Evidence Matters

By Robert Harrington, M.D., FAHA, President, American Heart Association. Presented Sunday, Nov. 17, 2019, during the organization's Scientific Sessions.

Greetings and good afternoon. I hope you're all enjoying the American Heart Association's annual Scientific Sessions.

These days are filled with discussions about ways to expand our individual areas of science by everything from novel molecular mechanisms to new clinical trials, and how new ideas might contribute to the evidence we generate. I always go home energized and I bet you do too.

I'm very pleased that for the first time we're having Scientific Sessions in Philadelphia, one of America's most historic cities, with a longstanding commitment to invention and research as well as to clinical medicine. I want to thank the Committee on Scientific Sessions Programming – led by Drs. Donald Lloyd-Jones and Manesh Patel – for creating a program that matches our host city's commitment to scientific diversity and innovation, and that includes the great diversity of the people and perspectives gathered here – including those of you who've traveled from around the globe to be with us.

I particularly hope my message today resonates with all of you who are early in your career. In my day job as a Chair of Medicine at Stanford University, I appreciate your importance, and I especially want to reach out to you here. You are the future of our profession, of the AHA, of your home institutions, and of your communities around the world.

I'd also like to call out those who've been recognized by your AHA Councils for your contributions to science, and who are now designated Fellows of the American Heart Association.

OK, FAHAs, let me see you wave your pennants! Also, you'll see all of your names listed in the FAHA Lounge and the video playing throughout the convention center.

We are delighted to welcome you as partners in the AHA's mission, an idea that transcends borders as we seek to be a relentless force for a world of longer, healthier lives.

As you may know, I was an early adopter of communication tools like Twitter and podcasts because I believe these formats help amplify our work. I know many of you agree because I've seen provocative and fun social media posts the last few days – this morning, even. I hope you continue to use our meeting hashtag #AHA19.

We want this session to be interactive, too. We'll be posting some questions and asking you to respond. On the side screen, you'll see how to do that. If you haven't already, sign in now so you'll be prepared for the first question.

In multiple ways at this meeting, we'll be seeing evidence from all aspects of cardiovascular science and medicine and learning new ways to find and work with that evidence. Why is this so valuable? Because evidence matters.

Evidence matters in basic discovery science and in the translation of science from the bench to the bedside and then to the community. Evidence affects the quality of the care we provide, and it supports our advocacy for improvements in health policy. It's highly motivating to get up every morning knowing that we are part of one of the most important pursuits that humans can undertake: the search for truth.

We're living in a time when scientific misinformation abounds and is heavily promoted, often by those with self-interests. Facts seem to matter less, and truth may even be suppressed. But the truth always, eventually, wins. And, as both individual clinicians and scientists, and as an

organization committed to public health, people trust us. Along with that trust comes an obligation to accurately communicate the evidence and its implications. This goes beyond publishing our science. We need to combat the misinformation that can be so damaging to the health of our patients and the public.

On the other hand, of course, it's exciting to pursue ideas that might make a real difference in the lives of others. I see that excitement in students and early career scientists. But some of you may still be sorting out career choices and considering whether there's too much risk in a life spent pursuing new ideas. This leads us to our first set of questions. Get out your phones because I want to know what you think.

First, what area of research are you involved in? If you're involved in more than one, mark them all.

Next, those involved in research may be worried about where you'll find support for your ideas. Here are some of the options. Tell us what organizations are supporting your research.

Funding is a perpetual challenge in the pursuit of evidence, but I want to be sure you recognize the AHA's pivotal role. The AHA is the largest nonprofit funder of cardiovascular and stroke research outside the Federal government with about $500 million dollars in research grant obligations at any one time. Last year, we invested over $180 million dollars to fund more than 830 new research projects, with over 75% of those awards going to early career investigators All told, we have invested $4.5 billion dollars in research funding. We've supported the early careers of 14 Nobel Prize winners, and we can support your research, too. In addition to these investments,

we're committed to strong advocacy to protect and expand essential funding options, particularly the NIH and other federal research agencies.

