Accelerator program fueling another scientific innovation

The American Heart Association’s Science & Technology Accelerator Program, which aims to bring potentially breakthrough innovations from bench to bedside, recently invested in BioKier, a company that could revolutionize blood sugar control in diabetics and decrease the incidence of myocardial infarction and stroke.

The investment, the second made by the Accelerator program, supports use of natural dietary substances delivered through a novel oral method that replicates the improvements in glucose control observed in obese people with Type 2 diabetes who have undergone intestinal bypass surgery to lose weight.

“One of the bottlenecks in improving patient care is transforming good ideas from being just an idea to a therapeutic or a diagnostic that is produced and used in practice,” said Gordon Tomaselli, MD, FAHA, former AHA president and Chief of Cardiology at Johns Hopkins University School of Medicine in Baltimore. Tomaselli is a member of the Accelerator Committee, which selects research proposals to receive investment funding.

Post-cardiac arrest patients with initial non-shockable rhythms could benefit from therapeutic hypothermia

ew research presented Saturday suggests that therapeutic hypothermia can improve outcomes for post-cardiac arrest patients who initially have a rhythm that does not require defibrillation.

This is noteworthy because prior therapeutic hypothermia studies on patients with initial non-shockable rhythms were inconclusive for improving hospital discharge and neurologically intact survival.

The 2010 American Heart Association Guidelines for CPR and ECC include a Class I recommendation for the use of therapeutic hypothermia in comatose survivors of VF cardiac arrest. In addition, there is a Class IIb recommendation to consider using therapeutic hypothermia for comatose survivors with PEA or asystole as an initial rhythm. The European Resuscitation Council recommends therapeutic hypothermia for all comatose survivors of cardiac arrest, although the guidelines note a lower level of evidence favoring hypothermia for initial non-shockable rhythms.

“The therapeutic hypothermia has historically been recommended for cardiac arrest patients with a shockable rhythm,” said the study’s lead author, Anne Grosskreutz, MS, from the University of Pennsylvania in Philadelphia. “Absent a randomized, controlled clinical trial in patients with nonshockable rhythms, pulseless electrical activity or asystole, the utility of therapeutic hypothermia in this population has been debated. We found that patients did better in terms of both neurologic outcomes and survival if they received therapeutic hypothermia.”

The study’s researchers used propensity analysis to create a quasi-experimental trial design using propensity-matched pairs. Therapeutic hypothermia for all comatose survivors of cardiac arrest, although the guidelines note a lower level of evidence favoring hypothermia for initial non-shockable rhythms.

PTEN inhibition improves heart function and survival following cardiac arrest

Rescuers have developed an experimental PTEN-inhibiting compound that could offer a novel strategy for the treatment of cardiac arrest with or without hypothermia. Results from an in vivo trial of the compound in sudden cardiac arrest were presented Saturday. PTEN (phosphatase and tensin homolog deleted on chromosome 10) is one of the key regulators of Akt. But familiar compounds known to inhibit PTEN tend to have broad effects that make them less suitable as a potential pharmacologic agent. Hydroxy(oxo) vanadium 3-hydroxypyridine-2-carboxylic acid trihydrate (VO-OHpic), the compound in the trial, is a more PTEN-specific inhibitor. In the trial, VO-OHpic was administered to C57BL6 mice 30 minutes prior to KCl-induced asystolic cardiac arrest. The mice were evaluated for neurologically intact survival 72 hours after CPR was administered, and cardiac function was assessed using a Millar catheter. Blood lactate, glucose and cytokine levels also were measured. Activation of the Akt kinase in cardiac and brain tissues was assessed using phosphorylation of Akt, GSK3β and phospholamban as markers.

The VO-OHpic compound significantly increased 72-hour survival from 10 percent to 50 percent, reported Jing Li, MD, research assistant professor at the University of Illinois Hospital & Health Sciences System in Chicago. At 30 minutes after return of spontaneous circulation, VO-OHpic significantly increased LVPmax and dP/dt max with continued benefit seen for at least two hours. VO-OHpic also significantly increased lactate clearance and decreased plasma glucose level, Li said.

Plasma levels of the anti-inflammatory cytokine IL-10 increased, while plasma levels of pro-inflammatory IL-1β decreased. The compound also increased the phosphorylation of Akt, p-GSK3β and the Akt target phospholamban. Li said.

PTEN continued on page 6
Highlights from the Program Chair

By Robert Harrington, MD, FAHA, FACC, Committee on Scientific Sessions Program Chair

The 2013 Scientific Sessions kicked off in appropriate fashion on Saturday with a daylong program focusing on our Early Career attendees, along with the first of three AHA Cardiovascular Evening Symposia. Today we delve into the “heart” of the meeting, beginning with the always popular Sunday Morning Programs. These sessions are a chance for groups within the AHA to take a deep dive into their scientific areas. For example, there will be an excellent session devoted to imaging techniques in the interventional lab and in the evaluation of complex procedures and patients, and another session highlighting some of the top trials in interventional cardiology over the past year. The meeting officially kicks off this afternoon with the Opening Session, featuring AHA President Mariell Jessup, MD, FAHA, who will address advances and limitations in the management of patients with heart failure. Always an important part of the Opening Session is the acknowledgment of our members who have excelled in one or more of our mission areas, and I invite everyone to join me in congratulating them for their service. The Opening Session concludes with the annual Lewis A. Conner Memorial Lecture, which will be delivered by Jane Newburger, MD, MPH, a renowned clinician and researcher who will discuss clinical advances and outcomes in congenital heart disease.

After the Opening Session, the first of this year’s Late-Breaking Clinical Trials sessions convenes. The four trials scheduled to be presented today are all in the area of acute cardiovascular or cerebrovascular care. We will hear about a randomized trial of blood pressure reduction among patients with ischemic stroke and two trials from the world of resuscitation science that examine hypothermia strategies for out-of-hospital cardiac arrest patients. At last year’s Scientific Sessions in Los Angeles, we debuted a new session called “Case Theaters: Learning at the Movies.” These sessions proved to be so popular that we are offering them again this year. They feature a variety of clinical experts, all of whom have recorded an interventional or surgical case that will serve as the starting point for a discussion among a moderator, a panel and the audience. Today’s cases include a patient with valvular heart disease and another with peripheral artery disease.

This afternoon’s schedule also features another perennial favorite, “Best of AHA Specialty Conferences.” Attendees will hear key messages and get cutting-edge updates from some of the year’s top specialty meetings, including information on ATVB, basic science, QCOR, NPAM and hypertension. There is also a terrific joint session today between the AHA and ACC that will highlight the recently updated chronic heart failure guidelines. And finally, for those still anxious for further education this evening, the second AHA Cardiovascular Evening Symposium takes place tonight at the Omni Dallas Hotel. Tonight’s symposium will focus on the challenges, both new and old, in managing heart failure.

Late-Breaking Clinical Trials — LBCT.01 | 4–5:28 p.m. Sunday | Hall E
Acute Cardiovascular and Cerebrovascular Care

<table>
<thead>
<tr>
<th>TRAILS</th>
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<tr>
<td>Nitrites in Acute Myocardial Infarction</td>
<td>This trial was designed to assess the efficacy of sodium nitrite in reducing myocardial injury in patients with acute ST elevation MI.</td>
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<tr>
<td>Blood Pressure Reduction Among Acute Ischemic Stroke Patients: A Randomized Controlled Clinical Trial</td>
<td>This trial was designed to test the effectiveness of blood pressure reduction on short-term case-fatality and dependency among patients with acute ischemic stroke.</td>
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<tr>
<td>Randomized Clinical Trial of Pre-hospital Induction of Mild Hypothermia in Out-of-Hospital Cardiac Arrest Patients Using a Rapid Infusion of 4°C Normal Saline</td>
<td>The aims of this randomized clinical trial were to determine whether early in-field cooling improves survival, functional status in resuscitated cardiac arrest patients.</td>
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<tr>
<td>Target Temperature Management 33°C versus 36°C after Out-of-hospital Cardiac Arrest, a Randomized, Parallel Group, Assessor Blinded Clinical Trial</td>
<td>This randomized trial was designed to investigate the optimal target temperature management strategy after out-of-hospital cardiac arrest with regard to survival, neurological function and safety.</td>
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Special Session | SS.01 | 3:45–5 p.m. Sunday | Room C147
Best of AHA Specialty Conferences
Presentations:
- Arteriosclerosis, Thromboi and Vascular Biology
- Basic Cardiovascular Sciences
- Quality of Care and Outcomes Research
- Epidemiology/Nutrition, Physical Activity and Metabolism
- High Blood Pressure Research

