SUNDAY

American Heart Association®
SCIENTIFIC SESSIONS 2013

DAILY NEWS

NOVEMBER 17, 2013

INSIDE

Go Red For Women tomorrow

Remember to wear red Monday in honor of the movement raising awareness that heart disease is the No. 1 killer of women.

American Heart Association. Go Red for women

Go Red For Women is nationally sponsored by macy's

PTEN inhibition improves heart function and survival following cardiac arrest

Researchers 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.

Jing Li, MD

PTEN continued on page 6

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.

Gordon Tomaselli, MD, FAHA

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.

ACCELERATOR PROGRAM continued on page 13

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

New 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.

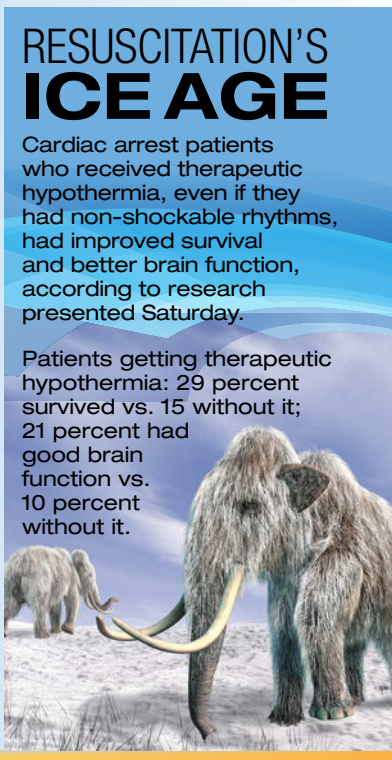
This is noteworthy because prior therapeutic hypothermia studies on patients with initial non-shockable rhythms were inconclusive for improving hospital discharge and neurologically intact survival.

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.

"Therapeutic hypothermia has historically been recommended for cardiac arrest patients with a shockable rhythm," said the study's lead author, Anne Grossestreuer, 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 these patients did better in terms of both neurologic outcomes and survival in our study."

The study's researchers used propensity analysis to create a quasi-experimental trial design using

HYPOTHERMIA continued on page 7



TODAY AT SESSIONS

Don't miss today's highlighted presentations and events. For a complete schedule, see the Final Program or view it online at **scientificsessions.org**.

8–10:50 a.m.

Current State of Physical Activity Patterns and Burden of Disease: A Global Perspective

Ballrooms C3 & C4

8–11 a.m.

Groundbreaking Studies in the Practice of Cardiovascular Medicine: Circulation Editors' Choices

Room D227

1–3 p.m.

Opening Session

Hall E

3–3:45 p.m.

Learning at the Movies: Closing a Perivalvular Leak

Hall F, Case Theater

3:45–5 p.m.

Best of AHA Specialty Conferences

Room C147

3:45–5 p.m.

Joint AHA/ACC Session – ACCF/AHA Guidelines for Management of Chronic Heart Failure: 2013 Update

Room C147

4–4:45 p.m.

Learning at the Movies: Endovascular Atherectomy for Patient with Peripheral Artery Disease

Hall F, Case Theater

4–5:28 p.m.

Late-Breaking Clinical Trials I

Hall E

7–9 p.m.

AHA Cardiovascular Evening Symposium – Heart Failure: Challenges Old and New

Dallas Ballroom BC, Omni Dallas Hotel

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.


Robert Harrington, MD, FAHA, FACC

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. Sunday'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

TRIALS	DESCRIPTIONS
Nitrites in Acute Myocardial Infarction	This trial was designed to assess the efficacy of sodium nitrite in reducing myocardial injury in patients with acute ST elevation MI.
Blood Pressure Reduction Among Acute Ischemic Stroke Patients: A Randomized Controlled Clinical Trial	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.
Randomized Clinical Trial of Pre-hospital Induction of Mild Hypothermia in Out-of-Hospital Cardiac Arrest Patients Using a Rapid Infusion of 4oC Normal Saline	The aims of this randomized clinical trial were to determine whether early in-field cooling improves survival, functional status in resuscitated cardiac arrest patients.
Target Temperature Management 33°C versus 36°C after Out-of-hospital Cardiac Arrest, a Randomized, Parallel Group, Assessor Blinded Clinical Trial	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.

