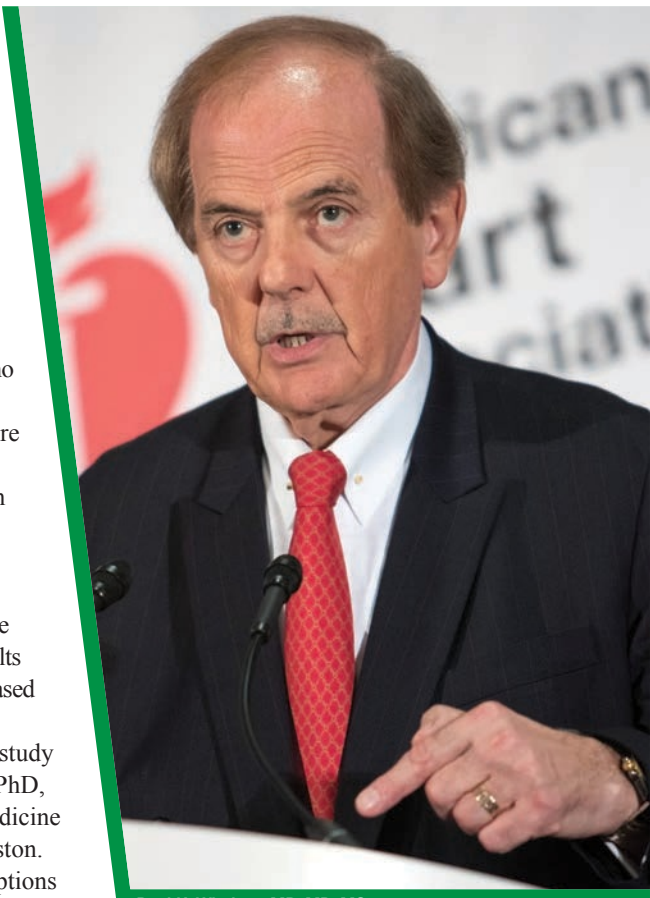
SPRINT results do not provide a floor for blood pressure reduction, Whelton said, but the data confirm that lower is better. Study participants with a systolic blood pressure of 120 mm Hg or lower had a 25 percent reduction in the first occurrence of myocardial infarction, non-MI acute coronary syndrome, stroke, acute decompensated heart failure and cardiovascular disease death compared to those meeting the standard goal of less than 140 mm Hg. Risk reduction ranged from 43 percent for cardiovascular death to no effect on acute coronary syndrome.

Lowering systolic blood pressure to 120 mm Hg or below also conferred a 27 percent decrease in the risk of all-cause mortality.

Whelton said the study had been expected to run four to five years. Instead, it was stopped in August due to the benefits seen to date. The results reported at Scientific Sessions are based on 3.26 years of follow-up.

"This study is a triumph," said study discussant Marc A. Pfeffer, MD, PhD, FAHA, the Dzau Professor of Medicine at Harvard Medical School in Boston. "As clinicians, we have a lot of options

SPRINT TRIAL continued on page 4



Paul K. Whelton, MB, MD, MSc

Genetic risk factors for coronary heart disease should inform patient care, study finds

The debate over the clinical utility of genetic risk information may be ending. Disclosing genetic risk factors for coronary heart disease can benefit clinical outcomes, according to a study presented during Monday's Late-Breaking Clinical Trials session.

"We have demonstrated that you can put genetic risk data into the electronic health record and use it in clinical decisionmaking," said Iftikhar J. Kullo, MD, professor of medicine at the Mayo Clinic in Rochester, Minnesota. "Genetic risk information can be effectively used at the point of care to guide therapy."

Kullo is lead author on "The Effect of Disclosing Genomic Risk of Coronary Heart Disease on Low-density Lipoprotein Cholesterol Levels: The Myocardial Infarction Genes (MI-GENES) Study."

Iftikhar J. Kullo, MD

MI-GENES randomized 203 patients at intermediate risk for cardiovascular events to receive a 10-year assessment of CHD based either on conventional risk factors or conventional risk factors plus a genetic risk profile. The primary outcome was LDL cholesterol levels six months after a risk assessment discussion between patient and physician.

LDL cholesterol levels fell in both groups, but the improvement was significantly larger in the genetic risk group.

Kullo said the decline in cholesterol was largely the result of increased initiation of statins by patients who knew their genetic risk scores.

Primordial prevention

Two other studies presented Monday showed that behavioral strategies can alter behavior to reduce risk factors in younger individuals. Such primordial risk reduction strategies offer enormous public health advantages.

LATE-BREAKING continued on page 15

TODAY AT SESSIONS

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

9–10:15 a.m.
Atrial Fibrillation: State of the Art and Future Direction
Hall D

9–10:15 a.m.
Precision Medicine
Chapin Theater

9–10:15 a.m.
Hypertension and Diabetes Mellitus: The Foundation of Both Heart and Kidney Disease
W109

10:45 a.m.–Noon
Genetics in Clinical Practice
W109

10:45 a.m.–12:10 p.m.
Late-Breaking Clinical Trials III: ACS and PCI: The Continuum of Care
Hall D

12:30–1:30 p.m.
Distinguished Scientist Lecture
Chapin Theater

2–3:15 p.m.
Plaque Vulnerability, Imaging, and Cardiovascular Risk: The Bedside Meets the Bench
Hall D

2–3:15 p.m.
Clinical Care Across the Age Continuum: Creating Bridges to Improve Care and Outcomes from age 0-100
Chapin Theater

3:45–5 p.m.
Improving Outcomes in Women's Cardiovascular Health
Hall D

3:45–5 p.m.
Best of Other Cardiovascular Meetings (Domestic and International)
W109

3:45–5:03 p.m.
Clinical Science: Managing Risk Factors for CAD—Clinical Trial Updates
Chapin Theater

'Step it Up!' at Sessions

It's Wear Sneakers Day at Scientific Sessions, an opportunity to show your personal commitment to an active, heart-healthy lifestyle by wearing sneakers to today's activities.

It's also an opportunity to demonstrate the AHA's support of the U.S. Surgeon General's Step It Up!

campaign, which encourages Americans of all ages and abilities to walk more and also encourages communities to create safe, accessible places for people to walk and wheelchair roll.

American Heart Association CEO Nancy Brown urged leaders across the nation to commit resources to "designing streets built to be shared, so their own communities come to life with the bustling of neighbors bicycling to work, walking kids to school, taking a morning jog or walking to the bus or train station."

Sessions attendees can post pictures of themselves wearing sneakers on social media using the hashtag #AHA15.

And don't miss today's special lecture by U.S. Surgeon General Vice Admiral Vivek H. Murthy, MD, MBA. He will discuss "Better Prevention, Wellness, and Health Promotion" during the special session on precision medicine that begins at 9 a.m. in the Chapin Theater. ▼

HIGHLIGHTS FROM THE PROGRAM CHAIR

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

Frank W. Sellke, MD, FAHA

Today, we put on our running shoes, tennis shoes and basketball shoes to show our support and to acknowledge that exercise is a key factor in maintaining good cardiovascular health and preventing heart disease and stroke.

A highlight of the day's program is the Distinguished Scientist Lecture, which will be presented by geneticist Christine Seidman, MD, of the Brigham and Women's Hospital. Seidman will present her lecture, "Genetics of Heart Disease: From Mutation to Mechanism," at 12:30 p.m. in the Chapin Theater. Not long after, Keith A. A. Fox, BSc, MBChB, FRCP, will present the annual Paul Dudley White Lecture at 2 p.m. in Hall D. His lecture is titled "Identification of the Vulnerable Plaque: From Bench to Bedside."

We also have another great lineup of Late-Breaking Clinical Trials planned. Today's theme is "ACS and PCI: The Continuum of Care," and the session begins at 10:45 a.m. in Hall D.

The first late-breaking trial to be presented is PROACT-4, which looked at point-of-care troponin testing in the ambulance for patients with chest pain. Then we will hear about the clinical benefit of intravascular ultrasound guidance in second-generation DES implantation from the IVUS-XPL study. Next, Long-Term Tolerability of Ticagrelor in the PEGASUS-TIMI 54 Trial, a follow-up of the PEGASUS trial, will be presented. After that we'll hear a new analysis of the DAPT study, which investigated the benefits and risks of 30 months versus 12 months of dual antiplatelet therapy in patients undergoing PCI with drug-eluting or bare-metal stents. The session will conclude with findings from the RIVER-PCI trial evaluating the efficacy of ranolazine in patients with a history of chronic angina and ICR after PCI.

The results of these trials should be of interest to general and interventional cardiologists, as well as to other physicians caring for patients with cardiovascular disease.

We also have a few special sessions planned that will focus on precision medicine and clinical care across the age continuum. Also today, you won't want to miss "Best of Other Cardiovascular Meetings (Domestic & International)," which will summarize the most important events and findings from meetings of the American College of Cardiology, the European Society of Cardiology and Heart Rhythm Society, to name a few.

This afternoon's Clinical Science: Special Reports session, which begins at 3:45 p.m. in the Chapin Theater, is titled "Managing Risk Factors for CAD—Clinical Trial Updates." The session will open with an update on cholesterol treatment targets and clinical outcomes from the JUPITER trial, and continue with results from a population-based study from Canada looking at the relationship between high-density lipoprotein cholesterol and cardiovascular and non-cardiovascular mortality. Next up will be results from the ACCORDION Follow-on BP study, which assessed the long-term effect of intensive versus standard systolic blood pressure lowering on the incidence of cardiovascular events or death in people with type 2 diabetes and high cardiovascular risk. The final presentation will examine results from a population-based study of revascularization of patients with diabetes and multivessel coronary disease.

Today's plenary sessions include "Atrial Fibrillation: State of the Art and Future Direction," "Hypertension and Diabetes" and "Improving Outcomes in Women's Cardiovascular Health." And today's joint sessions include presentations planned in conjunction with the Sociedad Chilena de Cardiología, the European Society of Cardiology, the Society for Cardiovascular Angiography and Interventions, EgIC of Egyptian Society of Cardiology, the InterAmerican Society of Cardiology, the AHA Council on Cardiovascular and Stroke Nursing and the Preventive Cardiovascular Nurses Association.