Special Session | SS.02 | 3:45–5 p.m. Sunday | Ballrooms C1 & C2
Joint AHA/ACC Session: ACCF/AHA Guidelines for Management of Chronic Heart Failure: 2013 Update
Presentations:
- CRT Update
- Biomarkers to Guide Diagnosis and Treatments
- Heart Failure Pharmacology: An Update
- What’s New in Cell Therapies for Heart Failure
- Mechanical Support for the Failing Heart
Jessup to discuss heart failure’s past and future

American Heart Association President Mariell Jessup, MD, FAHA, FACC, FESC, will explore the remarkable yet troubling history of heart failure during her Presidential Address during the Opening Session on Sunday.

The title of her address, “The Heart Failure Paradox: An Epidemic of Scientific Success,” reflects the fact that more than 20 million people worldwide are struggling with the growing problem of heart failure—but those numbers are growing in part because of advances in other areas.

Jessup, Professor of Medicine at the University of Pennsylvania School of Medicine and Medical Director of Penn’s Heart and Vascular Center, will weave a timeline of important developments in heart failure treatment, clinical trials and compelling personal stories over the span of her 30-plus-year career.

“There is this fascinating chain of events in the treatment of heart failure, and I am eager to share this story,” Jessup said. “I hope people come away with a deeper understanding of how this epidemic has spread—and some thoughts about what we can do next.”

Her talk will explore the larger lessons that help healthcare professionals deal with the epidemic. For example, she will discuss the dramatic change in the outlook of some heart failure patients.

For many patients who are now treated successfully, Jessup recalled the not-so-distant past when “we could only stand by helplessly, with few ways to save them.”

Distant past when “we could only stand by helplessly, with few ways to save them.”

Jessup noted that even with a firm foundation of early studies in heart failure with reduced ejection fraction, there remains much to do.

“There are too many hospitalizations and an unacceptably high 30-day mortality rate,” she said. “There are too many patients developing heart failure as a result of obesity and diabetes.”

And she added, with new innovations to sustain ill patients, which patients can most benefit is still unknown.

“So somehow we have to connect current and future research more intimately with the well-being of our patients,” she said.

“And we must have renewed efforts into the prevention of heart failure.”

Major AHA awards

Several major awards will be presented after the Presidential Address:

American Heart Association Chairman Bartie Dennis will present the Charles J. Hinton, Jr., MD, Distinguished Scientist Award for excellence in volunteer service to Ileana Piña, MD, MPH, FAHA, a professor in the department of medicine and the department of epidemiology and population health at Albert Einstein College of Medicine in New York.

Six top scientists will be named AHA Distinguished Scientists: Kenneth E. Bernstein, MD, FAHA; Bruce M. Pasy, MD, PhD; Paul M. Ridker, MD, MPH; Jonathan G. Seidman, PhD; Jonathan S. Stamler, MD; and Alan R. Tall, MB, BS. (See full story on the Distinguished Scientists page 14.)

The Basic Research Prize will be presented to Jeffrey A. Towbin, MD, FAHA, Professor of Pediatrics at Cincinnati Children’s Hospital Medical Center.

The Clinical Research Prize will be awarded to Thomas Brott, MD, Professor of Neurology and Director for Research at the Mayo Clinic Jacksonville – Neurology in Florida.

The Population Research Prize will be presented to Lewis H. Kuller, MD, DrPH, MPH, FAHA, Professor Emeritus in the Department of Epidemiology and Distinguished University Professor of Public Health Graduate School of Public Health at the University of Pittsburgh.

The Eugene Braunwald Academic Mentorship Awards will be awarded to Mark Josephson, MD, FAHA, Chief of Cardiovascular Medicine at Beth Israel Deaconess Hospital and Herman Dana Professor of Medicine in the Division of Cardiovascular Medicine at Harvard Medical School.

The Research Achievement Award will be presented to Roberto Bolli, MD, FAHA, Professor of Medicine, Physiology and Biophysics Chief, and Division of Cardiovascular Medicine Director at the Institute of Molecular Cardiology at the University of Louisville.

Career Progression: Åsa Gustafsson

When Åsa Gustafsson enrolled at the University of California-San Diego from her native Sweden, she had no idea what she wanted to be when she grew up.

“I started out as an economics major,” she said. “Then I changed to marine biology, and then again to marine molecular biology. I knew I wanted to do medical research but when I applied to graduate school, I didn’t really know what direction I’d go.”

It was in graduate school, also at UCSD, that she found clarity for her career path.

“I became interested in researching heart disease and how to prevent development of heart disease. I learned that preventive medicine is the best medicine,” she said.

And she found that the best way to understand things like why cells die after a myocardial infarction and how we can prevent this from occurring, I found my specialty.

The road from Stockholm to San Diego, and from potential marine biologist to award-winning medical researcher, has landed Gustafsson at UCSD’s Skaggs School of Pharmacy and Pharmaceutical Sciences, where she is an associate professor.

Her main research ambition is to better understand the molecular pathways that regulate the life and death of cardiac myocytes. Also important is her association with the American Heart Association and her desire to help young researchers.

Each day in this spot, we will profile an investigator in various career stages, from early career to distinguished veteran.

“The AHA supported me since I was in graduate school, I was awarded a predoctoral fellowship in 1999 and a postdoctoral fellowship in 2003. I’m pretty sure I wouldn’t be where I am today without that support,” Gustafsson said.

“Gradually, I moved to the other end of the situation, first by reviewing grant applications for the AHA and eventually by becoming the first chair of the BCVS Early Career Committee. I was fortunate enough to get these great opportunities by attending lots of scientific meetings, not by staying home in the lab and office.”

She also is on the Marcus Award Committee and the BCVS Leadership Committee. In the latter role, she continues to focus on creating programs and events for early career investigators.

“We’ve been working hard to put together programs for them at Scientific Sessions,” she said. “It’s been a real positive change the last few years, realizing the need to invest in future generations.”

Gustafsson, who won the 2010 Killam Memorial Award from the Western Pharmaceutical Society, likes attending sessions because of the collegial atmosphere and the learning opportunities.

“Often you have the top leaders in the field presenting new research,” she said. “There are so many sessions going on at once, so many choices, from basic research to clinical. Unfortunately, sometimes there are too many choices!”

She knows there will be anxious moments for first-time presenters at this year’s Scientific Sessions.

“One thing everyone remembers is the first time you have to present an oral abstract in front of hundreds of people,” Gustafsson said. “There are distinguished and experienced investigators in the audience who will ask questions. It’s very nerve-wracking but ultimately very rewarding. Above all, remember to enjoy the moment.”

Was she nervous when she first presented, in Chicago in 2006?

“You bet I was — and I still get nervous,” she said. “You’re going up there in front of your colleagues to present your work. They are going to ask you questions and you’d better know the answers!”

SUNDAY, NOVEMBER 17, 2013

MEMBER SPOTLIGHT

Diane Treat-Jacobson, PhD, RN
University of Minnesota School of Nursing, Associate Professor, Chair, Adult and Gerontological Health Cooperative Unit

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

I have been a member since 1988, when I was in graduate school.

Why did you join?

I joined at the suggestion of my graduate school faculty advisor, who was active in the Cardiovascular Nursing Council. This provided me with an opportunity to increase my exposure to cardiovascular nursing scientists as I began to develop my own research career.

Are you involved in any AHA councils?

I have been involved in the Cardiovascular and Stroke Nursing Council since 1989 and I have been a Fellow since 2008 and in the PVD working group since 2003. I am on the Leadership Committee of the PVD Council and was inducted as an Inaugural Fellow in 2009.