Special Session | SS.01 | 3:45–5 p.m. Sunday | Room C147

Best of AHA Specialty Conferences	Presentations: • Arteriosclerosis, Thrombosis 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.

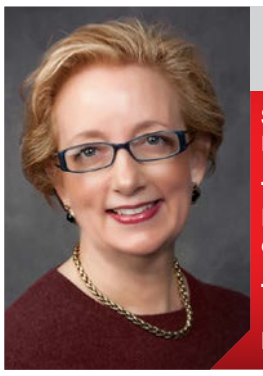
"There is this fascinating chain of events in the treatment of heart failure, and I am eager to share this story," Jessup said. "I hope people will come away with a deeper understanding of how this epidemic has spread – and some thoughts about what we can do next."

Her talk will explore the larger lessons that can 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."

Jessup outlines some of the clinical trials and medications that brought us to this point, sharing insights into what it was like to be treating patients during times of dramatic shifts in treatment.

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."



LECTURE PREVIEW

Speaker: Mariell Jessup, MD, FAHA, FACC, FESC

Title: The Heart Failure Paradox – An Epidemic of Scientific Success

Time: 1–3 p.m. Sunday

Location: Hall E

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

"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 Bernie Dennis will present the Chairman's 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. Psaty, 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 on 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

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

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 I changed again to 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 failure," she said. "I wanted to know 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.

"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 Pharmacological Society, likes attending Sessions because of the collegial atmosphere and the learning opportunities.

"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 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!" ▼

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 nurse 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 CVSN 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. Newburger, 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."

LECTURE PREVIEW

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

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."

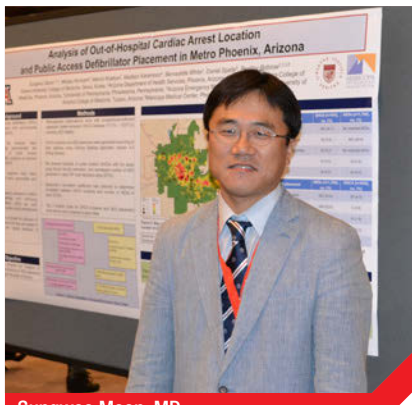
With the advent of the American Heart Association's recent guidelines on the evaluation and management of neurodevelopmental disorders in children, pediatric specialists now have tools to better identify these disorders, intervene early and help CHD children perform better in school and ultimately perform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

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

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.

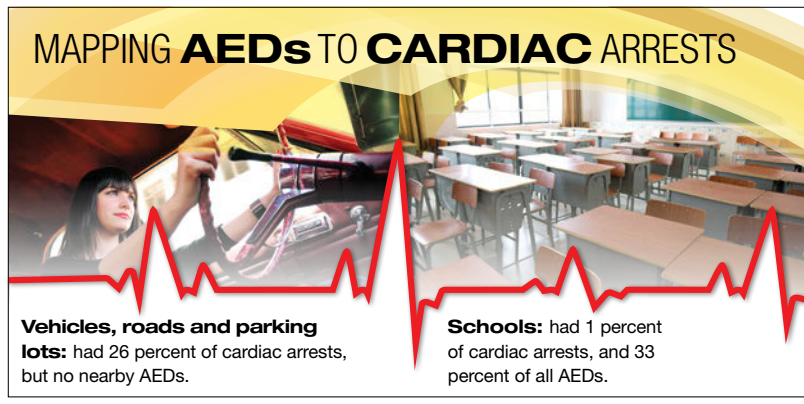
The state recorded 6,556 geocoded, adult, out-of-hospital cardiac arrests during the study period. The study population included arrests occurring in the Metro Phoenix area and excluded events that were in healthcare facilities, traumatic arrests, or they occurred after the arrival of emergency medical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



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: Astra Zeneca, Bristol-Myers Squibb | Pfizer, Daiichi Sankyo, Eisai, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Solae, 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. ▼

PTEN continued from 1

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." ▼

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, Grossestreuer 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." ▼

These boots were made for running!