This is the final day the exhibit hall will be open, so take a final walk around the hall to see what's new from our industry colleagues. After another outstanding day covering all aspects of cardiovascular science, the day concludes with several council dinners at the Rosen Centre Hotel. Enjoy the day at Scientific Sessions. ▼

Late-Breaking Clinical Trials — LBCT.03 | 10:45 a.m.–12:10 p.m. Tuesday | Hall D

ACS and PCI: The Continuum of Care

TRIAL	DESCRIPTION
Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROACT-4)	This trial was designed to test the addition of point-of-care troponin testing in the ambulance for patients with chest pain. *Funded by the Heart and Stroke Foundation of Canada.*
Clinical Outcomes of Intravascular Ultrasound Guided Everolimus-Eluting Stents Implantation in Long Coronary Lesions	This study evaluates whether intravascular ultrasound (IVUS) results in better clinical outcomes compared to angiography-guided implantation in patients who have long coronary lesions.
Long-Term Tolerability of Ticagrelor in the PEGASUS-TIMI 54 Trial	This trial was designed to evaluate the efficacy and safety of ticagrelor with two dosing strategies for chronic secondary prevention. The trial also addresses why ticagrelor is discontinued more than placebo and the long-term outcomes for patients who continue it.
Individualizing Treatment Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: An Analysis of the DAPT Study	The Dual Antiplatelet Therapy Study was an international, multicenter, double-blinded, randomized trial that investigated the benefits and risks of 30 months versus 12 months of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention with drug-eluting or bare-metal stents. This DAPT Study analysis looked at models to predict outcomes to individualize DAPT treatment and improve long-term outcomes.
Angina and Quality of Life Following PCI With Incomplete Revascularization: Results From the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial	This trial randomized patients with a history of angina and incomplete revascularization after PCI to ranolazine or placebo, and followed them for ischemia-driven hospitalization or revascularization and patient-reported angina and quality of life during follow-up.

Clinical Science: Special Reports — CS.03 | 3:45–5:03 p.m. Tuesday | Chapin Theater

Managing Risk Factors for CAD—Clinical Trial Updates

TRIAL	DESCRIPTION
Cholesterol Treatment Targets and Clinical Outcomes: A JUPITER Trial Update	This analysis of the completed JUPITER trial addresses whether or not on-treatment target levels of LDLC, non-HDLC and apo B are relevant for event reductions attributable to statin therapy, an issue relevant for current guidelines.
Relationship Between High-Density Lipoprotein Cholesterol and Cardiovascular and Non-Cardiovascular Mortality: A Population-Based Study of More than 630,000 Individuals Without Prior Cardiovascular Conditions in Ontario, Canada	This population-based study from Canada looks at the relationship between high-density lipoprotein cholesterol and cardiovascular and non-cardiovascular mortality.
Long-term Cardiovascular Effects of 4.9 Years of Intensive Blood Pressure Control in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes Follow-On Blood Pressure Study (ACCORDION Follow-on BP Study)	This study assessed the long-term (10-year) effect of 4.9 years of intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic blood pressure lowering on the incidence of cardiovascular events or death in 4,733 people with type 2 diabetes and high cardiovascular risk.
Revascularization in Patients With Diabetes and Multivessel Coronary Artery Disease: A Population-Based Evaluation of Outcomes	Results from a real-world experience in revascularization of patients with diabetes and multivessel coronary disease from British Columbia.

Mitral valve replacement more durable than repair, study finds

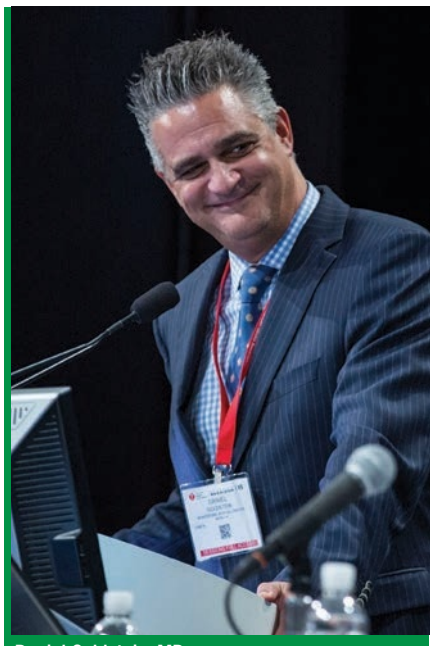
Replacing mitral valves is more durable than repairing valves and results in fewer heart failure events and fewer cardiovascular readmissions, according to research presented at Scientific Sessions.

On Monday, lead author Daniel Goldstein, MD, professor of cardiovascular and thoracic surgery at the Montefiore Einstein Center for Heart and Vascular Care in the Bronx, New York, presented results from "Two-Year Outcomes following Mitral Valve Repair or Replacement for Severe Ischemic Mitral Regurgitation." The results are similar to the study's one-year data reported in 2014.

"Until this trial, there was no evidence on whether we should repair or replace the mitral valve," Goldstein said. "The differences we see in these results are clinically significant."

Alain Carpentier, MD, PhD, professor emeritus at Pierre and Marie Curie University in Paris, France and widely regarded as the father of modern mitral valve repair, also discussed the study.

"Up to now, valve repair has been seen as superior to valve replacement," Carpentier said. "This study brings important new information, especially for younger surgeons. If these results are confirmed, the young surgeon with little experience with valve repair should not feel guilty about replacing a valve, because it is the more durable procedure."


Daniel Goldstein, MD

Researchers in the Cardiothoracic Surgical Trials Network randomized 126 patients to mitral valve repair and 125 to mitral valve replacement. About three-quarters of the patients were men, the median age was 69 years, 83 percent were Caucasian and a third had diabetes.

The one-year results showed no difference between the two groups in left ventricular end systolic volume index (LVESVI), no differences in clinical endpoints and no differences in quality of life metrics. But mitral regurgitation graded moderate or higher occurred in about 34 percent of repair patients compared to three percent of replacement patients.

Two-year results were similar, with no difference in LVESVI, mortality or MACCE between the two groups.

Mitral regurgitation was significantly higher in the repair group, at about 59 percent compared to two percent. And while the overall rate of serious adverse events was similar, the repair group had a slightly higher but statistically significant rate of heart failure, a substantially higher rate of cardiovascular readmissions and lower quality-of-life scores.

Both groups had progressive numbers of device failures over time, but the repair group failure rates were significantly higher at 30 days, six months, 12 months and two years.

"We are seeing that replacement proves a more durable correction of mitral regurgitation than does mitral valve repair," Goldstein said. "I feel much less uncomfortable replacing a valve than I did a few years ago. At the same time, we need to learn how to predict who will do well with repair because there is a substantial portion of repair patients — almost 43 percent — who do not have recurrance. But until we have a reliable predictor for successful repair, I would feel comfortable doing a replacement as the initial procedure." ▼

CAREER PROGRESSION

BRADLEY S. MARINO, MD, MPP, MSCE, FAHA

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

Bradley S. Marino, MD, didn't envision his career taking the path that it has.

"If you told me when I started my career as an attending that I'd be doing research looking at the impact of neurodevelopmental, psychosocial and physical morbidities on quality of life, functional status and behavioral or emotional outcomes for pediatric heart patients, I would not have believed it," said Marino, professor of pediatrics and medical social sciences at the Feinberg School of Medicine at Northwestern University in Chicago.

Marino became interested in pediatric heart patients as a first-year cardiology fellow at an outpatient clinic. Patients were surviving, but they were returning to the clinic with significant neurodevelopmental and psychosocial comorbidities.

"There was a huge, huge gap of knowledge about quality of life, functional status and how multiple surgeries and hospitalizations were affecting the behavior and emotional status of these young patients," he said.

Today, Marino is a passionate advocate for this population of survivors. His work is focused on modifying the care paradigm from mortality prevention to morbidity prevention. His goal is to develop interventions that promote resilience and prevent neurodevelopmental and psychosocial comorbidities that affect quality of life for pediatric heart patients.

Marino said he was fortunate early in his career when a mentor got him involved in the Pediatric Subcommittee of the AHA's Emergency Cardiac Care Committee.

"The colleagues, research partners and friendships I've made through the AHA have obviously dramatically helped me in my career progression," he said. "It's created natural research networks for me and allowed for collaboration. From a learning standpoint, I see the best of the science every year."

Marino has held several volunteer leadership positions at the American Heart Association. He is currently vice chair of the Council on Cardiovascular Disease in the Young and will become chair of the council next year. He also serves as co-chair of the council's Cardiopulmonary Resuscitation in Infants and Children with Cardiac Disease Writing Group. He's a member of the council's Congenital Cardiac Defects Science Subcommittee and also serves as a liaison from the council to many other AHA committees. Outside the council, he serves on the Scientific Sessions Program Committee and the Emergency Cardiovascular Care Pediatric Resuscitation Forum.

Marino said a highlight of his volunteer work was his involvement with the Congenital Cardiac Defects Science Subcommittee.

"That was a wonderful experience," he said. "I got to work on scientific statements, specifically the neurodevelopmental statement that came out in 2012, which I think has been one of the really important papers that's come out regarding long-term outcomes in pediatric cardiology." ▼

MEMBER SPOTLIGHT

Mahasin S. Mujahid, PhD, MS

Assistant Professor of Epidemiology, University of California, Berkeley, School of Public Health

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

I have been an AHA/ASA Professional Member since 2011.

Why did you join?

I was first introduced to the AHA when I was a fellow at the Ten-Day Seminar on the Epidemiology and Prevention of Cardiovascular Disease. At that time, I was completing my postdoctoral studies at Harvard University as a Robert Wood Johnson Health and Society Scholar. I was very nervous because I didn't know how much my work as a social epidemiologist would be valued.

Contrary to my expectations, I had a wonderful experience learning from and interacting with many of the leaders in cardiovascular epidemiology. They helped me think through my research agenda as well as strategies for my professional development. That planted a wonderful seed of curiosity about whether I would receive the same kind of support as an early career investigator within the AHA. After beginning my faculty position at UC Berkeley, I became a member and I have not been disappointed!

Are you involved in AHA councils?

I am a member of the Council on Epidemiology and Prevention (EPI).

What do you enjoy most about this role?

I have had wonderful opportunities to network with early-stage and senior investigators. This networking helped facilitate the mentorship team of my career development award, of whom many are active members of the AHA. In 2012, I was invited by the former chair of the EPI Council to participate in a working group to think critically about the social determinants of cardiovascular health and how to best profile the extensive research in this area. We recently published an AHA scientific statement, "Social Determinants of Risk and Outcomes for Cardiovascular Disease."

How else are you involved with the AHA?

I am chair of the Social Determinants of Health Scientific Subcommittee and a faculty instructor for the AHA Ten-Day Seminar on the Epidemiology and Prevention of Cardiovascular Disease.

Why is membership valuable to you?

The AHA has a strong commitment to improving the cardiovascular health of all Americans, including those groups disproportionately burdened with poor cardiovascular health. This commitment is underscored by the launch of the EmPowered to Serve program. The AHA has partnered with faith-based organizations, affordable housing and other strategic alliances to transform environments by creating a sustainable culture of health.