What do you enjoy most about these roles?

Being involved in these two councils has allowed me to combine my longstanding professional interest in cardiovascular disease with my current research and clinical focus on peripheral artery disease. I enjoy working with my colleagues and friends in promoting the awareness and timely management of peripheral artery disease and raising the profile of PAD within the broad community of cardiovascular clinicians.

How else are you involved with AHA?

Early in my professional career, I received a Scientist Development Grant that helped to launch my program of research. I also have participated in several writing groups which have been extremely satisfying and educationally enriching. I was able to participate in the development of the PAD Performance Measures and PAD Data Standards. I have also served on several Scientific Statement Writing Groups including: Women and PAD; Measurement and Interpretation of the ABI; Cardiovascular Health: The Importance of Measuring Health Status; and Critical Limb Ischemia: Epidemiology and Treatment.

Why is membership valuable to you?

I value being a part of the CSVN and PVD Councils and appreciate the AHA as a scientific and professional resource. I enjoy networking with colleagues and presenting my research findings at Scientific Sessions.

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

Membership in the AHA provides a wealth of resources that are useful for clinicians and scientists who are dedicated to the prevention and treatment of cardiovascular diseases. There are opportunities to develop interdisciplinary collegial relationships with individuals nationally and internationally. There are great programs for mentorship of new scientists and clinicians, as well as excellent funding opportunities. I always recommend AHA membership to my mentees who are beginning their careers with a focus on cardiovascular diseases.
Conner Lecture to address ‘seismic shift’ in treating congenital heart disease

About 32,000 infants are born in the United States every year with congenital heart disease (CHD), but the survival of CHD patients has improved greatly since the advent of open-heart surgery in the 1950s, said Jane W. Newberger, MD, MPH, presenter of this year’s Lewis A. Conner Memorial Lecture.

“The purpose of my lecture is to increase awareness in the cardiovascular community of the remarkable journey in this field and of challenges that this population faces,” said Newberger, Commonwealth Professor of Pediatrics at Harvard Medical School and Associate Cardiologist-in-Chief for Academic Affairs at Boston Children’s Hospital. She will present her award lecture, “Beyond Mortality – Outcomes in Congenital Heart Disease,” during Sunday’s Opening Session, which begins at 1 p.m. in Hall E at the convention center.

“Only a few decades ago, 20 percent of children born with CHD survived to adulthood,” Newburger said. “In the current era, survival is expected for the great majority of CHD patients, and more adults than children are now living with congenital heart disease. With this seismic shift, we have recognized long-term postoperative morbidities in this population.”

Patients with congenital heart disease are more likely to have medical, neurocognitive and psychosocial morbidities compared to the general population, she explained. Once these patients reach adulthood, they may face obstacles concerning employability. Since the late 1980s, Newburger and colleagues have conducted research into neurocognitive and behavioral outcomes and the quality of life of CHD patients through clinical trials and prospective cohort studies.

“We have found a broad spectrum of neurodevelopmental outcomes in these patients,” she said. “The majority of individuals who have undergone surgery for CHD are thriving. However, if we compare CHD patients as a group with the normative population, we find that a great proportion of the CHD group has ongoing problems.”

Neurodevelopmental disabilities can be related to genetic factors associated with both heart and brain development. Research into genetic factors associated with congenital heart lesions, such as the research funded by the National Heart, Lung, and Blood Institute’s Bench-to-Bassinet initiative, has led to an explosion of knowledge about these genetic factors, Newburger said.

The development of neurocognitive problems also may be related to altered cerebral hemodynamics in utero; that is, altered patterns of blood flow and substrate supply to the fetal brain. After birth, the brain can be affected by the sequelae of heart disease itself, such as failure to thrive and severe cyanosis, the procedures used to treat heart disease or hemodynamic instability before and after heart surgery.

“The brain is the last frontier in many ways,” Newburger said. “We’ve become much better at protecting the brain during surgery. In recent years, we have been focusing on protection of the brain from stresses such as low blood pressure in the perioperative period. We also have better ways of cerebral monitoring after surgery.”

With the advent of the American Heart Association’s recent guidelines on the evaluation and management of neurodevelopmental disorders in children, pediatric specialists now have tools to better identify these disorders, intervene early and help CHD children perform better in school and ultimately perform better in the workplace, Newburger said.

As more children with CHD survive to adulthood, their care is shifting from the exclusive purview of pediatric cardiologists to care by adult cardiologists, she added.

“A whole new subspecialty of cardiology has been established to serve the burgeoning population of adults with congenital heart disease, and centers of excellence are now dedicated to their care,” Newburger said. “With improvements in survival, it has been estimated that one in every 150 young adults will have congenital heart disease in the next decade.”

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Speaker: Jane W. Newburger, MD, MPH
Title: Lewis A. Conner Memorial Lecture: Beyond Mortality – Outcomes in Congenital Heart Disease
Time: 1–3 p.m. Sunday
Location: Hall E
AED placement contributes to underutilization

Lifesaving automated external defibrillators are underutilized at least in part because the devices are not available to the public in the places where out-of-hospital cardiac events most commonly occur, according to a study presented Saturday at Scientific Sessions.

Sungwoo Moon, MD, professor of medicine at Korea University in Seoul, South Korea, and visiting professor at the Bureau of Emergency Services and Trauma System at the Arizona Department of Health Services and the University of Arizona College of Medicine in Phoenix, is lead author of a study comparing the location of AEDs with the location of out-of-hospital cardiac arrests. The study’s results were not a surprise, he said.

“Our data reaffirm that AEDs are only used in 2 to 3 percent of out-of-hospital cardiac events even though there are hundreds of thousands of them deployed across the country,” Moon said. “We have identified one of the reasons AEDs are used so seldom. This kind of analysis might be used to help place AEDs more effectively.”

Using a state-wide registry in Arizona, out-of-hospital cardiac arrests and AED locations in metropolitan Phoenix were geocoded using GIS technology between January 2010 and December 2012.

The state recorded 6,556 geocoded, adult, out-of-hospital cardiac arrests during the study period. The study population included arrests occurring in the Metro Phoenix area and excluded events that were in healthcare facilities, traumatic arrests, or they occurred after the arrival of emergency medical service, leaving 654 events for analysis.

Registry data showed a total of 2,826 AEDs in Arizona that could be accurately geocoded. There was a weak correlation between the location of out-of-hospital cardiac arrests and the AEDs (r=0.274, p=0.002), Moon said. The largest proportion of cardiac arrests – 25.9 percent – occurred in cars, roads or parking lots, but no AEDs were identified in any of these areas.

The greatest AED concentration – 32.7 percent – was in schools, but only five out-of-hospital cardiac arrests occurred in schools during the two-year study period.

“We have to measure the incidence and the location of cardiac arrest events as well as the location and the use of AEDs,” Moon said. “Without this kind of information, we have no idea how effective public-access defibrillation really is. Communities everywhere have to go through this kind of analysis. Measuring the incidence and process of care for cardiac arrest in public places, and including AEDs in that measurement, is the first step in putting more AEDs in places where they are more likely to be needed and used.”

This is a preliminary study designed to help define the mismatch between AED need and AED placement, Moon noted. The next step is creating a system for rescuers to locate the nearest AED in real time. While professional personnel likely will use the existing emergency medical dispatch system, lay rescuers could access the same information using smartphone technology.

“It has been shown time and again that AEDs are incredibly effective when they are used,” Moon said. “We need to coordinate need for AEDs and location of AEDs and make those locations findable in real time. With the technology we already have, this is very doable.”

Join in our Annual Awardee Group Photo at Scientific Sessions

- Annual Research Awardee Photo with AHA President Mariell Jessup, MD, FAHA
- Monday, November 18 at 1:45 PM
- Hall F Lobby by the Early Career Lounge
- Participants will receive a special lapel pin!
Leaders gather for 2nd annual Corporate Forum Symposium

The American Heart Association held the second Corporate Forum symposium, bringing together leading corporations in a shared effort to build healthier communities.