2013 American Heart Association Fun Walk/Fun Run

When: 6:15 a.m. Tuesday
Where: Reverchon Park
Free registration: AHA Fun Walk/Fun Run booth – Hall C/D lobby

OK, you probably don't want to wear your best boots, but make sure to lace up your favorite running shoes for some Texas-sized fun and exercise Tuesday morning as the sun comes up over the heart of "Big D." Whether you take part in the 5k run or the 1-mile walk, your refreshment and T-shirt will be waiting for you at the finish line.

To register – it's free! – visit the AHA Fun Walk/Fun Run booth in the Hall C/D lobby of the convention center.

Case Theaters return with updated format, new topics

The Scientific Sessions Case Theaters will feature discussions about both common and new procedures and therapies from the perspective of world-renowned clinicians, and this year attendees will have a number of ways to interact with presenters.

The Case Theaters will be held in back-to-back sessions starting Sunday at 3 p.m., Monday at 2 p.m. and Tuesday at 9 a.m., in the Poster Hall. Attendees will be able to use an Audience Response System (ARS) to respond to the presentation and open microphones to comment or ask questions.

"We have designated stopping points where we ask the panel and audience what their thoughts are," said Manesh R. Patel, MD, Chair of the Case Theater working group and Associate Professor of Medicine at Duke Clinical Research Institute. "We sometimes review the data of both ARS and verbal questions at that point. So there's a broad way for people to be interactive and get their questions answered."

The goal is to provide the membership with the best practices regarding the decision-making, technical aspects and management of both common and new procedures that are performed in cardiovascular patients around the world.

Each Case Theater lasts 45 minutes. The case is presented in the first 10 minutes, followed by a panel and audience discussion centered on the decision-making about the patient's care. Then the procedure is presented, followed by more discussion. During the last 10 minutes, outcomes and post-procedure care are discussed.

The presenters, chosen based on the topic, are charged with condensing information about a case to fit the allotted time. Neither the audience nor the discussion panel, which consists of a diverse group of experts, will hear the case before it's presented at the Case Theater.

"We want everyone to hear it for the first time and give us their thoughts as they go through it," Patel said.

The topics this year are structural heart disease, vascular surgery, VAD + transplant, electrophysiology, TAVR and heart failure management. Each topic will be presented once.

"Case Theaters allow attendees a unique opportunity to evaluate some of the routine and cutting-edge therapies that are being offered to patients with a broad spectrum of disease," Patel said. "It allows them to see the heart team in action, whether that be surgeons and cardiologists or vascular surgeons and vascular medicine specialists, or electrophysiologists and heart failure doctors working together."

Attendance is expected to match or surpass the 600 from last year, which was the debut of Case Theaters at Sessions. The Poster Hall's location and more intimate environment are expected to help increase audience engagement.

"This year, there will be more time during each Case Theater presentation for people to ask questions and consider the available evidence and issues," Patel said.

If Case Theaters continue to be engaging, high-demand events, organizers are considering more upgrades.

"We think that if it's as popular as it was last year, then we may expand the topics and the ways that people can interact with the cases," Patel said. ▼

Digital study aims to leverage patient data, reduce heart disease

The American Heart Association is collaborating 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 disease.

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 technologies, 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 much cheaper, significantly faster and more nimble, and I would argue, potentially more robust," said Jeffrey Olgin, MD, Galo-Chatterjee Distinguished Professor of Medicine and Chief of UCSF'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

Enrollees must be at least 18 and have Internet access. 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, glucose or activity 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 expected to do the same, "we will have 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 UCSF study. "This opens the possibility of embedding randomization within this digital research platform to conduct clinical trials."

Potential game-changers

The volume of data collection possible through the program could ultimately change the way doctors diagnose key heart-health issues such as whether blood pressure is adequately controlled, Antman said.

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 community monitoring site – 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 a more 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 said.