Equally exciting is the recent funding of four centers as part of the AHA Strategically Focused Research Network on Disparities in Cardiovascular Disease. This work is important and timely. I am excited to be a part of an organization whose mission is directly in line with my passion for working to improve the health status of marginalized populations.

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

The AHA is a one-stop shop for early-stage investigators. It provides fruitful opportunities to build scientific collaborations and networks, apply for research funding, develop leadership skills and serve local communities as we work together to achieve the AHA 2020 Impact Goals. ▼

Precision Medicine Initiative to begin enrolling volunteers next year

The end of Daylight Saving Time was a sleep disrupter. Body clocks had to adjust.

What happened to your sleep rhythms? Did you have other health ramifications?

Sensors and other technological advances can generate such raw data and a new era is forming around the collection and interpretation of it. This is part of the foundation of precision medicine, which was the subject of a Monday presentation by Gary H. Gibbons, MD, director of the National Heart, Lung, and Blood Institute.

Gibbons used the recent time change as an example of the power and promise of precision medicine.

"Imagine if you could get tens or hundreds of thousands of people to share their data about what happened to them when we shifted the timing of when they get up and go to sleep by an hour," he said in an interview following his lecture. "If people are willing to volunteer and participate in something where we strategically ask certain questions, and we monitor the data for its research integrity and accuracy, then we can do things to scale in ways that weren't imaginable 10 years ago.

"Those are the kinds of things that are now possible."

The concept of precision medicine is in its infancy. Having the tools to answer myriad questions is the first step. Next comes figuring out how to make it work and dealing with issues ranging from accuracy to privacy, reliability and methods for sharing data. Finding those solutions is a goal of the Precision Medicine Initiative announced by President Obama during his State of the Union address earlier this year.


Gary H. Gibbons, MD

A key component in the initiative is creating a study group of at least 1 million Americans willing to share their health data. Enrollment is expected to begin early next year.

Gibbons stressed the importance of people not only signing up, but being actively involved in the process.

"It's their data," he said. "So they really ought to be guiding what happens to their information that's part of the research development and creation of the database and cohort. We also need to think about how we can return the results to the participant so they can be empowered to understand the information and engage their care providers in helping interpret that information and decide what's best to do."

In his presentation, Gibbons illustrated what the study may do for a participant through the tale of a fictional 40-year-old, African-American woman named Carla.

Carla's DNA profile reveals that she's at a higher risk of kidney and cardiovascular disease. She chooses to be monitored, leading to the discovery of high blood pressure. She then receives recommended lifestyle modifications to help control her blood pressure. She also begins taking blood pressure-lowering medicine and she keeps it in a "smart bottle" that notifies her if she misses a dose.

"As a result of this prescription, her blood pressure normalizes and Carla remains healthy," Gibbons said. "At the end of the day, that's part of our shared mission, that's part of the opportunity of precision medicine and that's hopefully what our ongoing partnership will do for the Carlas of the next decade."

Gibbons also brought up a key point about the treasure trove of data that will mark this new era: We're going to need people to sort through it all.

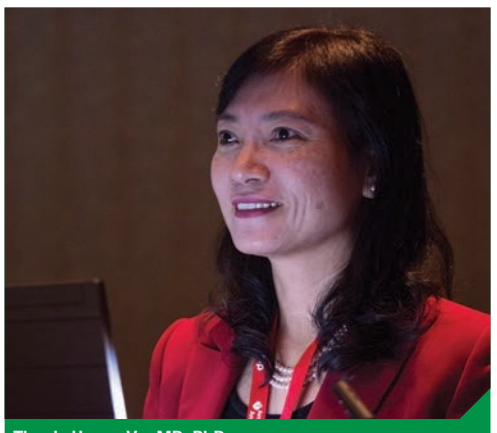
He laughed as he noted that while a human genome can be sequenced in less than a day, "actually analyzing it still takes much more than a day."

"I think this is an incredible challenge, but it's also an incredible opportunity to bring in new thoughts — mathematicians, computer scientists, economists, physicists — people who think about big data and data sets, and how and what those data mean.

"I think we need to encourage more people to come in and help us collectively solve this problem for the nation," he continued. "We need more data scientists, we need more quantitative scientists and we are developing a platform of training programs related to quantitative science." ▼

Consistent healthy lifestyle associated with better quality of life in old age

Not smoking, exercising frequently and having normal body mass index are tied to improved quality of life in older individuals, according to findings reported during an oral session on Monday from the Chicago Heart Association Detection Project in Industry study (CHA).


Thanh-Huyen Vu, MD, PhD

"Our findings underscore the importance of consistently maintaining ideal healthy lifestyle practices in older age for better maintenance of quality of life," said Thanh-Huyen Vu, MD, PhD, of the department of preventive medicine at Northwestern University's Feinberg School of Medicine in Chicago. "It is important that healthcare providers promote the benefits of maintaining and improving healthy lifestyle practices over time for their elderly patients. It is never too late to practice a healthy lifestyle."

The study included 4,074 participants who participated in the health survey in 1996 and at least two more surveys in 2001, 2003 and 2012.

With 16 years of follow-up in a cohort of men and women 65 and older, Vu reported that participants who maintained a high number of healthy lifestyle practices had the best (higher score and slower decline) HRQOL over time even after adjustment for potential confounding factors such as age, sex, race, education, marital status, alcohol intake and comorbidities.

HRQOL was measured using Health Status Questionnaire-12, which reflects both physical and mental well-being.

When the HRQOL scores were analyzed for the physical and mental components separately, participants with a medium and high number of healthy lifestyle practices were likely to have physical component scores three-times better than those who practiced a poor lifestyle, Vu said. For the mental components scores, those with medium and high healthy lifestyle practices were likely to have 1.9-times better mental component scores.

Accounting for baseline healthy lifestyle practice and risk factor (e.g., high blood pressure, high cholesterol, diabetes) levels measured four decades ago, Vu said that the data still remained significant. For example, among participants who had zero healthy lifestyle practices at baseline in 1996, the odds ratio for having the best HRQOL at all subsequent surveys was 2.5 (95 percent confidence interval) for participants who had better healthy lifestyle practices compared with those who always had poor healthy lifestyle practices. ▼

SPRINT TRIAL continued from page 1

to treat high blood pressure. These data give us additional motivation to use those options. More intensive management of high blood pressure, below a commonly recognized target, significantly reduces rates of cardiovascular disease and lowers risk of death."

The study included 4,678 participants randomized to intensive treatment and 4,683 to standard treatment. The participants were an average of 68 years old, had systolic blood pressure between 130 mm Hg and 180 mm Hg with or without medication, and had at least one additional cardiovascular disease risk factor. Prespecified subgroups included individuals with chronic kidney disease (28.5 percent), history of cardiovascular disease (20.1 percent), and 75 years or older (28.2 percent). Individuals with diabetes were excluded from the trial.

About 36 percent of the cohort was female, 30 percent African-American and 11 percent Hispanic. Nearly 91 percent were on hypertensive medication at baseline, taking a mean of 1.8 medications.

Participants had their blood pressure taken monthly for the first three months and every three months thereafter. All received free hypertensive medications from all major hypertensive drug classes and were assessed periodically for orthostatic hypotension and related symptoms. Investigators were free to prescribe any hypertensive medication, although the protocol recommended familiar diuretics, ACE inhibitors, calcium channel blockers and ARBs with the largest bodies of clinical evidence.

At the time the study was halted, participants in the intensive group were taking a median of 2.8 hypertensive medications, Whelton said, a typical addition of one drug to existing regimens. The benefit of lowering systolic blood pressure was similar across all subgroups, he added.

Adverse event profiles were similar across the two groups, although there was a signal for reduced glomerular filtration rate in participants in the intensive treatment group who did not have chronic kidney disease at baseline. Individuals who had chronic kidney disease at baseline did not seem to fare any worse with intensive blood pressure lowering.

The intensive treatment group also had increased risk for hypotension and syncope, but not for injurious falls.

"We saw a very impressive separation between the two arms after about a year that became more dramatic over time," Whelton said. "We deemed the benefits of intensive blood pressure lowering far outweigh the potential for risks in this population."

Recently, *The Lancet* published a meta-analysis, "Effects of Intensive Blood Pressure Lowering on Cardiovascular and Renal Outcomes: Updated Systematic Review and Meta-analysis." Not all of the trials in the latest *Lancet* meta-analysis reported information on the safety of more intensive lowering of blood pressure. SPRINT provides that critical information and is a contemporary trial that provides clinicians and patients not only with an estimate of the benefits of intensive BP lowering but also the potential adverse effects of such a strategy. All of that information is needed for fully informed decisionmaking for this condition that affects 80 million Americans. ▼

Total artificial heart shows promise for end-stage cardiac insufficiency patients

The facts about end-stage cardiac insufficiency, which affects nearly 5 million people in the U.S., justify the development of total artificial hearts for destination therapy, according to Alain Carpentier, MD, PhD, who delivered the Lasker Awardee Lecture on Monday.

End-stage cardiac insufficiency has an annual mortality rate of about 45 percent, and the hope for heart transplantation is limited not only by the shortage of donors, but often by contraindications such as pulmonary hypertension.

Carpentier, who is widely regarded as the father of mitral valve repair, is professor emeritus at Pierre and Marie Curie University in Paris, France. He is also co-inventor of the CARMAT total artificial heart, which has been implanted into three patients in Europe thus far, and has been approved for a fourth.

Carpentier said the CARMAT (Carpentier-Matra) heart offers advantages over previously developed artificial hearts, which could be susceptible to thromboembolism, among other potential complications.

"The advantage I have is the fact that I developed valvular bioprostheses more than 30 years ago, and because [CARMAT hearts] use biological tissue, they display superior hemocompatibility, allowing us to avoid the use of anticoagulants," he said. "This stimulated my interest in the development of an artificial heart, thinking that if we can use these materials, we would probably at least minimize the problems they encounter with thromboembolic complications."

The CARMAT heart is a bioprosthetic total artificial heart, comprising two separate ventricles, two pulsatile pumps, four bioprosthetic valves and two bioprosthetic membranes.

"It's important to note that the pump is within the heart itself and not in a console separated from the heart. All of the components, including the electronics, are incorporated into a single compliance chamber between the two ventricles," Carpentier explained. "The function is quite different than the existing devices. We tried to really mimic cardiac function because the aim is destination therapy, not something that could be used as a bridge to transplant."

After more than 30 years of development and countless experiments, the first CARMAT total artificial heart was implanted into a 76-year-old male patient in December 2013. That patient survived for 74 days after the operation, which was more than twice the survival time of the previously longest-surviving artificial heart recipient.