The AHA is proud to collaborate with corporations that set the standard worldwide for innovation and that are equally admired for their commitment to community health. Current Corporate Forum members are: AstraZeneca, Bristol-Myers Squibb | Pfizer, Daiichi Sankyo, Eisai, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Solac, Takeda and Walmart.

The second symposium – held Friday at the Omni Hotel – provided an opportunity for members to better understand the AHA’s mission of building healthier lives, free of cardiovascular diseases and stroke. Executives also were able to discuss how commitment to social progress and corporate success go hand in hand to create a framework for success in building healthier and more prosperous communities.

The symposium was facilitated by Co-Chair Gordon Tomaselli, MD, FAHA, former AHA president and Chief of Cardiology at Johns Hopkins University; and Co-Chair John Agwunobi, MBA, MPH, Senior Vice President of Health and Wellness for Walmart; Kyle Peterson, Managing Director at consulting firm FSG; and AHA Chief Executive Officer Nancy Brown.

In a separate experiment, VO-OHpic increased the contractile velocity of heart muscle cells as well as the total ATP content and the ATP/ADP ratio during ischemia.

“This treatment improved cardiac and brain function, improved metabolic recovery and reduced systemic inflammation in our mouse model and we saw dramatically improved survival,” Li said.

There are about 1,000 out-of-hospital cardiac arrests each day in the United States, with less than 10 percent surviving. CPR and defibrillation may successfully restart the heart following cardiac arrest, Li noted, but patients still die of cardiac and neural dysfunction, abnormal metabolic effects and systemic inflammation related to post cardiac arrest syndrome.

“This is the only leading cause of death – in the same category as lung cancer, breast cancer and AIDS – where we have no drug available to improve survival,” Li said.

Therapeutic hypothermia is recommended for patients who remain comatose after being resuscitated from out-of-hospital cardiac arrest. Reducing body temperature to between 32 and 34 degrees Celsius for 12-24 hours has been shown to reduce mortality and morbidity, but it can take several hours to achieve that temperature. Multiple research groups seek a pharmacologic agent that can be easily administered soon after cardiac arrest to mimic or enhance hypothermia’s positive effects.

“Our real goal is to understand the mechanism of PTEN inhibition so we can focus on pharmacologic and biologic drug development,” Li said. “Drugs derived from this kind of research have the potential to save thousands of lives.”

PTEN continued from 1

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“This is the only leading cause of death – in the same category as lung cancer, breast cancer and AIDS – where we have no drug available to improve survival,” Li said.

Therapeutic hypothermia is recommended for patients who remain comatose after being resuscitated from out-of-hospital cardiac arrest. Reducing body temperature to between 32 and 34 degrees Celsius for 12-24 hours has been shown to reduce mortality and morbidity, but it can take several hours to achieve that temperature. Multiple research groups seek a pharmacologic agent that can be easily administered soon after cardiac arrest to mimic or enhance hypothermia’s positive effects.

“Our real goal is to understand the mechanism of PTEN inhibition so we can focus on pharmacologic and biologic drug development,” Li said. “Drugs derived from this kind of research have the potential to save thousands of lives.”
**HYPOTHERMIA continued from 1**

Data from the Penn Alliance for Therapeutic Hypothermia (PATH) registry. PATH includes 16 hospitals that recorded 522 cardiac arrest patients with an initial non–shockable rhythm between 2000 and 2013. To control for confounding, researchers utilized propensity score matching, which included 405 of the patients for analysis. The primary results were good neurologic outcome as measured by Cerebral Performance Category (CPC) score, 1–2 (good) or 3–5 (poor), and survival to hospital discharge.

The patient and arrest characteristics used to estimate the propensity to receive therapeutic hypothermia included patient age, gender, location of the arrest, whether the arrest was witnessed, the presence of an initial nonshockable rhythm and downtime without cardiac rhythm. The mean age of propensity-scored patients was 63 years; 51 percent were male; and 60 percent had an initial rhythm of pulseless electrical activity.

Of the patients who did not receive therapeutic hypothermia, 15 percent survived to hospital discharge compared with 29 percent of patients who received therapeutic hypothermia. Among patients who did not receive therapeutic hypothermia, 10 percent had a CPC score of 1 or 2 at discharge compared to 21 percent of patients who received therapeutic hypothermia. Patients who received therapeutic hypothermia had more than twice the odds of survival to discharge (OR=2.8) and good neurologic outcome (OR=3.5) compared to patients who did not receive therapeutic hypothermia.

The study’s results support the use and benefit of therapeutic hypothermia in cardiac arrest patients with an initial non–shockable rhythm, Grosse-Truthe said. “We’re hoping that this study will encourage more clinicians to consider cooling patients with initial nonshockable rhythms,” she said. “If this happens, the next step from a research standpoint is to follow these patients prospectively.”

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**PROVEN SUPERIOR TO CLOPIDOGREL IN REDUCING CV DEATH AT 12 MONTHS**

CV death secondary end point: RRR with BRILINTA plus aspirin was 21% (ARR 1.1%) vs clopidogrel plus aspirin.1

**INDICATIONS**

BRILINTA is indicated to reduce the rate of thrombotic CV events in patients with acute coronary syndrome (ACS) (unstable angina [UA], non–ST–elevation MI [NSTEMI], or ST–elevation MI [STEMI]). BRILINTA has been shown to reduce the rate of a combined end point of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin >100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin >100 mg daily.

**BLEEDING AT 12 MONTHS, there was no significant difference in Total Major Bleeding (which includes Fatal and Life-Threatening bleeding) for BRILINTA plus aspirin vs clopidogrel plus aspirin (11.6% vs 11.2%).**

There was a somewhat greater risk of Non–CABG-related Major plus Minor Bleeding for BRILINTA plus aspirin vs clopidogrel plus aspirin (4.5% vs 3.8%), respectively. PLATO trial did not show an advantage for BRILINTA compared with clopidogrel for CABG-related Bleeding (Total Major 65.5% vs 66.3% and Fatal/Life-Threatening 7.9% vs 7.5%, respectively).2

**WARNINGS AND PRECAUTIONS**

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin doses >40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

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**ADVERSE REACTIONS**

- The most commonly observed adverse reactions associated with the use of BRILINTA vs clopidogrel were Total Major Bleeding (11.6% vs 11.2%) and dyspnea (14% vs 6%).
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradycardic rhythm.
- PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

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**Please see Brief Summary of Prescribing Information, including Dosed WARNINGS, on the adjacent pages.**

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**References**

BRILINTA® (ticagrelor) Tablets

WARNING: BLEEDING RISK

BRILINTA has no antithrombotic agents, can cause significant, sometimes fatal bleeding (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Do not use BRILINTA in patients with active peptic ulcer disease, duodenal peptic ulcer disease, or GI bleeding (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Do not use BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG) (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Susceptible bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Auspicy DOSE AND BRILINTA EFFICACY

Maintenance doses of aspirin above 100 mg may reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with 75-100 mg per day (see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES (14) in full Prescribing Information).

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND Usage

Acute Coronary Syndromes

BRILINTA is a P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-Q wave myocardial infarction, or STEMI). BRILINTA has been shown to reduce the risk of a composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis (see Clinical Studies (14) in full Prescribing Information). BRILINTA has been studied in ACS in combination with aspirin. The maintenance dose of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg/day (see WARNINGS and PRECAUTIONS and Clinical Studies (14) in full Prescribing Information).

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at the scheduled time.

CONTRAINDICATIONS

History of intracranial hemorrhage: BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of repeated ICH (in this population) (see CLINICAL STUDIES (14) in full Prescribing Information).

Active bleeding: BRILINTA is contraindicated in patients with active peptic ulcer bleeding such as peptic ulcer or intracranial hemorrhage (see WARNINGS and PRECAUTIONS and ADVERSE REACTIONS (6.1) in full Prescribing Information).

Severe Hepatic Impairment: BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding of reduced synthetic capacity of clotting proteins (see CLINICAL PHARMACOLOGY (12.1) in full Prescribing Information).