The study enrolled more than 4,000 participants in its first few months and the pace of enrollment is increasing rapidly. Olgin said he conservatively estimates it will take 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," Olgin said. "What's hard for people to appreciate is that with most traditional research studies, every person you enroll 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 cardiovascular diseases and stroke by 20 percent by 2020.

"We believe innovative platforms like the Health eHeart study can help us identify and implement the behavior modifications needed to reach ideal cardiovascular health," Antman said.

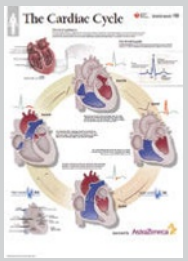
The AHA launched a major outreach effort via its patient and health provider networks this fall, through national media outreach and social media platforms in an effort to drive enrollment in the study. At Sessions, AHA will be introducing the study at council meetings and assist with registering subjects 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.

Heart Failure Guidelines Pocketcard
Booth 339
Pick up this practical quick reference of the ACCF/AHA Guideline for the Management of Heart Failure. Limited quantitities are available at the AHA HeartQuarters.



The Cardiac Cycle Wall Chart

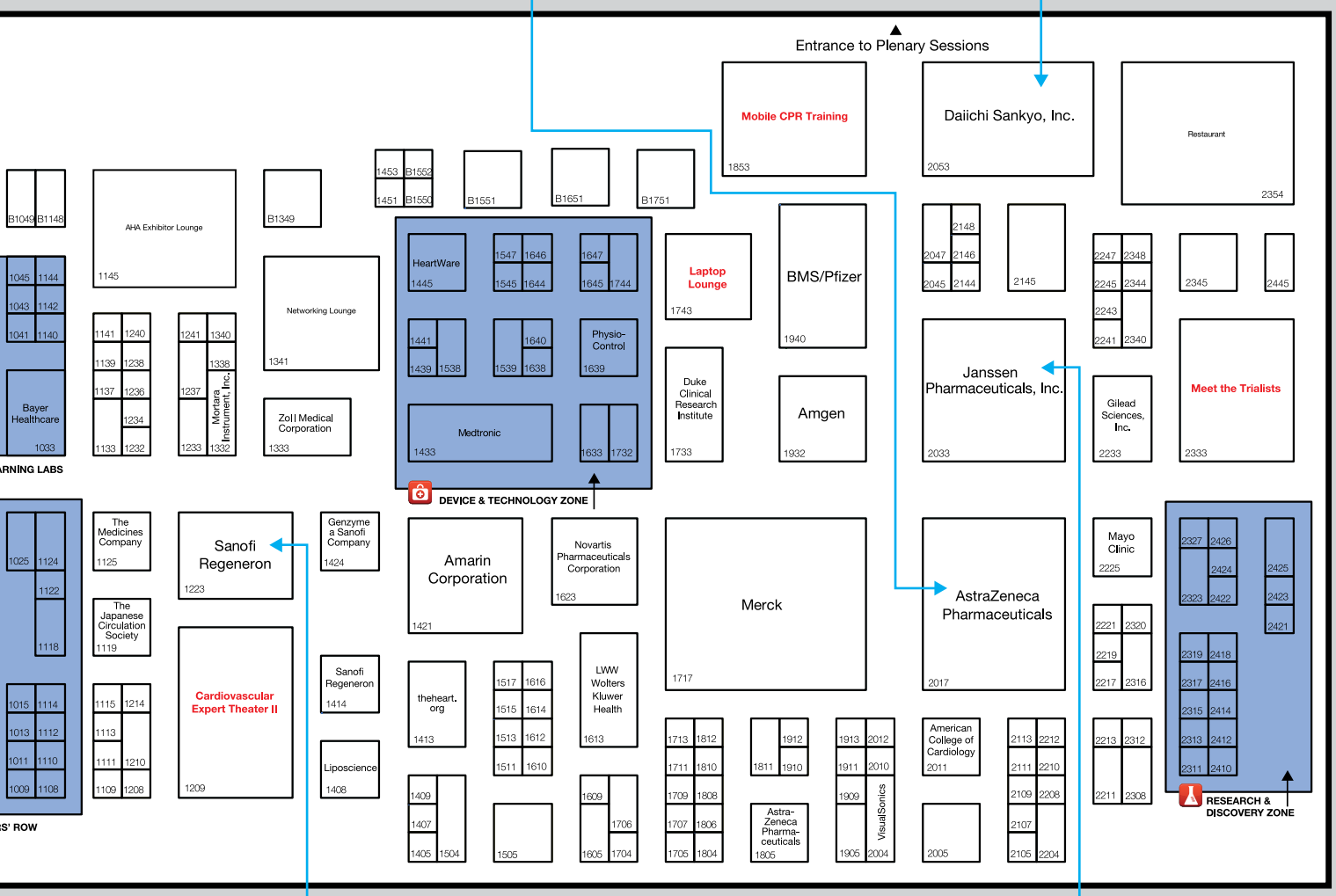
Booth 2017

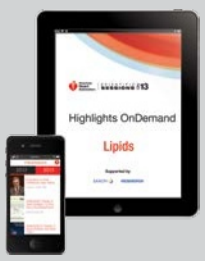
Take home a personalized poster on *The Cardiac Cycle*.

Highlights OnDemand app (Atrial Fibrillation)

Booth 2053

This app provides complimentary viewing of select presentations from 2012 and 2013, including synchronized slides and audio. Available for iPhone®, iPad® or Android™ devices. Visit Booth 2053 for unlock code.





Highlights OnDemand app (Lipids)

Booth 1223

This app provides complimentary viewing of select presentations from 2012 and 2013, including synchronized slides and audio. Available for iPhone®, iPad® or Android™ devices. Visit Booth 1223 for unlock code.

Abstracts on Disc

Booth 2033