The second implant was performed in August 2014 on a 68-year-old male, who survived 270 days. The third implant took place in April 2015, and that 73-year-old male patient is still alive after 215 days.

"All three patients had end-stage heart disease and were suffering from terminal cardiac insufficiencies," Carpentier said. "There was no operative mortality in the three patients — all woke up nicely and were fully mobilized within two days of the operation."

Describing the cumulative clinical experience, which adds up to 559 days of function so far, Carpentier said there was no hemolysis, no thromboembolism, no acquired Willebrand syndrome and no infection recorded in any of the three cases, which he calls "quite remarkable."

Carpentier lauded the potential life-changing benefits for patients, concluding with a video of a transplant recipient nearly eight months after the operation. The patient said he was not bothered by the weight or noise of the prosthesis, and that he was thankful for his physical condition and the extra time the operation had given him with his family.


Alain Carpentier, MD, PhD

"I did not set out to do this because I was interested in doing something that was high-tech or prestigious," Carpentier said. "We are cardiologists and we are cardiac surgeons, and what we are most interested in is the comfort and the quality of life of our patients. We use high technology — lifeline technology — to provide appropriate care and deliver the best quality of life for our patients." ▼

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New SVT guideline offers treatment alternatives

An updated guideline for managing adult patients with supraventricular tachycardia offers new treatment options and opportunities for shared decisionmaking. The guideline, which was jointly published by the AHA, the American College of Cardiology and the Heart Rhythm Society in August, replaces the guideline published in 2003.

"The new guideline, unlike previous guidelines, stresses shared decisionmaking with the patient in all environments," said lead author Richard L. Page, MD, the George R. and Elaine Love Professor and Chair of Medicine at the University of Wisconsin School of Medicine & Public Health in Madison. "We urge clinicians to consider the patient's preferences and treatment goals and their individual situations when considering treatment options."

SVT is a constellation of irregular cardiac rhythms that does not include atrial fibrillation, but still affects about two people per 1,000 in the United States and accounts for about 50,000 emergency department visits annually. Paroxysmal SVT affects about 570,000 individuals and is most common in women and older adults.

The new guideline is largely iterative, Page said, but it contains important changes that should affect clinical practice. Drug therapy is largely unchanged, although one new agent, ivabradine, is now recommended for the management of patients with inappropriate sinus tachycardia.

Ablation techniques have improved significantly since the previous guideline, Page said, including techniques that minimize radiation exposure. A section of the guideline devoted to pregnant women offers alternatives that were not previously available.

"If necessary, one can now do electrophysiology studies and ablation with minimal radiation exposure to the mother and the fetus," Page said. "This opens new possibilities in clinical practice that were not available in prior years."

Another section provides recommendations for patients who are asymptomatic but exhibit Wolff-Parkinson-White pattern. Developing recommendations to manage asymptomatic patients based on a systematic review of the current evidence was one of the goals of the guideline task force and was supported by a separate evidence review.


Richard L. Page, MD

"We have fully addressed, based on the latest information, the best way to approach patients with Wolff-Parkinson-White pattern, or preexcitation, who have no symptoms," Page said. "This has been an area of a fair amount of discussion in recent years and a notable lack of agreement."

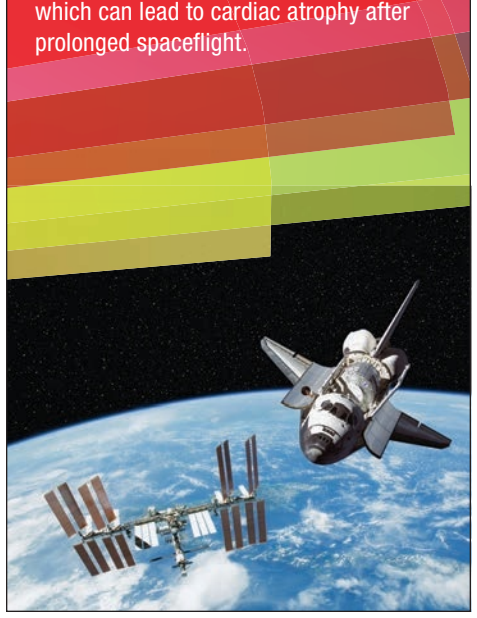
Page said that there were no major changes, but some significant updates are included nonetheless.

"We have developed algorithms for the recognition of SVT, as well as algorithms for both acute therapy and ongoing management of these arrhythmias, based on the type of arrhythmia that is encountered," Page said.

The guideline task force and writing committee used evidence-based methodologies to evaluate all available data at the time of writing. Literature searches focused on randomized controlled trials, but also included registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews and expert opinion. ▼

Spaceflight linked to cardiac atrophy

Researchers sent 15 medaka fish to the International Space Station to examine how microgravity affects the structure and gene expression of cardiac muscle. During a poster session Monday, they reported that microgravity increases autophagy-related genes and decreases sarcomeric protein gene expression, which can lead to cardiac atrophy after prolonged spaceflight.



Paul Dudley White lecturer will discuss novel techniques to detect at-risk plaques

Findings about the mechanisms and manifestations of CAD and how they can be applied clinically is the focus of today's Paul Dudley White International Lecture.

Professor Keith A.A. Fox, BSc, MBChB, FRCP, will deliver "Identification of the Vulnerable Plaque: From Bench to Bedside" from 2 to 2:30 p.m. in Hall D at the beginning of plenary session *Plaque Vulnerability, Imaging, and Cardiovascular Risk: The Bedside Meets the Bench.* He will discuss acute coronary syndromes and the events leading to plaque rupture, including novel techniques to detect at-risk plaques.

"Much of the focus in acute coronary syndromes has been on treatment after the myocardial infarction presentation," said Fox, who is the Duke of Edinburgh Professor of Cardiology at the University of Edinburgh in the United Kingdom and has investigated acute coronary arterial disease for decades. "Up to now, we have lacked the tools to accurately define which subjects are most at risk, and more importantly, which plaques are quiescent and which are prone to rupture."

Fox will review new data on tools, including the use of CT PET with fluorine 18 imaging, now available to assess and identify plaques at risk for rupture.

"My goal is to refocus the discussion on upstream events in an effort to prevent acute coronary syndrome events," he said. "I'll be reviewing key links between the underlying biology of inflammation and the clinically applicable translation of this research into predicting ACS events and, ultimately, preventing those events."

Professor Keith A.A. Fox, BSc, MBChB, FRCP

LECTURE PREVIEW

Paul Dudley White International Lecture: Identification of the Vulnerable Plaque: From Bench to Bedside
2–2:30 p.m. Tuesday
Hall D

Fox's research extends from underlying biological mechanisms to *in vitro* and *in vivo* studies to clinical trials. His ongoing work is investigating the mechanisms of inflammation and plaque rupture in acute coronary syndromes and antithrombotic therapies.

Fox is chair of several large multi-national studies on acute coronary syndromes, including the Global Registry of Acute Coronary Events (GRACE), an international observational outcomes database for patients hospitalized with ACS, which includes 100 hospitals in 14 countries. He is also lead investigator for studies on novel anti-thrombins, anti-coagulants and antiplatelets.

Fox is international associate editor of the *European Heart Journal* and deputy editor of the *Journal of the American College of Cardiology* (Europe). He was recently honored by the American College of Cardiology as one of four "Legends in Cardiology" for 2015. ▼

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Novel technologies reveal genetics underlying heart disease

Investigators at Brigham and Women's Hospital and Harvard Medical School are using novel molecular technologies to discover underlying genetic causes of heart disease.

Christine Seidman, MD, FAHA, will discuss this research and its clinical implications during the Distinguished Scientist Lecture Tuesday at Scientific Sessions. Her lecture, "Genetics of Heart Disease: From Mutation to Mechanism," begins at 12:30 p.m. in the Chapin Theater.

Seidman, who is the Thomas W. Smith Professor of Medicine and Genetics at Harvard Medical School and director of the Cardiovascular Genetics Center at Brigham and Women's Hospital in Boston, said researchers are using novel genomic and cell biologic technologies to improve the identification of causes and mechanisms for heart disease. By combining next-generation sequencing technologies with the capacity to selectively mutate iPS-derived cardiomyocytes, there are unparalleled opportunities to study heart disease in human tissues and cells, she said.

"Using these platforms, we can study the full spectrum of heart disease — from congenital heart malformations, cardiac remodeling in young adults and heart failure," she said. "Rarely do we have breakthrough technologies that can do all of that in one fell swoop. These new tools really allow us to discover the secrets of heart disease."

Recent research has shown that congenital heart disease, particularly severe malformations that occur with considerable morbidity and mortality, are caused by *de novo* DNA mutational events, Seidman said. These mutations, which alter genes that affect developmental transcription, provide insights into the molecules and pathways that are required to build a heart.

This information is particularly important when counseling parents and families on the likelihood of recurrent heart malformation in subsequent children, Seidman noted. For *de novo* mutations, the risk of recurrence is low.

"Increasingly, we have also understood that the new mutations affect more than just the heart. This information can help us better predict interventions that may help these children," Seidman said. "These findings imply that there will be new opportunities to improve clinical outcomes in children with severe congenital heart malformations, which is wonderful."

The same technologies have been used in the study of cardiomyopathy in young people.

"The most common cause of sudden death on the athletic field is hypertrophic cardiomyopathy, and now we know it is a genetic disease of the sarcomere, the contractile unit in heart muscle cells," Seidman said. "Analyses of sarcomere proteins with these mutations have improved our understanding of the consequences of abnormal cardiac contraction."

This research paved the way for preclinical trials in mice, which in turn has led to clinical trials in humans.

Broad-based sequence analyses of adults with dilated cardiomyopathy and heart failure have also revealed mutated genes. The production of cardiomyocytes and micro-tissues carrying these mutations has improved researchers' understanding of specific molecules that are essential for cardiac function, providing new opportunities to reduce the considerable burden of heart failure, Seidman said.


Christine Seidman, MD, FAHA

LECTURE PREVIEW

Distinguished Scientist Lecture: Genetics of Heart Disease: From Mutation to Mechanism
12:30–1:30 p.m. Tuesday
Chapin Theater

"This is an amazing new cardiovascular world," she said. "In many instances, we're just learning what genetic variants in cardiac sequences mean. But in some instances, we've been able to take them forward to build models and to elucidate pathophysiologic mechanisms. From that comes opportunity for therapy." ▼

Role of VV in coronary spasm

In a study presented Monday at Scientific Sessions, researchers provided the first evidence that adventitial vasa vasorum (VV) formation is enhanced at the spastic coronary segments associated with Rho-kinase activation in vasospastic angina patients. This suggests the important role of adventitial VV in the pathogenesis of coronary spasm.