Hemagglutination: BRILINTA is contraindicated in patients with hemagglutination and/or titrator or any component of the product (see Adverse Reactions (6.1) in full Prescribing Information).

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. Major + Minor is a somewhat greater risk than did clopido-
grel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg (see Dosage and Administration and Clinical Studies (14) in full Prescribing Information).

Moderate Hepatitis Impairment: BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Bleeding

In PLATO, bleeding was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. BRILINTA was usually mild to moderate in intensity and often resolved during continued treatment, but occasionally required discontinuation (1.5% of patients taking BRILINTA versus 0.1% of patients taking clopidogrel). If a patient develops new, prolonged, or worsening bleeding during treatment with BRILINTA, withhold another antiplatelet drug that may enter into treatment. If it is determined to be withheld to BRILINTA, no specific treatment is required. Continue BRILINTA without interruption. In the case of intolerable idiopathic bruising and other situations of bleeding, BRILINTA may be discontinued, and another antiplatelet agent used. In a substudy, 1998 patients who took PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference in FEV1 and FVC. Therefore, the clinical effect of ticagrelor on pulmonary function was assessed within months after one month or after 6 months of chronic treatment.

Discontinuation: BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily interrupted, resume use with clopidogrel or an alternative antiplatelet agent, as rest as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong inhibitors of Cytochrome CYP3A CYP3A and have recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even when chronic nonsteroidal anti-inflammatory drugs (NSAIDS) (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Intracranial hemorrhage (ICH) is a potentially fatal event. Intracranial hemorrhage is a rare event and has been observed in patients treated with ticagrelor (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). Intracranial hemorrhage is a rare event and has been observed in patients treated with ticagrelor (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

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INDICATIONS AND Usage

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Moderate Hepatitis Impairment: BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.
Digital study aims to leverage patient data, reduce heart disease

T he American Heart Association is coordinating with researchers at the University of California, San Francisco in a study that uses digital devices that harness patient data to better identify how to prevent and manage cardiovascular diseases.

The Health eHeart study, launched in March, aims to enroll 1 million patients from around the world. The long-term, ongoing research project will use data collected by smartphones and other personal digital technology, in addition to other electronically available medical data and patient-provided information.

“This is one of the most exciting and truly innovative and transformative research approaches that I’ve seen in my career as a clinical investigator,” said Elliott Antman, MD, FAHA, President-elect of the AHA and a Professor of Medicine at Brigham and Women’s Hospital. “When I see patients in my practice, I introduce the study to them and invite them to join.”

The study is considered a large-scale, digital version of the 65-year old Framingham Heart Study, which has conducted some of the most influential medical research in history.

“This changes the way we think about and even perform clinical research and leverages available technology to make clinical research more efficient, significantly faster and more nimble, and I would argue, potentially more robust,” said Jeffrey Oliff, MD, Gulo-Chatterjee Distinguished Professor of Medicine and Chief of UCSC’s Division of Cardiology and Principal Investigator for the Health eHeart study.

The Health eHeart study comes at a time when chronic diseases, such as heart disease and stroke, are expected to play a greater role in the quality of life and longevity of an aging population.

How the study works

Enrollments must be at least 18 and have Informed Consent Participants sign up online and answer a series of questions about demographic information, personal and family medical history and lifestyle habits to establish a baseline.

Every six months, they’ll be asked to answer additional questions about activities and health events.

Participants also may choose to share additional data from smartphone applications or other wireless devices such as digital scales, blood pressure monitors, offering researchers almost real-time data that are much more difficult to acquire with traditional studies.

Antman signed up as a research subject himself for the study and linked his smartphone and digital sensor data to the information he provided in the baseline questionnaire he completed.

With thousands of other study participants available, Antman said the potential for finding new treatments is high. “It’s the capability of seeing big data being streamed, almost in real time as people are going about their daily activities,” said Antman, who co-chairs the Scientific Advisory Committee for the AHA’s health eHeart study.

For example, rather than relying on simple “snapshots in time”—such as blood pressure readings taken periodically at the doctor’s office or occasionally at a local pharmacy or grocery store—researchers could analyze the frequent readings taken using digital blood pressure monitors that interface with a smartphone. This could provide a more complete and detailed picture of how a person’s blood pressure fluctuates over weeks to months.

“The concept of what is ‘normal’ or ‘abnormal’ blood pressure might change when we have the comprehensive picture of a person’s BP over time,” Antman said. “We don’t know yet what this will reveal, but it could change the way we diagnose hypertension and the way we judge whether it is adequately controlled.”

Those answers from such research could get to health providers more quickly. This could provide powerful information in a fraction of the time with far less expense than traditional studies, which can take several years to enroll subjects, Antman said.

“We might be able to test interventions in a matter of six to 12 months compared to the many years it often takes in traditional studies,” Antman noted.

The study enrolled more than 4,000 participants in its first few months and the pace of enrollment is increasing rapidly. Oliff said he expected to enroll 12,000 participants in the next five years to recruit 1 million enrollees, although initial research projects already are underway.

“We’re already close to approaching in a few months what would be considered a pretty large traditional research cohort,” Oliff said.

“What’s hard for people to appreciate is that with most traditional research studies, every person you enrol costs more money. This is completely the opposite. For every subject we enroll, the study gets cheaper.”

Collaborating on the study is a natural fit for the AHA, which set an ambitious goal of improving the cardiovascular health of all Americans by 20 percent while reducing deaths from heart disease and stroke by 20 percent by 2020.

“We believe innovative platforms like the Health eHeart study can help us identify and implement low-cost, high-value interventions needed to reach ideal cardiovascular health,” Antman said.

The AHA launched a major outreach effort via its patient and health provider networks this fall, through national media outreach and AHA scientific meetings. The goal is to create a broad effort to drive enrollment in the study. At Sessions, AHA will be introducing the study at council meetings and assist with registering subjects at its HeartQuarters booth on the exhibit floor throughout the week.
## 2013 Scientific Sessions Exhibitors

### Science & Technology Hall
- **Sunday**: 11 a.m.–5 p.m.
- **Monday**: 9 a.m.–5 p.m.
- **Tuesday**: 11 a.m.–2:30 p.m.

### Lunch & Learn
- **Sunday**: 11 a.m.–1 p.m.
- **Monday**: 12–2 p.m.
- **Tuesday**: 12–2 p.m.

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SUNDAY, NOVEMBER 17, 2013

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Sunday's Theater Demonstrations

CV EXPERT THEATER I
Booth 108
11 a.m.–12:15 p.m.
Chronic Management of Obesity: The Role of a Unique, Once-Daily Treatment

12:30–1:30 p.m.
A Paradigm Shift in the Treatment of Thrombosis

CV EXPERT THEATER II
Booth 1209
11:20–11:50 a.m.
Considering Heart Rate in Cardiovascular Disease: A Focus on Heart Failure

12:20–12:50 p.m.
Anticoagulation to Reduce the Risk of Stroke in Patients with Nonvalvular Atrial Fibrillation (NVAF)

HEARTQUARTERS THEATER
Booth 339
11:15–11:50 a.m.
Sessions OnDemand™ Premium Product Demonstration
Demonstrator: Diane Panino

1–2 p.m.
Endovascular Therapy for Acute Ischemic Stroke: Current Status and Future Directions (Stroke journal webinar)
Webinar Presenter: Tudor Jovin, MD

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Claiming your CME/CE for Sessions 2013
Presenter: Michelle Bruno, MLA
Learn the process for claiming continuing medical education credit and certificates either onsite or from any device with an Internet connection.

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THE QUESTION AFIB EXPERIENCE
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Work underway to set 2015 AHA CPR & ECC Guidelines

The rigorous evaluation of new research on emergency cardiovascular care and resuscitation to update AHA guidelines in 2015 is well underway, thanks to the work of scientists and healthcare providers around the world. The 2015 publication of the American Heart Association’s Guidelines for CPR and ECC since 1966. The effort went global in 1992 with the creation of the International Liaison Committee on Resuscitation (ILCOR), which provides a forum for the professional organizations worldwide and provides a multinational base of evidence for resuscitation practices.