This enduring tool allows you to search all the abstracts presented at Scientific Sessions by full text, author, title or topic. Limited quantities are available.

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

VIVUS

12:30–1:30 p.m.

A Paradigm Shift In The Treatment of Thrombosis

Janssen

CV EXPERT THEATER II

Booth 1209

11:20–11:50 a.m.

Considering Heart Rate in Cardiovascular Disease: A Focus on Heart Failure

Amgen

12:20–12:50 p.m.

Anticoagulation to Reduce the Risk of Stroke in Patients with Nonvalvular Atrial fibrillation (NVAF)

Pfizer

HEARTQUARTERS THEATER

Booth 339

11:15–11:50 a.m.

Sessions OnDemand™ Premium Product Demonstration

Demonstrater: Diane Perrino

12–1 p.m.

Endovascular Therapy for Acute Ischemic Stroke: Current Status and Future Directions (Stroke journal webinar)

Webinar Presenter: Tudor Jovin, MD

1–2:30 p.m.

AHA Mobile Guidelines Workshop

Presented by Da Chang, with Guideline Central

Learn how to access the digital guidelines on the app.

3–3:30 p.m.

Claiming your CME/CE for Sessions 2013

Presenter: Michelle Bruns, MLA

Learn the process for claiming continuing medical education credit and certificates either onsite or from any device with an Internet connection.

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 is the result of an ongoing, global effort that starts years in advance.

The American Heart Association has been developing guidelines around 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 between key resuscitation 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 built 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.


William H. Montgomery, MD

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 2010, more than 600 ILCOR volunteers from 29 countries reviewed 277 topics presented by more than 350 authors.

"It's a very rigorous process and volunteer-driven," said Montgomery, who also is an AHA volunteer. "Individuals around the world and very committed scientists and practitioners give much of their time to this."