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Visit this one-stop shop for the newest research and features from research labs around the world.

Retail Row

Visit these exhibitors to shop for a variety of leisure products.

Tuesday's Theater Demonstrations

Cardiovascular Expert Theaters

Booth 1601

Noon–12:45 p.m.
The Evolving Cholesterol Landscape
Amgen

1:15–2 p.m.
Updates in Anticoagulation
Daiichi Sankyo, Inc.

Booth 1559

Noon–12:45 p.m.
Updates in Anticoagulation
Daiichi Sankyo, Inc.

1:15–2 p.m.
Understanding the Ongoing Risk of Atherothrombosis Beyond the Culprit Lesion
AstraZeneca

Booth 163

Noon–12:45 p.m.
Re-Evaluating Anticoagulation Management Across the Patient Journey
Boehringer Ingelheim Pharmaceuticals, Inc.

1:15–2 p.m.
Practical Implications of the Landmark OPAL-HK Study for Hyperkalemia Patients
Relypsa, Inc.

HeartQuarters Theater

Booth 859

10:15–11 a.m.
Hypertension CPC Case: A Woman With Treatment-Resistant Hypertension
Presenters: Gemma Currie and Christian Delles, University of Glasgow

11:15 a.m.–Noon
Video

12:15–12:45 p.m.
Introduction to new My American Heart Website Using the Professional Online Network
Presenter: Kerstin Wiggins

12:45–1:15 p.m.
Mission Possible: Building Cardiac Systems of Care
Presenter: Paula Feather, BA, MBA

1:15–2 p.m.
Professional Education: Claim Credit, Education On-Demand, Opportunities for AHA CME at Your Institution or Practice
Presenter: Michelle Bruns, MLA, Director, Professional Education

2–2:30 p.m.
You're the Cure Video: Learn More About the Latest Advocacy Work You're The Cure Advocates Are Doing to Improve Heart Health in Our Communities, States and Country

Home time following stroke associated with hospital factors

Hospital factors play a significant role in determining whether stroke survivors spend more time at home in the immediate 90 days to one year following their stroke, according to findings presented at a poster session Monday at Scientific Sessions.

"Home time is a relatively novel outcome measure and one that is a high priority outcome for stroke survivors," said Emily C. O'Brien, PhD, of the Duke Clinical Research Institute in Durham, North Carolina. She noted that three of the study co-investigators are stroke survivors and bring a unique perspective to the study.

The findings from the PROSPER study showed that factors such as the volume and severity of stroke patients that a hospital treats, and the hospital's geographic location were significant in determining whether stroke survivors spent more time at home.


Emily C. O'Brien, PhD

Hospitals handling high stroke volume were associated with 0.18 and 0.42 more home-time days over the 90-day and one-year periods, respectively. Stroke survivors discharged from rural locations were likely to spend 1.30 and 2.17 more home-time days over the 90-day and one-year periods, respectively, compared with stroke survivors discharged from urban locations.

In comparison with hospitals in the Northeast, stroke patients discharged from hospitals in the West were likely to experience the highest home time — 3.25 and 5.16 more home-time days over the 90-day and one-year periods, respectively.

O'Brien and her research colleagues used two unique data sources in the study: the Get With The Guidelines (GWTG) Stroke database, a national initiative for improving the quality of stroke care, and the Medicare claims database, which allowed the PROSPER investigators to follow patients after discharge.

The 156,869 ischemic stroke patients from 989 hospitals participating in the GWTG initiative were linked with Medicare claims following discharge. Home time was determined when claims were not linked to inpatient hospital stay, time spent in rehabilitation centers or Medicare-certified skilled-nursing facilities.

Median home time over the first 90 days following discharge and one year following discharge were determined as relevant outcome measures. Across all of the hospitals in the GWTG initiative, overall median home time over the first 90 days was 59.5 days and 270 days over a year. When adjusted for variables, median home times were 59.3 days and 270 days for the 90-day and one-year periods, respectively.

"There is a significant variation in home time across the hospitals participating in the GWTG Stroke initiative." O'Brien said. "Hospital stroke volume and rural location were associated with more days spent at home following a stroke."

The PROSPER investigators also reported on patient characteristics for the four quartiles of 90-day home time, with quartile one showing the lowest 90-day home time (between 30.9 and less than 55.7 days) and quartile four representing survivors who spent more than 63.2 days at home. Patients in the lowest home-time quartile were frailer compared with the higher quartiles — median age was 82 years, 62.2 percent were female, 31.1 percent had atrial fibrillation, 31.1 percent had diabetes and 12.2 percent had heart failure. Patients in the highest 90-day home quartile had a median age of 77 years, 51 percent were female, 18.9 percent had atrial fibrillation, 27.2 percent had diabetes and 5.7 percent had heart failure. ▼

Weight history influences the likelihood of subclinical myocardial injury

Maintaining a stable or normal body mass index through adulthood greatly reduces the risk of subclinical myocardial injury in individuals without cardiovascular disease, according to data presented during a poster session Monday.

"Our study shows that overweight and obesity, even from young adulthood, was associated with increased risk for subclinical myocardial injury and likely subsequent heart failure," said Chiadi Ndumele, MD, MPH, the Robert E. Meyerhoff Assistant Professor in the department of medicine at Johns Hopkins University in Baltimore. "It underscores the importance of maintaining a normal weight from an early age for the optimal prevention of CVD."

Past studies have demonstrated the association between obesity and the development of heart failure, as well as the toxic effect of obesity on the myocardium as reflected by elevated levels of high-sensitivity troponin T [hs-cTnT], noted Ndumele. However, those studies were limited by linking a single weight measurement or BMI with outcomes. What is unknown is the association of weight history with myocardial injury.

"The current analysis attempts to provide insights into that association," Ndumele said.

Ndumele's study linked BMI patterns over time with elevations in hs-cTnT in 9,472 participants from the Atherosclerosis Risk in Communities (ARIC) study, an ongoing, prospective, multicenter epidemiologic study initiated in 1987 with 15,792 individuals to determine the causes of CVD in the community. Participants without CVD included in the study had a BMI ≥18.5 (measured in kilograms per square meter).

Patterns of BMI changes were evaluated in different ways — all providing similar results. In one analysis, BMI categories were cross-tabulated at ARIC visit 4 and age 25. Ndumele reported that within each visit-4 BMI category, a higher past BMI category at age 25 was associated with a higher chance of elevations in hs-cTnT. Individuals who were obese at both time points were at the highest risk of subclinical myocardial injury and were at a five-fold higher risk of showing elevations in hs-cTnT compared with individuals who were in the normal BMI category at both time points, he reported.


Chiadi Ndumele, MD, MPH

In another analysis, Ndumele and colleagues linked risk of subclinical myocardial injury with BMI years — a measure of cumulative weight that was the product of the mean BMI values obtained from visits 1 to 4 and at age 25, and the mean number of years from age 25 to visit 4. For this cohort of individuals, BMI years ranged from -307 to 1,205. Ndumele reported that for every 100 BMI years, individuals had a 27 percent higher likelihood of showing elevated hs-cTnT.

BMI was determined at ARIC visit 4 and compared with BMI at ARIC visit 1 and at age 25. BMI was categorized as normal (18.5 to 24.9), overweight (25 to 29.9), and obese (≥30). Subclinical myocardial injury was determined from elevations in hs-cTnT (≥14 nanograms per liter) at ARIC visit 4, which occurred between 1996 and 1999. BMI at age 25 was determined from weight reported by participants at visit 1 when ages ranged from 45 to 64 years. ▼

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LATE-BREAKING continued from page 1

"If we can get the risk behavior under control, we could significantly reduce risk factors for cardiovascular disease," said Bonnie Spring, PhD, ABPP, director of the Institute for Public Health and Medicine and professor in preventive medicine-behavioral medicine, psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine in Chicago. "We can obtain large-scale change in risk behavior using technology and remote coaching."

Spring is lead author of "Clinical Trial of a Mobile Health Intervention for Simultaneous versus Sequential Diet and Activity Change." The study looked at four risk behaviors: low fruit and vegetable intake, high saturated fat intake, low physical activity levels and high leisure screen time.

Researchers compared two strategies: coaching to change risk behaviors sequentially or simultaneously. Both strategies used a smartphone app, weekly coaching calls and wireless accelerometers. And both worked similarly well to increase fruit and vegetable intake, decrease saturated fat intake, reduce leisure screen time and increase physical activity.

In the second study, Spanish researchers used peer-group intervention to effect behavior change. Peer support can change substance abuse behaviors, noted Valentín Fuster, MD, PhD, professor of medicine at Mount Sinai Hospital in New York, suggesting that a similar strategy could help modify behavior to reduce cardiovascular risk factors.

Fuster is principal investigator of "Impact of a Comprehensive Lifestyle Peer Group-Based Intervention on CV Risk Factors: A Randomized Controlled Trial."

The study's researchers recruited 648 women in six Spanish cities. Participants were between 25 and 50 years of age, overweight to obese, relatively inactive, smoked and had hypertension. They were randomized to usual care or 12 monthly peer-group meetings to discuss risk factors and strategies for change. Outcomes were based on a BEWAT score comprising blood pressure, exercise, weight, alimentation and tobacco.

The control group showed no change, Fuster said, but the intervention group showed statistically and clinically significant improvements one year later. The largest improvement was decreased tobacco use. Participants who attended seven or more sessions showed the greatest improvements in all five areas.

"Wider adoption of such a program could have meaningful impact on cardiovascular health promotion," Fuster said.

Secondary prevention

Varenicline shows promise in secondary prevention in patients with acute coronary syndrome who use tobacco, according to another study. Fewer than a third of ACS patients remain abstinent from smoking following discharge, and smoking cessation therapy usually fails in this population.

"This is the highest risk population that has been exposed to varenicline," said Mark J. Eisenberg, MD, MPH, FAHA, professor of medicine at McGill University in Montreal, Canada. "And this is the first trial of pharmacotherapy started in hospital that has shown positive effects in smoking cessation."

Eisenberg is lead author of "The Efficacy and Safety of Varenicline, a Selective α4β2 Nicotinic Receptor Partial Agonist, for Smoking Cessation in Patients Hospitalized with Acute Coronary Syndrome: A Randomized Controlled Trial." The multicenter trial compared 12 weeks of varenicline against placebo. The primary endpoint was smoking cessation at week 24. Patients in both groups received low-intensity smoking cessation counseling at baseline and at six follow-up visits.

The varenicline group showed 60 percent abstinence at four weeks and 57.7 percent abstinence at 12 weeks compared to 37.7 percent and 36.4 percent for the control group.