In addition to the AHA, ILCOR comprises the European Resuscitation Council, Heart and Stroke Foundation of Canada, Australian and New Zealand Committee on Resuscitation, Resuscitation Council of Southern Africa, InterAmerican Heart Foundation, and Resuscitation Council of Asia.

The CPR and ECC guidelines are based on the best and most up-to-date evidence-based research. They provide the basis for how resuscitation should be taught and performed to result in the best possible survival from cardiac arrest and other cardiovascular emergencies. “They form the basis for the community of programs that saves lives,” said William H. Montgomery, MD, recently retired Associate Professor of Anesthesiology at the University of Hawaii School of Medicine and Coordinator for the ILCOR 2015 Consensus Conference to be convened in February 2015.

For each five-year cycle, ILCOR volunteers systematically sift through emerging research to determine the most important topics for review, put new evidence through a rigorous evaluation and present it in a global forum to consider any revisions to existing guidelines.

The Consensus Conference is the culmination of the evidence review process. The results are adopted and published by ILCOR as the “International Consensus on CPR and ECC Science with Treatment Recommendations” (CoSTR). Councils may choose to use CoSTR to update their own resuscitation guidelines. The scale of the project is significant. In February 2015, nearly 500 ILCOR members, including volunteer clinicians, researchers, and experts, will meet in Atlanta to begin the process of reviewing and updating the existing guidelines.

The results are adopted and published by ILCOR as the “International Consensus on CPR and ECC Science with Treatment Recommendations” (CoSTR). Councils may choose to use CoSTR to update their own resuscitation guidelines. The scale of the project is significant. In 2010, new evidence resulted in a recommendation to make a key change in the CPR sequence from A-B-C, or airway, breathing, chest compressions, to C-A-B, doing chest compressions first, followed by airway and breathing. Another major change was the recommendation for untrained lay rescuers to use Hands-Only™ CPR.

ILCOR is working to transition from the five-year cycle to offering updates continuously as new research is published. This shift won’t be made for years, but it’s an important step, Montgomery said. “Lifesaving information or teaching techniques could be put into place sooner,” he said. “We’re moving the survival needle in a positive way, but we could move it better and faster if we could move to a more continuous review of the science.”

ILCOR also is switching to a new way of rating the quality of scientific evidence and strength of recommendations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) addresses the extent to which one can be confident that adherence to the recommendation will do more good than harm.

“This effort is helping us to also reduce the hours needed by volunteers while bringing the science into practice quicker,” Montgomery said.

Montgomery said the AHA’s drive behind ILCOR’s work is crucial to its success. ILCOR is leveraging technological innovations, developed and supported by the AHA, to guide and assist volunteer reviewers through the evidence review process.

“ILCOR greatly appreciates the support that AHA provides,” he said.

The feeling is mutual, as the AHA is honoring ILCOR at Sessions with the Award for International Group Collaboration to Advance Resuscitation. The award will be presented Sunday at 9:45 a.m. in the Trinity Ballroom of the Omni Dallas Hotel.
Treatment creates ‘artificial short gut’

The rapidly rising incidence of diabetes, a major risk factor for atherosclerosis leading to heart attack and stroke, prompted the committee to select this diabetes therapy. Between 1988 and 2008, the prevalence of diabetes among Americans increased by 128 percent, according to the American Diabetes Association. Today, the ADA reports, more than 8 percent of the U.S. population has been diagnosed with diabetes (90 to 95 percent of these have Type 2).

When the natural substances L-glutamine and sodium butyrate, contained in everyone’s diet, reach the colon, they bind there with receptors which increase insulin secretion and appear to decrease insulin resistance. Normally, these substances are absorbed as soon as they leave the stomach, but when the gut is shortened by Roux-en-Y intestinal bypass surgery, these substances manage to reach the colon.

“Before patients even start to lose weight after surgery, their insulin levels and responses improve, and their blood sugar improves,” Tomaselli said.

BioKier’s novel treatment creates an “artificial short gut” by delivering these dietary compounds intact from the mouth to the colon, where they create the same beneficial effects observed after gut shortening surgery.

The Accelerator program’s investment, made in July, in concert with Broadview Ventures and North Carolina Biotech Center, will allow BioKier to conduct two phase 1 clinical trials. One will validate the mechanism of action of each compound, already demonstrated in the accepted diabetes rat model, and the other is designed to prove the chronic efficacy of each compound compared with placebo over the course of one month. In addition, the joint investment will fund formulation of the capsule and its in vivo human validation.

“The potential impact of the BioKier investment is enormous,” Tomaselli said.

“At first it will be reduction in morbidity and perhaps lives saved, but ultimately it should lower [healthcare] cost from a healthier population.”

Tomaselli said the diabetes treatment could be available within three to five years since both nutrients being tested have the Food and Drug Administration’s “generally recognized as safe” designation and L-glutamine is already approved to treat short bowel syndrome.

First investment produces blood test to detect myocardial infarction, stroke

The Accelerator program’s inaugural investment lent financial support to Philadelphia-based diagnostics company CytoVas, LLC, and its blood test that predicts an asymptomatic person’s risk for myocardial infarction or stroke – in essence, identifying the marathon runner at risk for sudden death in his next race. CytoVas’s Vascular Health Profile (VHP) provides a cytomtric fingerprint of the health of the vascular endothelium based on ratios between circulating endothelial progenitor cells and circulating microparticles from breakdown of platelets and certain types of cells.

The phase 2 study funded by the Accelerator program is testing the VHP’s ability to assess and monitor response to Lipitor (atorvastatin) among patients proven to be at high risk for myocardial infarction or stroke by accepted standards, who also have high cholesterol. Findings from the study are expected in late 2014. Ideally, the blood test would be added to the standard screening for high blood pressure, cholesterol and fasting blood glucose that routinely accompany standard clinical evaluations, Tomaselli said.

“The test would be a method to further define someone’s risk of having a significant cardiac event in the next 10, 20 years or even in a lifetime,” he said. Such information would assist clinicians in prescribing appropriate preventive care.

In addition, CytoVas can license the blood test to drug companies to include in clinical trial protocols to assess the efficacy and toxicity of investigational drugs. By detecting changes in the smoothness of vascular lining, CytoVas’s VHP could potentially mitigate the risk of missteps such as Pfizer encountered with torcetrapib, which proved to lower cholesterol remarkably yet significantly increased risk for cardiovascular events. In addition, CytoVas ultimately could compile the data it assisted in collecting in such trials to file for its own premarket approval (PMA) of the VHP blood test by the FDA, paving the way for it to become part of everyone’s annual health evaluation.

Future investments made by the Accelerator program will focus on health information technology and innovations to diagnose, prevent and treat stroke as well as cardiovascular innovations.

About $2 million has been donated to the program, which is funded solely through direct philanthropic contributions to the program itself. The program invests in products so that any return on investment can also be reinvested into accelerating more innovations to market.

Learn more about the Science & Technology Accelerator Program at myamericanheart.org/accelerator. For more information about the projects being funded by the program, visit the BioKier and CytoVas exhibits in the Emerging Science & Technology Showcase (booth 423) of the Exhibit Hall.
Distinguished Scientists to be honored Sunday

The American Heart Association will honor six researchers at 2013 Distinguished Scientists during Sunday’s Opening Session, which will begin at 1 p.m. in Hall E. These annual awards recognize association members for significant, original and sustained scientific contributions that have advanced the association’s mission: Building healthier lives, free of cardiovascular diseases and stroke.

This year’s recipients are:

Kenneth E. Bernstein, MD, FAHA

Bernstein has studied the physiology and biochemistry of the renin-angiotensin system (RAS) since 1987. His research concerns two important areas: the angiotensin II (AT1) receptor and angiotensin-converting enzyme (ACE). He was one of two first who cloned and characterized the structure of ACE, and his cloning of cDNA encoding the AT1 receptor was a major discovery in understanding the RAS.