CoSTR and the resulting guidelines can trigger significant changes in how CPR and ECC are taught and performed. For example, 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. ▼

ACCELERATOR PROGRAM continued from page 1

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 cytometric 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. ▼

SUNDAY

American Heart Association. Scientific Sessions 2013 DAILY NEWS

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Distinguished Scientists to be honored Sunday

The American Heart Association will honor six researchers as 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 who first cloned and characterized the structure of ACE, and his cloning of cDNA encoding the AT1 receptor in 1991 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 overturn dogma concerning intracellular signaling by seven transmembrane receptors and provided insight into why angiotensin II has many physiologic effects in addition to blood pressure control. More recently, 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 the 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, multicenter studies, including the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and the Women's Health Initiative. His research interests include cardiovascular epidemiology, epidemiological methods, myocardial infarction, stroke, hypertension, diabetes, drug safety, pharmacoepidemiology, genetics, genomics and pharmacogenetics.

Psaty recently collaborated with investigators from several national and international cohort studies 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

DISTINGUISHED SCIENTISTS continued on next page

DISTINGUISHED SCIENTISTS continued from previous page

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

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.

Best known for his 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 men and women, and demonstrate that these biomarkers independently predicted incident diabetes and hypertension. His group also observed that statins reduce inflammation and might be effective in patients with low levels of low-density lipoprotein (LDL) who have a persistent inflammatory response. The research group also developed and validated the Reynolds Risk Score.

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 an NHLBI-funded training grant in cardiovascular epidemiology that has produced several talented, young, clinical cardiovascular investigators.

Jonathan G. Seidman, PhD, FAHA

Seidman and his wife, Christine Seidman, MD, operate the Seidman Laboratory, where they study the genetic basis for human disease with a focus on heart disease. The lab's research interests range from the discovery of genetic variants in rare and common cardiovascular phenotypes to elucidation of how genetic variations alter signaling mechanisms in model organisms – information that has been translated into novel therapeutic interventions in human patients. The laboratory applies high-throughput genomic sequencing for basic investigations and for clinical application.

A member of the Genetics Department at Harvard Medical School in Boston since 1981, Seidman also belongs to the Genetics Society of America and the American Society of Human Genetics.

Seidman previously received the Gill Heart Institute Award for Outstanding Contributions to Cardiovascular Research. He and his wife have received the Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research, the Lefoulon-Delalande Foundation Grand Prix for Science and the Katz Prize for Cardiovascular Research awarded by Columbia University School of Medicine.

Jonathan S. Stamler, MD, FAHA

Stamler discovered the protein S-nitrosylation, a ubiquitous and conserved mechanism for controlling protein function and the prototypic redox-based signal. S-nitrosylation has emerged as a principal mechanism through which nitric oxide signals and is recognized as central to the understanding of multiple aspects of cardiovascular physiology and disease.

Stamler also discovered novel enzymatic functions for hemoglobins in bacteria, yeast, worms and mammals. He also discovered the enzymatic basis of nitroglycerin bioactivation and identified novel enzymatic activities that govern NO bioactivity in the cardiovascular system and elsewhere, including S-nitrosylases and denitrosylases. His work anchors the development of new therapeutic approaches to disease characterized by aberrant S-nitrosylation.

Director of the Institute of Transformative Molecular Medicine and the Harrington Discovery Institute at Case Western Reserve University and Hospitals in Cleveland, Stamler has published more than 250 original articles and two books. He also has co-founded five companies and serves on several editorial and scientific advisory boards. He is the author of more than 125 patents and patent applications.

Alan R. Tall, MB BS, FAHA

Internationally recognized for his work in plasma lipoprotein metabolism and atherosclerosis, Tall and his collaborators discovered mutations in the cholesteryl ester transfer protein (CETP) gene that are associated with dramatically increased high-density lipoprotein (HDL) and reduced LDL levels. This research established the role of CETP in the regulation of lipoproteins and identified CETP as a potential therapeutic target. Recent studies have uncovered new links between the regulation of cellular cholesterol homeostasis by cholesterol efflux pathways and the regulation of cell proliferation, with relevance to both atherosclerosis and neoplastic disorders.

A member of the Association of American Physicians, Tall has served on the Board of Scientific Councilors of the National Heart, Lung, and Blood Institute, the Research Committee and the ATVB Council of the American Heart Association.