"We only need to treat seven patients to gain an additional abstinence," Eisenberg said. "This is a substantial finding in secondary prevention in this very high risk group."

Individuals with both cardiovascular disease and diabetes are another high-risk group, and the subject of the study "Empagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk."

"Blood sugar lowering alone has no effect on cardiovascular events, although it is helpful to minimize microvascular complications," said Silvio E. Inzucchi, MD, professor of medicine and director of the Yale Diabetes Center in New Haven, Connecticut and lead author of the study. "Most glucose-lowering drugs have no effect on cardiovascular events or have deleterious effects. We may be seeing a change."

The trial compared empagliflozin, a sodium glucose cotransporter 2 agent, against placebo in patients with both established cardiovascular disease and type 2 diabetes.

SGLT2 agents reduce renal glucose reabsorption, thus increasing urinary glucose excretion.

In the study, 7,020 patients were randomized and treated. Patients in the empagliflozin group had a 34 percent reduced risk for heart failure hospitalization or cardiovascular death, 39 percent reduction in hospitalization or death from heart failure, and an 11 percent reduction in all-cause hospitalization.

"It is tempting to say it is a class effect for SGLT2 agents, but we don't have the data yet," Inzucchi said. "Studies in other SLGT2 agents should be disclosed over the next two or three years. For now, empagliflozin, in addition to standard care, reduced heart failure hospitalization or cardiovascular death in both patients with and without heart failure at baseline." ▼

Folic acid mitigates doxorubicin-induced cardiomyopathy

Doxorubicin, used in cancer treatment, is associated with acute cardiomyopathy. However, research presented during a poster session on Monday suggests folic acid (FA) might be a new and immediate therapeutic approach to reduce doxorubicin (DOXO)-induced cardiomyopathy.

"Although not currently used in the clinic, we are working to move FA into clinical trials," said Yanti Octavia, MD, of Erasmus Medical Center and Maastricht University in the Netherlands.

To determine the effects of DOXO alone or DOXO and FA on cardiac functions, Octavia and colleagues reported data from echocardiography showing that DOXO-treated mice have lower than normal left-ventricular function. In mice treated with DOXO and FA, left-ventricular functions were equivalent to sham controls.

Compared with sham controls, significantly more mice treated with DOXO died (70 percent versus 0 percent; $p<0.01$). In addition, significantly fewer mice treated with DOXO and FA died (41 percent versus 70 percent for DOXO; $p<0.01$).

DOXO-induced mortality was correlated to increased fibrosis and apoptosis, Octavia reported. All measurements were determined with histochemistry or immunohistochemistry on left ventricle section 10 days after DOXO treatment.

Corresponding with lower left-ventricular function, significantly higher fibrosis was seen in DOXO-treated mice compared with doxorubicin and FA treated mice (9.4 percent versus 5.2 percent; $p<0.05$). Apoptosis was also significantly higher in DOXO-treated mice (1.10 percent versus 0.56 percent for DOXO+FA; $p<0.05$). In all studies, the lowest rates of fibrosis and apoptosis were seen in sham controls.

The study's findings indicated that DOXO-treated mice showed a dysregulation of mitochondria through increased oxygen consumption. Again, this was mitigated with FA, Octavia said. Taken together, these data suggest that FA could function as a modulator of endothelial nitric oxide synthase (eNOS) and subsequently reduce DOXO-induced cardiomyopathy.

The researchers looked at the modulation of eNOS function in several ways. In normal function, eNOS is sequestered as a dimer. Dysregulation of eNOS leads to eNOS uncoupling, which is measured by estimating levels of the dimer and monomer of eNOS in immunoblots following immunoprecipitation of left ventricular lysates.

Sham controls showed "very smeared" monomer bands of eNOS, indicating almost all eNOS was present as a dimer. In contrast, lysates from DOXO-induced mice showed an increase in eNOS monomers, indicating eNOS uncoupling. Judging from the phosphorylation of eNOS, higher eNOS activity was shown in sham mice compared with DOXO-treated mice

In all experiments with DOXO+FA, FA was shown to restore eNOS activity through recoupling of eNOS, and through increased phosphorylation of eNOS, Octavia reported. ▼

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Adult CHD patients fare worse on heart transplant waitlists

Of adults waiting for heart transplants, patients with congenital heart disease are sicker and fare worse while waiting for a transplant compared with their non-CHD counterparts, according a retrospective analysis of registry data in the United States.

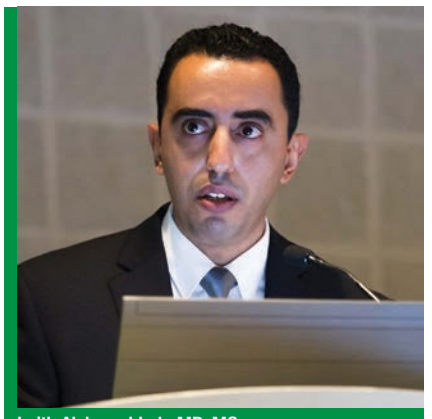
The study, conducted at the University of Iowa Hospital and Clinics, was presented during an oral session Monday. Data from the Scientific Registry of Heart Transplant Recipients were collected for 1,257 adult CHD subjects and compared to 37,248 non-CHD patients between 1999 and 2014.

"Death while waiting for a transplant, or delisting because patients were too sick to undergo transplantation, were among the worst outcomes," said Laith Alshawabkeh, MD, MSc, senior fellow at Boston Adult Congenital Heart and Pulmonary Vascular Disease at Brigham & Women's and Boston Children's Hospitals.

The researchers analyzed mortality while waiting for a transplant, and 180-day probability of death or delisting due to increased morbidity, between the CHD and non-CHD cohorts. All patients who received a transplant or were delisted due to improvement were censored in the analysis.

At the time of United Network for Organ Sharing (UNOS) listing, more CHD patients were listed at Status 2 (the lowest priority UNOS status) compared with the non-CHD cohort, 60.9 percent versus 42.3 percent, respectively. Alshawabkeh reported that of patients who died or worsened at median follow-up of 124 days, 56.5 percent (134 of 237) were initially listed in the lowest priority status in the CHD cohort compared with 39.7 percent (2,533 of 6,377) in the non-CHD cohort.

Among patients at the top of the wait list (UNOS Status 1A), probability of death or delisting due to worsening status at 180 days was greater for CHD patients (41 percent) compared to non-CHD patients (29 percent). Similarly, 180-day mortality was higher for the CHD group (29 percent) compared to the non-CHD cohort (21 percent). For patients in UNOS Status 1B or 2, no significant differences in one-year mortality or delisting were reported.


Laith Alshawabkeh, MD, MSc

Median age was 35 years for the CHD cohort and 56 years for the non-CHD cohort. The majority of subjects were male, but more females were listed in the CHD cohort. Most CHD patients had prior cardiac surgery, but had significantly lower prevalence of coronary artery disease.

Alshawabkeh noted that prior studies did not show differences in the outcomes for CHD compared to non-CHD adult patients because they did not assess the patients in their listing status groups. There were fewer patients listed as Status 1A in general, so differences in outcomes were masked when the groups were assessed in total, he explained.

Most previous studies have looked at post-transplant outcomes, added Alshawabkeh, noting that this is one of the few studies to look at the differences in outcomes between CHD and non-CHD patients while on a transplant list.

One possible explanation for the study's findings is adult CHD patients being listed too late in their disease course, Alshawabkeh said. In stratifying patients for heart transplants, the UNOS criteria do not take into account the challenges associated with congenital heart disease. Furthermore, there is poor understanding of the natural history, risks and triggers for heart failure in CHD patients, he said. ▼

TARGET: BP continued from page 1

high blood pressure and commit to high levels of controls in their patient populations.

Although Target: BP is the first collaborative initiative between the AHA and the AMA, both associations have long recognized high blood pressure as a major health threat. Each organization already has a number of community-based initiatives and online tools in place to help people understand and control their risks for high blood pressure.

The associations will use those resources and more to support Target: BP participants. They will also recognize healthcare providers who achieve measurable improvements — in particular, those who achieve 70, 80 or 90 percent blood pressure control in their patient populations.

More than 50 healthcare systems and clinics serving nearly 18 million people have already committed to participate in Target: BP. Participating organizations will be asked to provide basic details about their organizations and patients through the Target: BP website. Once enrolled, participants will gain regular access to evidence-based AHA guidelines and a variety of up-to-the minute tools, including the AHA/ACC/CDC Hypertension Treatment Algorithm.

For more information or to join the effort, visit www.heart.org/targetbp. ▼

Following guidelines significantly improves bystander CPR, ROSC

According to researchers in Taiwan, a dispatcher-assisted telephone cardiopulmonary resuscitation (DATCPR) system increased bystander CPR (BCPR) rates almost two-fold for patients experiencing out-of-hospital cardiac arrest.

The study was reported by Patrick Chow-In Ko, MD, MSc, from the department of emergency medicine at the National Taiwan University Hospital in Taipei, during an oral session Monday that was part of the Resuscitation Science Symposium.

Ko and his colleagues compared outcomes in patients with OHCA between October and December 2014 to a control group from the same months in 2012 before resuscitation guidelines were modified in Taiwan. The 2013 guideline changes included modifications to the way dispatchers talk to bystanders. For example, prior to 2013, bystanders were asked whether the subject was breathing or not; the modified guidelines require bystanders to be asked whether the subject is breathing "normally" or not.

After the guideline update, the BCPR rate (35 percent) was significantly higher compared to the 2012 cohort (20.6 percent). And more patients (10.4 percent) in the 2014 cohort returned to spontaneous circulation (ROSC) upon arrival at the hospital compared to the 2012 cohort (6.6 percent). Initial shockable rhythm, laryngeal mask airway and endotracheal intubation were similar across the two cohorts.


Patrick Chow-In Ko, MD, MSc

After adjusting for variables such as witnessed arrest, shockable rhythms, age, sex and pre-hospital time intervals, Ko reported that patients in the 2014 group had a two-fold higher (5.5 percent versus 2.6 percent) chance of achieving a good neurologic outcome as measured by Cerebral Performance Category (CPC) scores.

Taiwan uses a centralized, computer-aided dispatch system, Ko said. After receiving a call, an ambulance is expected to be dispatched within 60 seconds. The system is considered horizontal because the call from a dispatcher is transferred to a nurse in the emergency system.

"Following resuscitation guidelines significantly improved outcomes even in their horizontal system, where it might be expected that the dispatcher system was expected to take more time," said Ko, noting that future studies are needed to evaluate the quality of chest compressions delivered with BCPR.