Currently Director of Experimental Pathology and Professor of Pathology and Biomedical Sciences at Cedars-Sinai Medical Center in Los Angeles, Bernstein helped elucidate a number of critical insights concerning intracellular signaling by seven transmembrane receptors and provided insight into why angiotensin II has many physiologic actions, including its effects in the kidney. Bernstein’s lab created a series of mice with unique mutations and studied their physiology to gain insight into why angiotensin II receptor agonists and antagonists have effects in the kidney.

Bernstein’s lab created a series of mice with unique mutations in the ACE gene, focusing on the physiologic role of ACE in individual tissue types, such as the heart and kidney. He previously received the AHA’s Novartis Prize for Hypertension Research and the AHA’s Basic Research Prize.

Bruce M. Psaty, MD, PhD, FAHA

Psaty, a principal investigator for several large epidemiologic studies, has served as a cardiovascular disease epidemiologist at the coordinating centers of several NIH-funded clinical trials, the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and the Women’s Health Initiative. His research interests include cardiovascular epidemiology, especially genetic and environmental methods, myocardial infarction, stroke, hypertension, diabetes, drug safety, pharmacoeconomics, genetics, and pharmacogenomics.

Psaty recently collaborated with investigators from several national and international cohorts to establish the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, which has published more than 120 meta-analyses of genome-wide association studies of a variety of phenotypes. Psaty is currently Co-Director of the Cardiovascular Health Research Unit at the University of Washington. He is a member of the U.S. Food and Drug Administration Science Board, the Safety Science Board, of the U.S. Food and Drug Administration.

Adempas® (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY of prescribing information

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FOetal T oxICITY

Do not administer Adempas to a pregnant female because it may cause fetal harm (see Contraindications (4) and Use in Specific Populations (8.1)).

Female reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception (see use in Special Populations (8.8)).

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program (see Warnings and Precautions (8.2)).

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy in patients with WHO functional class II–IV and endogenous or patent pulmonary hypertension (PH) (65%) or PAH (35%) associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas is consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

4.2 Nitrites and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see Drug Interactions (7.2), Clinical Pharmacology (12.2)].

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or non-specific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Drug Interactions (7.1), Clinical Pharmacology (12.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered within 1 month before pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy test. For females, Adempas is contraindicated under the Adempas REMS Program [see Dosage and Administration (2.3), Warnings and Precautions (8.2) and Use in Specific Populations (8.1, 8.8)].

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program [see Instructions for Use in Specific Populations (3.1)]. Important requirements of the Adempas REMS Program include the following:

• Pregnant females must be certified with the program by enrolling and completing training.
• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
• Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
• Females must be certified with the program and must only be provided with Adempas for use by women who are pregnant. If a female is determined to be not pregnant, the pharmacist must notify the patient and withdraw the remaining supply of Adempas.

5.3 Hypersensitivity

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular failure or obstruction, restenosis, hypertension, autonomic dysfunction, or concomitant treatment with antihypertensive or strong CYP 3A4/5/PPG/BCRP inhibitors [see Drug Interactions (7.2), Clinical Pharmacology (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemorrhagic events included 5 (1%) patients taking Adempas compared to 0 placebo patients, including 3 events with fatal outcomes. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 1 with gastrointestinal bleeding, 1 with subdural hematoma, hematrhemiasis, and intra-abdominal hemorrhage.

5.5 Pulmonary Venous-Occulsive Disease

Pulmonary vasodilators may significantly women the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD).

Initial U.S. Approval: 2013

5.6 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. The safety data described below reflect exposure to Adempas in two, randomized, double-blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; placebo: n = 214) was between the age of 18 and 80 years [see Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH was similar to the safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490, placebo: n = 214) was between the age of 18 and 80 years [see Clinical Studies (14.1, 14.2)].

5.6.1 Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>22</td>
<td>20</td>
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<tr>
<td>Dyspnea and Gastritis</td>
<td>13</td>
<td>10</td>
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<tr>
<td>Diarrhea</td>
<td>14</td>
<td>11</td>
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<tr>
<td>Nausea</td>
<td>14</td>
<td>10</td>
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<tr>
<td>Constipation</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
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<td>7</td>
</tr>
<tr>
<td>Pulmonary veno-occulsive disease</td>
<td>5</td>
<td>3</td>
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Other events that were seen more frequently in riociguat compared to placebo included epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Antagonists of the adrenergic receptor are used in patients with PVOD. Because the safety profile is similar to that observed in the placebo controlled phase 3 trials, the drug safety of Adempas is not affected by concomitant use with these agents.

7.2 Pharmacokinetic Interactions with Adempas

Adempas is not metabolized in the liver. Concomitant use of drugs that are substrates or inhibitors of CYP3A4/5 or P-gp/BCRP may result in increased concentration of Adempas in vivo. Other drugs that are substrates of CYP3A4 or P-gp/BCRP may result in reduced concentrations of Adempas in vivo. Adempas is not metabolized in the liver. Concomitant use of drugs that are substrates or inhibitors of CYP3A4/5 or P-gp/BCRP may result in increased concentration of Adempas in vivo. Other drugs that are substrates of CYP3A4 or P-gp/BCRP may result in reduced concentrations of Adempas in vivo.
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DISTINGUISHED SCIENTISTS  continued from previous page

Committee of the FDA’s Mini-Sentinel Initiative, and the National Heart, Lung, and Blood Institute Advisory Councils.

Paul M. Ridker, MD, FAHA
Ridker’s research is focused on the design and conduct of multinational randomized trials, the development of inflammatory biomarkers for clinical and research use, the molecular and genetic epidemiology of cardiovascular diseases, and novel strategies for cardiovascular disease detection and prevention.

Ridker is currently Director of the Center for Cardiovascular Disease Prevention at the Brigham and Women’s Hospital in Boston. His longstanding commitment to the AHA’s research and clinical missions includes directing the Center for Biomedical Research and Outreach (CBRO) and serving as the Chair of the AHA’s Scientific Advisory Council.

Ridker is known for his groundbreaking work translating the biology of vascular inflammation into clinical practice, Ridker and his group were the first to use inflammatory biomarkers to predict cardiovascular risk in otherwise healthy women and men in prospective patients. They have demonstrated that these biomarkers independently predicted incident diabetes and hypertension. His group also observed that statins reduce inflammation and might be effective in lowering levels of low-density lipoprotein (LDL) who have a persistent inflammatory response. The research group also developed and validated the Reynolds Risk Score.

Jonathan G. Seidman, MD, FAHA
Seidman and his wife, Christine Seidman, MD, operate the Seidman Cardiovascular Program at the University of Pennsylvania’s Perelman School of Medicine. Dr. Seidman is a world-renowned expert in the cardiovascular genetics of complex disease.

Seidman previously received the Gill Heart Institute Award for Outstanding Contributions to Cardiovascular Research. He and his wife have received the Robert W. and Maureen Myers Award for Distinguished Achievement in Cardiovascular Research, the Lefoulon-Delalande Foundation Grand Prix for Science and the Katz Prize for Cardiovascular Research awarded by the University of Colorado School of Medicine.
‘Sunshine Act’ reporting starts, but under a new name

A
fter years of development and months of delay, the “Sunshine Act” has taken effect.

Open Payments, now the official name of what had been called the Physicians Payments Sunshine Act, offers “a national disclosure program that promotes transparency by publishing the financial relationships between the medical industry and healthcare providers (physicians and hospitals) on a publicly accessible website developed by CMS,” according to the Centers for Medicare & Medicaid Services.

The program requires manufacturers of drugs, medical devices and biologics to collect and track payment, transfer and ownership information. Manufacturers and group purchasing organizations (GPOs) will submit reports to CMS annually, with most of the information available on a public website. Those reports will disclose all payments or transfers of value in the prior year, including: consulting fees and other compensation; honoraria; gifts; entertainment; food; travel, including the destination; education; research; charitable contributions; royalties or licenses; current or prospective ownership or investment interests; compensation for serving as faculty or for speaking at a medical education program; grants; and anything else required by the secretary of Health and Human Services.

Data collection for 2013 began in August and will continue through Dec. 31. In January, CMS is expected to launch the portal where individual reports are available for review. Manufacturers and GPOs should report all 2013 data by the end of March 2014, with physicians expected to have access to the reports starting in June 2014. The portal will allow physicians to contact manufacturers and GPOs to dispute the accuracy of a specific report.