Head of the Division of Molecular Medicine in the Department of Medicine of Columbia University, Tall previously received the Irvine Page Award from the AHA's ATVB Council and the Robert I. Levy Lectureship from the AHA's Lifestyle and Cardiometabolic Health (formerly Nutrition, Physical Activity and Metabolism) Council. ▼

‘Sunshine Act’ reporting starts, but under a new name

After 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 physicians can sign up to be notified when 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 Openpayments@cms.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 tab for a toolkit for ensuring accurate reports.

Scientific Sessions Supporters

The American Heart Association would like to acknowledge the following companies for their generous educational grant in support of the Scientific Sessions 2013 Education Programming:

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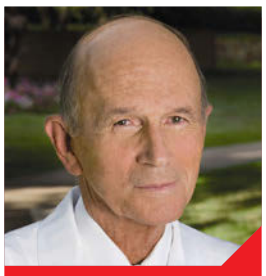
At 82, Father of Aerobics still full of pep


Kenneth H. Cooper, MD, MPH

In 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 Aerobic 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.

"For 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." ▼

Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

XARELTO® (rivaroxaban) tablets, for oral use

See package insert for full Prescribing Information

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**

***[see Warnings and Precautions and Adverse Reactions]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation: XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information]*.

Treatment of Deep Vein Thrombosis: XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

Treatment of Pulmonary Embolism: XARELTO is indicated for the treatment of pulmonary embolism (PE).

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism: XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) and Clinical Studies (14.1) in full Prescribing Information]*.

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered but has not been evaluated in clinical trials.

Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation: Avoid the use of XARELTO in patients with CrCl <15 mL/min since drug exposure is increased. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*

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 CrCl <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 CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

Use in Patients with Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Drug Interactions]*.

Risk of Pregnancy Related Hemorrhage: In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Patients with Prosthetic Heart Valves: The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning* and *Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning* and *Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 16326 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

Table 1: Bleeding Events in ROCKET AF*

Parameter	XARELTO N = 7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N = 7125 n (%)	Event Rate (per 100 Pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.

‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal.

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Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE: EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N = 4130 n (%)	Enoxaparin/ VKA† N = 4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* 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 in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

EINSTEIN Extension Study: In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

Table 3: Bleeding Events* in EINSTEIN Extension Study

Parameter	XARELTO† 20 mg N = 598 n (%)	Placebo† N = 590 n (%)
Major bleeding event‡	4 (0.7)	0
Decrease in Hb ≥2 g/dL	4 (0.7)	0
Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.3)	0
Gastrointestinal	3 (0.5)	0
Menorrhagia	1 (0.2)	0
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)
Any bleeding	104 (17.4)	63 (10.7)

* 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 adverse reactions 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 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487 n (%)**	**N = 4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3) (continued)

	XARELTO 10 mg	Enoxaparin†
Hip Surgery Studies	**N = 3281 n (%)**	**N = 3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206 n (%)**	**N = 1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study

System Organ Class Preferred Term	XARELTO N = 598 n (%)	Placebo N = 590 n (%)
Gastrointestinal disorders		
Abdominal pain upper	10 (1.7)	1 (0.2)
Dyspepsia	8 (1.3)	4 (0.7)
Toothache	6 (1.0)	0
General disorders and administration site conditions		
Fatigue	6 (1.0)	3 (0.5)
Infections and infestations		
Sinusitis	7 (1.2)	3 (0.5)
Urinary tract infection	7 (1.2)	3 (0.5)
Musculoskeletal and connective tissue disorders		
Back pain	22 (3.7)	7 (1.2)
Osteoarthritis	10 (1.7)	5 (0.8)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	6 (1.0)	2 (0.3)

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

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* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases 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.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole), increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30% to 160%. Significant increases in rivaroxaban exposure may increase bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors *[see Warnings and Precautions]*.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions]*.

Anticoagulants and NSAIDs/Aspirin: Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

XARELTO should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

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Labor and Delivery: Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

Nursing Mothers: It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

Females of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Renal Impairment: In a pharmacokinetic study, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE: In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Hepatic Impairment: In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

OVERDOSAGE:

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Active Ingredient Made in Germany

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