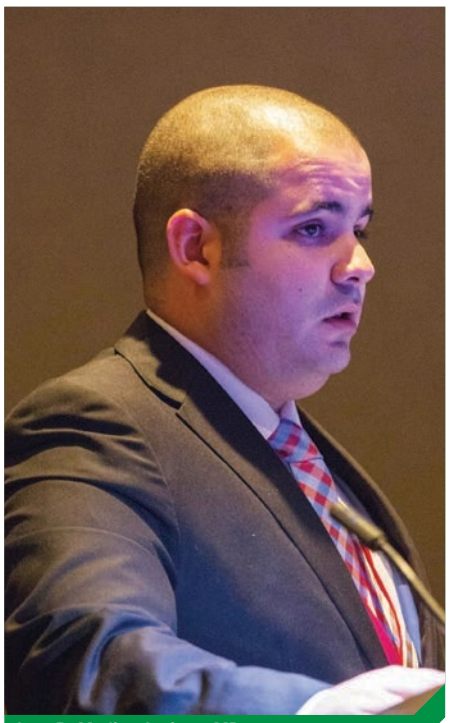
There were 1,437 OHCA in the Taipei metropolitan area during the study period. Patient demographics were similar across the two cohorts.

Study investigators reviewed audio recordings of confirmed OHCA. The system linked the emergency medical system information with the hospital process and outcomes data. ▼

Cardiac rehabilitation lowers risk for major cardiovascular events, study finds

According to research presented Monday at Scientific Sessions, higher patient participation in cardiac rehabilitation was associated with a lower risk of long-term major cardiovascular events in patients with coronary artery disease. For patients who participated in at least 12 cardiac rehabilitation (CR) sessions, major cardiovascular events were reduced by 15 percent.

"Cardiac rehabilitation offers a way to keep patients motivated and even one CR session can make a difference in the lives of patients who experienced a CAD event," said Jose R. Medina-Inojosa, MD, a fellow in prevention cardiology at the Mayo Clinic in Rochester, Minnesota.


Jose R. Medina-Inojosa, MD

Medina-Inojosa and his research colleagues conducted a retrospective, longitudinal, community-based study in Olmstead County, Minnesota. They followed 2,273 patients with a mean follow-up of six years. The study was aided by a record-linkage system from the Rochester Epidemiology Project, where all medical information for Olmstead County residents was captured in the database.

The CR program in the study was designed to include 36 sessions, with patients attending three sessions per week for three months. The comprehensive program uses physicians, nurses, nutritionists and exercise specialists.

Median CR attendance among study participants was 12, slightly higher than the national average of 10 to 11, Medina-Inojosa said. Based on a category analysis, the study showed that over six years, patients who participated in at least 12 CR sessions had a lower rate of major cardiovascular events and a hazard ratio of 0.81. After taking into account variables such as smoking, hypertension, diabetes and history of MI, the hazard ration for major cardiovascular events remained significant.

Even participating in a single CR session reduced the risk for major cardiovascular events, Medina-Inojosa said.

"CR programs reassure patients about what they can and cannot do. It provides social and medical support and addresses the anxieties and fears that patients have of another event occurring," he said. "These results provide evidence on the importance of the health advantages of CR and expand on the dose-response benefit of participating in CR sessions."

In the study, major cardiovascular events were defined as acute coronary syndrome (myocardial infarction or unstable angina), revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]), ventricular arrhythmias necessitating hospitalization, stroke or death from any cause. Of the 2,273 patients in the study, 817 patients had one or more of the following events: MI (73), unstable angina (113), CABG (53), PCI (260), ventricular arrhythmias (13), stroke (72) and death (243). ▼

Z-scores predict coronary events in patients with Kawasaki disease

In patients with Kawasaki disease, the severity assessment of coronary artery aneurysms (CAA) using the five-increment z-score for coronary arterial diameter can predict time-dependent occurrence of coronary events such as thrombosis, stenosis and obstruction, according to a poster presented Monday at Scientific Sessions.

Masaru Miura, MD, of the Tokyo Metropolitan Children's Medical Center, and his research colleagues analyzed data from 1,002 patients with Kawasaki disease in Japan who had received a coronary angiography between 1992 and 2011. Median age of the patients was 1.8 years. Body surface area and CAA diameter were available for the right coronary artery (RCA) in 741 patients and for the left anterior descending artery (LAD) in 609 patients.

The z-score for CAA was determined by echocardiography in the acute phase. Coronary events were analyzed based on small (z-score: <5.0), medium (z-score: ≥5.0 to >10.0), and large (z-score: ≥10.0) CAA using a five-increment scale that is scheduled to be included in the new American Heart Association criteria for the management of Kawasaki disease, Miura said.

Coronary events occurred in 11.2 percent of patients in the RCA group and 9.4 percent of patients in the LAD group, he reported.

In the RCA group, Miura reported 10-year event-free survival rates for coronary events of 100 percent, 95.5 percent and 64.9 percent for subjects with small, medium and large coronary artery aneurysms, respectively. Corresponding rates in the LAD group were 100 percent, 97.5 percent and 86.8 percent for small, medium and large CAA.

Statistical analysis indicated that the z-score of the CAA diameter was an independent risk factor for coronary events in both the RCA and LAD groups. Patients with a large CAA were at a three times higher risk of experiencing a coronary event compared with patients with medium CAA. The hazard ratio for coronary events was 2.8 for the RCA group and 3.2 for the LAD group.


Masaru Miura, MD

Miura presented a subanalysis showing that responsiveness to intravenous immunoglobulin therapy was significantly related to the occurrence of coronary events and that males with Kawasaki disease were more likely than females to experience coronary events.

These data are important to the clinical management of patients with Kawasaki disease, Miura said.

"For patients with CAA, the absolute diameter has previously been the most important index, but I believe that the z-score will replace it," he said "Additionally, the new management based on z-scores of diameters is clinically important for appropriate prevention of coronary events."

Z-scores can also predict occurrence of hard cardiac events such as angina pectoris, myocardial infarction or cardiac death, and procedures including cardiac intervention or bypass operation, Miura added. ▼

Corlanor® (ivabradine)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

1. INDICATIONS AND USAGE

Corlanor is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

4. CONTRAINDICATIONS

Corlanor is contraindicated in patients with:

- Acute decompensated heart failure
- Blood pressure less than 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
- Resting heart rate less than 60 bpm prior to treatment [*see Warnings and Precautions (5.3)*]
- Severe hepatic impairment [*see Use in Specific Populations (8.6)*]
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) [*see Drug Interactions (7.3)*]
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors [*see Drug Interactions (7.1)*]

5. WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Corlanor may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. Embryo-fetal toxicity and cardiac teratogenic effects were observed in fetuses of pregnant rats treated during organogenesis at exposures 1 to 3 times the human exposures ($AUC_{0\text{-}24hr}$) at the maximum recommended human dose (MRHD) [*see Use in Specific Populations (8.1)*]. Advise females to use effective contraception when taking Corlanor [*see Use in Specific Populations (8.3)*].

5.2 Atrial Fibrillation

Corlanor increases the risk of atrial fibrillation. In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients treated with Corlanor and 3.9% per patient-year in patients treated with placebo [*see Clinical Studies (14)*]. Regularly monitor cardiac rhythm. Discontinue Corlanor if atrial fibrillation develops.

5.3 Bradycardia and Conduction Disturbances

Bradycardia, sinus arrest, and heart block have occurred with Corlanor. The rate of bradycardia was 6.0% per patient-year in patients treated with Corlanor (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). Concurrent use of verapamil or diltiazem will increase Corlanor exposure, may themselves contribute to heart rate lowering, and should be avoided [*see Clinical Pharmacology (12.3)*]. Avoid use of Corlanor in patients with 2nd degree atrioventricular block, unless a functioning demand pacemaker is present [*see Contraindications (4) and Dosage and Administration (2)*].

6. ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Fetal Toxicity [*see Warnings and Precautions (5.1)*]
- Atrial Fibrillation [*see Warnings and Precautions (5.2)*]
- Bradycardia and Conduction Disturbances [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), safety was evaluated in 3260 patients treated with Corlanor and 3278 patients given placebo. The median duration of Corlanor exposure was 21.5 months.

The most common adverse drug reactions in the SHIFT trial are shown in Table 2 [*see also Warnings and Precautions (5.2), (5.3)*].

Table 2. Adverse Drug Reactions with Rates ≥ 1.0% Higher on Ivabradine than Placebo occurring in > 1% on ivabradine in SHIFT

	Ivabradine N=3260	Placebo N=3278
Bradycardia	10%	2.2%
Hypertension, blood pressure increased	8.9%	7.8%
Atrial fibrillation	8.3%	6.6%
Phosphenes, visual brightness	2.8%	0.5%

Luminous Phenomena (Phosphenes)

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency). Phosphenes are usually triggered by sudden variations in light intensity. Corlanor can cause phosphenes, thought to be mediated through Corlanor's effects on retinal photoreceptors [*see Clinical Pharmacology (12.1)*]. Onset is generally within the first 2 months of treatment, after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity and led to treatment discontinuation in < 1% of patients; most resolved during or after treatment.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of Corlanor: syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.

7. DRUG INTERACTIONS

7.1 Cytochrome P450-Based Interactions

Corlanor is primarily metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increases ivabradine plasma concentrations, and use of CYP3A4 inducers decreases them. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances.

The concomitant use of strong CYP3A4 inhibitors is contraindicated [*see Contraindications (4) and Clinical Pharmacology (12.3)*]. Examples of strong CYP3A4 inhibitors include azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone.

Avoid concomitant use of moderate CYP3A4 inhibitors when using Corlanor. Examples of moderate CYP3A4 inhibitors include diltiazem, verapamil, and grapefruit juice [*see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

Avoid concomitant use of CYP3A4 inducers when using Corlanor. Examples of CYP3A4 inducers include St. John's wort, rifampicin, barbiturates, and phenytoin [*see Clinical Pharmacology (12.3)*].

7.2 Negative Chronotropes

Most patients receiving Corlanor will also be treated with a beta-blocker. The risk of bradycardia increases with concomitant administration of drugs that slow heart rate (e.g., digoxin, amiodarone, beta-blockers). Monitor heart rate in patients taking Corlanor with other negative chronotropes.