Data will be made available to the public no later than Sept. 30, 2014. The Open Payments program will have an impact on professional education provided by the American Heart Association and other medical associations. Some industry leaders, for example, have said they will no longer support food or beverage for CME events.

Reporting exemptions exist, however, for professional education events such as Scientific Sessions. Through CMS clarification, a payment or transfer of value made by a third party to a covered recipient in conjunction with a CME activity is not reportable under the following conditions:

• The activity is accredited/providing credit through the Accreditation Council for Continuing Medical Education, the American Academy of Family Physicians, the American Dental Association’s Continuing Education Recognition Program, the American Medical Association or the American Osteopathic Association.

• The manufacturer doesn’t select the covered recipient or provide the third party with a distinct identifiable set of individuals to be considered as speakers for the certified CME activity.

• The manufacturer does not directly pay the covered recipient for the CME activity.

To learn the latest information about Open Payments, visit CMS.gov, which has a section devoted to the program. To have specific questions about Open Payments answered, email Openpaymentsinfo@hhs.gov.

The AHA/ASA Professional Education Center can also answer many questions about how Open Payments will impact learning, and the American Medical Association also has information available online. Go to ama-assn.org and click on the Advocacy link for a toolkit for ensuring accurate reports.

To find out more, go to OpenPayments.gov or contact CMS at (877) 656-5070.

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At 82, Father of Aerobics still full of pep

I n the early 1960s, when the great Space Race was being fueled by the escalating Cold War, a former track and basketball star from Oklahoma envisioned himself soaring through the Milky Way.

This tall, lanky fellow was an Army doctor, but the lure of space flight led him to transfer to the Air Force. He became certified in aerospace medicine. Then he developed training programs for astronauts – some for before they took off, others to help them remain in shape while floating weightlessly in outer space. All along, his sights were set on becoming among a select group of “science astronauts.”

Imagine how different life on Earth would be today if Kenneth H. Cooper, MD, MPH, hadn’t shifted gears.

Cooper actually was still in the Air Force when he published “Aerobics,” a book that did as much for the health of Americans as the Apollo 11 lunar landing did for the aerospace industry. Cooper’s book, by the way, came out first – more than a year before Neil Armstrong planted the U.S. flag on the moon.

That book is now available in more than 40 languages. Cooper has spoken in more than 50 countries, and written 18 more books. He is the “Father of Aerobics” and a big reason why the number of runners in the United States spiked from 100,000 when his book came out to 34 million in 1984.

Through his Cooper Aerobics Center, which opened in 1970 and continues to thrive, he’s improved the lives of countless patients, including former President George W. Bush. His influence is sure to continue for many generations – U.S. public schools this year replaced the Presidential Physical Fitness Test with Presidential Youth Fitness Program, which uses the FitnessGram developed by his Cooper Institute in 1982.

Cooper also has long been a supporter of the American Heart Association. He founded the Dallas Heart Walk, which has grown into the organization’s top annual fundraiser, drawing more than $5 million this year. At last year’s scientific sessions, he received the Chairman’s Award, which recognizes a volunteer who has significantly advanced the association’s strategic goals.

And this year he’s taking center stage again Monday afternoon as the keynote speaker for the Global Congress on Physical Activity.

First patient: Himself

A cardiac event is often a life-changing experience. For Cooper, a bout with arrhythmia during a water skiing trip in 1960 proved monumental.

From his playing weight of 168, Cooper had ballooned to 204, packing on the pounds through the stress of medical school and the start of his career. He ate the wrong things and didn’t exercise.

“Obesity is the most common manifestation of stress. It happened to me,” he said. “But I lost the weight within six months. There was no organized program. For me, it was just cutting calories and exercising. When I lost all that weight, a lot of my problems disappeared – hypertension, prediabetic, no energy, no pep. That changed my career.”

Having proven the benefits of preventive medicine and wellness in the military, he was ready to shift to the private sector.

The private sector, however, wasn’t ready for him.

When he opened his clinic in Dallas, naysayers told him, “You can’t limit your practice to taking care of healthy people. People only want to see their physicians when they’re sick.” And those were the kind ones. Others turned him in to the local medical society’s board of censors.

“They thought I was going to kill people by putting them on treadmills for stress testing,” Cooper said. “I’d been doing it in the Air Force for 10 years!”

The big picture turned out more clearly. Baby Boomers became exercisers, triggering a fitness craze that produced what he calls “the glory years of health in America.” As Boomers have aged, and future generations have made fitness a lower priority, health had spiraled in the wrong direction. It’s been 17 years since the Surgeon General recommended 30 minutes of physical activity most days of the week, and the statistics show that most Americans aren’t doing it.

“Many years, I’ve put people into five health categories, ranking them from very poor to excellent. Research constantly shows that major gains can be made by moving up just one category, even if it’s just from very poor to poor,” Cooper said. “If we can get the 50 million Americans who are totally inactive today to move up just one category, think of the dramatic effect that would have. Just by avoiding inactivity!”

Still going strong

At 82, Cooper is still full of pep.

“You can ask my staff – I’m the first person here in the morning and the last to leave,” he said. “I work out every day before I go home. I’ve controlled my stress that way.”

He gave up jogging eight years ago after breaking a leg while skiing. So he walks two miles over a half hour – an average of 15 minutes per mile – five days per week.

“That’s pretty fast for an old man,” he said, grinning again.

Cooper still gives lectures and is involved in all sorts of research projects, many relying on the extensive repository of data his organization has collected over the last 40-plus years. His base is growing, too, having opened a location in a Dallas suburb and eyeing clinics in Asia and Europe.

“It sure has been exciting,” he said, smiling. What he’s most proud of, though, is the paradigm shift in the way people view physical activity. While not enough Americans are heeding his prescription of being more active, at least everyone knows they should.

“We’ve gone from exercise being dangerous to exercise being mandatory,” he said. “That’s extreme. And it all started here.”

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XARELTO® (rivaroxaban) tablets

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Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CI Cr <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.[see Use in Specific Populations].

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CI Cr <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.[see Use in Specific Populations].

Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

* Treatment schedule: XARELTO 20 mg once daily, matched placebo once daily.

† In the RECORD clinical trials, the overall incidence rate of major bleeding leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 3: Bleeding Events* in XARELTO Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO®</th>
<th>Placebo†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>4.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Major bleeding event with ≥2 units of whole blood or packed red blood cells</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Transfusion of ≥2 units of whole blood or packed red blood cells</td>
<td>2.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Monophasia</td>
<td>1.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>32.4%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>104.1%</td>
<td>63.1%</td>
</tr>
</tbody>
</table>

Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule: XARELTO 20 mg once daily, matched placebo once daily.

‡ There were no fatal or critical organ bleeding events.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: In the RECORD clinical trials, the overall incidence rate of major bleeding leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.
Table 6: Bleeding Events in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3) (continued)

![Table content here](image-url)

Table 7: Other Adverse Reactions Reported by ≥1% of XARELTO®-Treated Patients in EINSTEIN Extension Study

![Table content here](image-url)

Table 8: Other Adverse Reactions Reported by ≥1% of XARELTO®-Treated Patients in RECORD 1-3 Studies

![Table content here](image-url)

XARELTO® (rivaroxaban) tablets

Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, unless distinctly due to dose of double-blind study medication

- Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1, 2, 3)
- Other clinical trial experience: In an investigational study of acute medically ill patients with suspected pulmonary embolism, XARELTO 10 mg twice daily, causes of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Other System/Organ Class: Hematological, Coagulation, Thrombosis

- Blood and lymphatic system disorders: anagryocytosis
- Gastrointestinal disorders: retropertitoneal hemorrhage
- Hypersensitivity: cholestasis, erthythematous rash
- Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema
- Nervous system disorders: central nervous hemorrhage, subdural hematoma, epidual hematoma, hemorrhaxis

Table 9: Excessive Thrombosis Risk in Patients with Implantable Cardioverter-Defibrillators

![Table content here](image-url)

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