7.3 Pacemakers

Corlanor dosing is based on heart rate reduction, targeting a heart rate of 50 to 60 beats per minute [*see Dosage and Administration (2)*]. Patients with demand pacemakers set to a rate ≥ 60 beats per minute cannot achieve a target heart rate < 60 beats per minute, and these patients were excluded from clinical trials [*see Clinical Studies (14)*]. The use of Corlanor is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, Corlanor may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Corlanor in pregnant women to inform any drug-associated risks. In animal reproduction studies, oral administration of ivabradine to pregnant rats during organogenesis at a dosage providing 1 to 3 times the human exposure ($AUC_{0\text{-}24hr}$) at the MRHD resulted in embryo-fetal toxicity and teratogenicity manifested as abnormal shape of the heart, interventricular septal defect, and complex anomalies of primary arteries. Increased postnatal mortality was associated with these teratogenic effects in rats. In pregnant rabbits, increased post-implantation loss was noted at an exposure ($AUC_{0\text{-}24hr}$) 5 times the human exposure at the MRHD. Lower doses were not tested in rabbits. The background risk of major birth defects for the indicated population is unknown. The estimated background risk of major birth defects in the U.S. general population is 2 to 4%, however, and the estimated risk of miscarriage is 15 to 20% in clinically recognized pregnancies. Advise a pregnant woman of the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Pregnant patients with left ventricular ejection fraction less than 35% on maximally tolerated doses of beta-blockers may be particularly heart-rate dependent for augmenting cardiac output. Therefore, pregnant patients who are started on Corlanor, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing.

Monitor pregnant women with chronic heart failure in 3rd trimester of pregnancy for preterm birth.

Data

Animal Data

In pregnant rats, oral administration of ivabradine during the period of organogenesis (gestation day 6-15) at doses of 2.3, 4.6, 9.3, or 19 mg/kg/day resulted in fetal toxicity and teratogenic effects. Increased intrauterine and post-natal mortality and cardiac malformations were observed at doses ≥ 2.3 mg/kg/day (equivalent to the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$). Teratogenic effects including interventricular septal defect and complex anomalies of major arteries were observed at doses ≥ 4.6 mg/kg/day (approximately 3 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$).

In pregnant rabbits, oral administration of ivabradine during the period of organogenesis (gestation day 6-18) at doses of 7, 14, or 28 mg/kg/day resulted in fetal toxicity and teratogenicity. Treatment with all doses ≥ 7 mg/kg/day (equivalent to the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$) caused an increase in post-implantation loss. At the high dose of 28 mg/kg/day (approximately 15 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$), reduced fetal and placental weights were observed, and evidence of teratogenicity (ectrodactylia observed in 2 of 148 fetuses from 2 of 18 litters) was demonstrated.

In the pre- and postnatal study, pregnant rats received oral administration of ivabradine at doses of 2.5, 7, or 20 mg/kg/day from gestation day 6 to lactation day 20. Increased postnatal mortality associated with cardiac teratogenic findings was observed in the F1 pups delivered by dams treated at the high dose (approximately 15 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$).

8.2 Lactation

Risk Summary

There is no information regarding the presence of ivabradine in human milk, the effects of ivabradine on the breastfed infant, or the effects of the drug on milk production. Animal studies have shown, however, that ivabradine is present in rat milk [*see Data*]. Because of the potential risk to breastfed infants from exposure to Corlanor, breastfeeding is not recommended.

Data

Lactating rats received daily oral doses of [^{14}C]-ivabradine (7 mg/kg) on post-parturition days 10 to 14; milk and maternal plasma were collected at 0.5 and 2.5 hours post-dose on day 14. The ratios of total radioactivity associated with [^{14}C]-ivabradine or its metabolites in milk vs. plasma were 1.5 and 1.8, respectively, indicating that ivabradine is transferred to milk after oral administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Corlanor may cause fetal harm, based on animal data. Advise females of reproductive potential to use effective contraception during Corlanor treatment [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population. However, Corlanor has only been studied in a limited number of patients ≥ 75 years of age.

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Corlanor is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population and an increase in systemic exposure is anticipated [*see Contraindications (4) and Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dosage adjustment is required for patients with creatinine clearance 15 to 60 mL/min. No data are available for patients with creatinine clearance below 15 mL/min [*see Clinical Pharmacology (12.3)*].

10. OVERDOSAGE

Overdose may lead to severe and prolonged bradycardia. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment, including intravenous (IV) fluids, atropine, and intravenous beta-stimulating agents such as isoproterenol, may be considered.

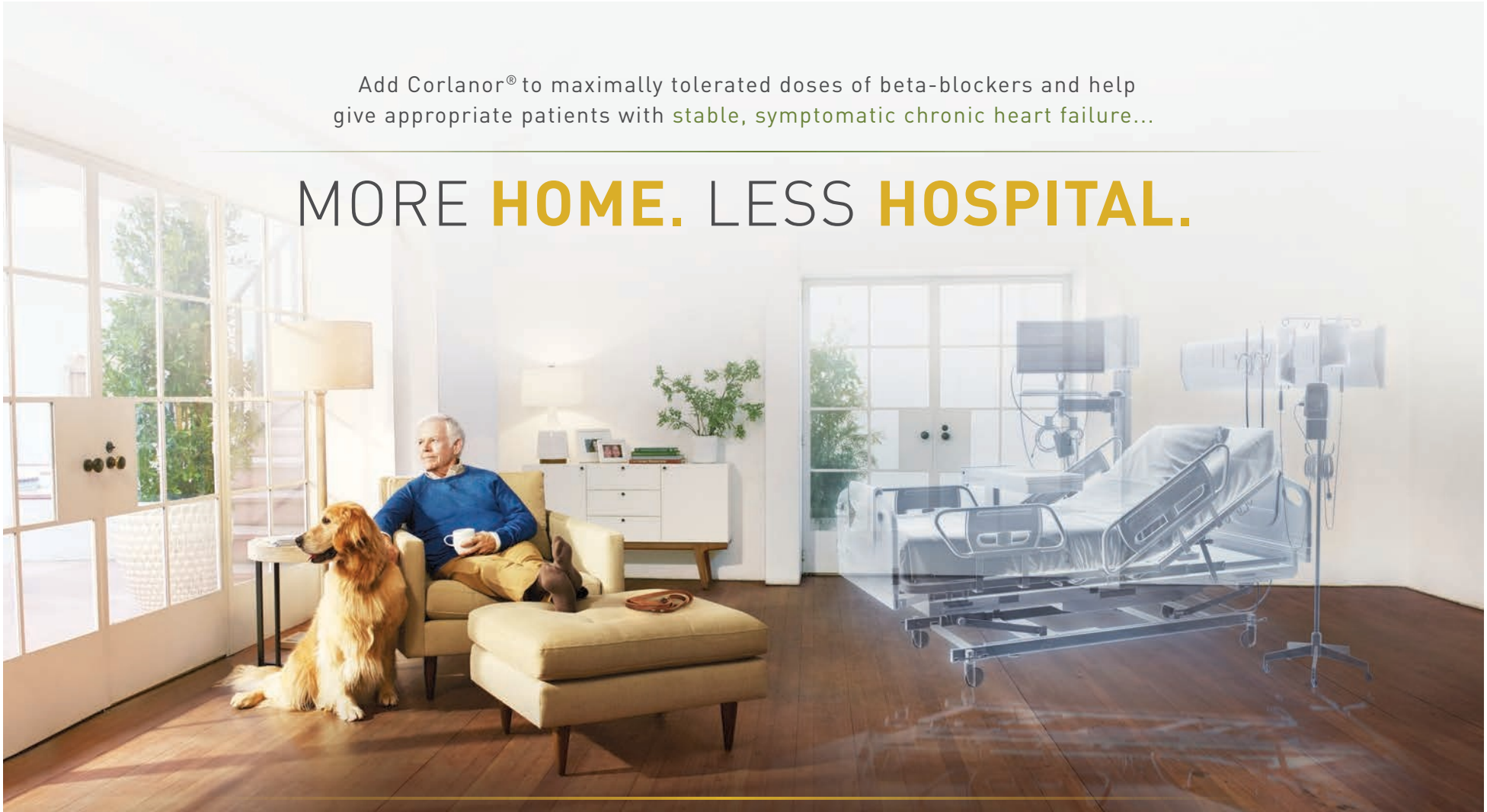
This Brief Summary is based on the Corlanor® Prescribing Information v1, 04/15

AMGEN®

Corlanor® (ivabradine)
Manufactured for: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
Patent: http://pat.amgen.com/Corlanor/

Add Corlanor® to maximally tolerated doses of beta-blockers and help give appropriate patients with stable, symptomatic chronic heart failure...

MORE **HOME.** LESS **HOSPITAL.**



Learn how you can **DO MORE with Corlanor®** to reduce the risk of hospitalization for worsening heart failure[1]

CorlanorHCP.com

Indication

Corlanor® (ivabradine) is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Important Safety Information

- **Contraindications:** Corlanor® is contraindicated in patients with acute decompensated heart failure, blood pressure < 90/50 mmHg, sick sinus syndrome, sinoatrial block, 3rd degree atrioventricular block (unless a functioning demand pacemaker is present), a resting heart rate < 60 bpm prior to treatment, severe hepatic impairment, pacemaker dependence (heart rate maintained exclusively by the pacemaker), and concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors.
- **Fetal Toxicity:** Corlanor® may cause fetal toxicity when administered to a pregnant woman based on embryo-fetal toxicity and cardiac teratogenic effects observed in animal studies. Advise females to use effective contraception when taking Corlanor®.
- **Atrial Fibrillation:** Corlanor® increases the risk of atrial fibrillation. The rate of atrial fibrillation in patients treated with Corlanor® compared to placebo was 5% vs. 3.9% per patient-year, respectively. Regularly monitor cardiac rhythm. Discontinue Corlanor® if atrial fibrillation develops.
- **Bradycardia and Conduction Disturbances:** Bradycardia, sinus arrest and heart block have occurred with Corlanor®. The rate of bradycardia in patients treated with Corlanor® compared to placebo was 6% (2.7% symptomatic; 3.4% asymptomatic) vs. 1.3% per patient-year, respectively. Risk factors for bradycardia include sinus node dysfunction, conduction defects, ventricular dyssynchrony, and use of other negative chronotropes. Concurrent use of verapamil or diltiazem also increases Corlanor® exposure, contributes to heart rate lowering, and should be avoided. Avoid use of Corlanor® in patients with 2nd degree atrioventricular block unless a functioning demand pacemaker is present.
- **Adverse Reactions:** The most common adverse reactions reported at least 1% more frequently with Corlanor® than placebo and that occurred in more than 1% of patients treated with Corlanor® were bradycardia (10% vs. 2.2%), hypertension or increased blood pressure (8.9% vs. 7.8%), atrial fibrillation (8.3% vs. 6.6%), and luminous phenomena (phosphenes) or visual brightness (2.8% vs. 0.5%).

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

Reference: 1. Corlanor® (ivabradine) Prescribing Information, Amgen.

AMGEN®

Cardiovascular

Corlanor® (ivabradine) 5 mg 7.5 mg tablets

DO MORE TO REDUCE RISK OF HF HOSPITALIZATION