Let me tell you a little about what led me to the pursuit of evidence. I've always been driven to figure out clinical problems, things we don't fully understand. Luckily for me, that's a key part of the evidence-generation cycle. We'll come back to more of the cycle later.

When I began my cardiology fellowship at Duke University in 1990, a major problem in interventional cardiology was coronary thrombosis during balloon angioplasty – remember, this was the pre-stent era and all we had was unfractionated heparin and aspirin. These clots could close vessels, so our patients needed urgent bypass surgery. Some had myocardial infarctions and some died. We needed solutions. And fortunately for me, I had the chance to pursue clinical questions in a supportive environment with mentors like Rob Califf, Richard Stack and Kerry Lee.

So, what did we need to solve this clinical problem? The basic science in thrombosis and vascular biology wasn't enough. We had to stratify the risk of our patients and test whether novel antithrombotic therapies could modify that risk. The evidence needed for the clinical development of these drugs required a series of large-scale, often global, randomized clinical trials, many designed and coordinated by our research group, and implemented with hundreds of collaborators worldwide. These clinical investigators recruited tens of thousands of patients. Teams of study coordinators and research assistants collected the data we needed.

As an interventional fellow and junior faculty member, I was increasingly included in protocol design discussions, in steering committees, and in learning how to coordinate these global trials. I learned how to assemble, analyze and present the data at meetings and ultimately to

regulatory authorities. I loved the cath lab, but it was thrilling to learn about the clinical investigation of new drugs, and to see those drugs make enough of a difference for patients that they're still in clinical use today. An essential lesson I learned was that simplicity in integrating research into practice settings was key to making these trials happen.

I also learned that clinical trials involving medical products often require the collaboration and support of industry. Because of this, independence in the design and conduct of a trial, and in the analysis and dissemination of its results, is essential for maintaining the public's trust in the evidence. At the Duke Clinical Research Institute, we developed a system for remaining independent from industry sponsors while still being collaborative. That independence was critical in convincing policymakers that our evidence was trustworthy. Because of the important intersection between evidence generation and regulatory policy development, we worked with these federal regulators on issues related to drug development, review and approval. This even led to my serving as a member -- and a two-term chair -- of the FDA's Cardiovascular and Renal Drugs Advisory Committee. If you're invited to participate in this process at any level, I encourage you to do it. My federal colleagues tell me the process needs us.

Throughout the 1990s and 2000s, the need for independent academic oversight of randomized clinical trials led us and others around the world to build academic, clinical, data and statistical coordinating centers that could serve as hubs for collaborative research. And the AHA pushed hard for having all clinical trials listed on a central source – clinicaltrials.gov -- which has become an important international resource, assuring that negative trials don't just disappear.

These initiatives demonstrated that evidence matters, and trustworthy evidence matters even more.

Before we discuss putting this evidence into practice, I want to hear from you again.

Have you ever changed your practice on the basis of a single clinical trial?

Now tell us about those game changers. Send the name of a clinical trial that proved conventional wisdom wrong.

We're constantly working to use data like this to keep our clinical practice guidelines timely, accessible and trustworthy. But there's not as much of the highest-quality evidence, such as that derived from multiple randomized clinical trials, as we need. When we assessed our Clinical Practice Guidelines in 2009, this highest level of evidence was only available to support 11% of recommendations, and it is not improved today, according to a more recent study. This knowledge gap certainly provides an opportunity to do better. To create that <u>better</u> evidence. But, again, how can we support that research?

For many clinical questions, companies have no financial incentives to fund trials. In the U.S., our major federal funder for cardiovascular disease research is the NHLBI. The government has seen an excellent return on the NHLBI's investment in public health through support of clinical trials. Some recent noteworthy successes include SPRINT and – as you heard yesterday at our opening Late-Breaking Clinical Trial session – the ISCHEMIA trial. Unfortunately, despite these successes, the fiscal reality is that NHLBI funds for such practice-changing clinical trials are still very limited. Fortunately, a few other sources, such as PCORI, has become available in recent years. But

more resources are needed. What if we created a nationwide learning healthcare system? And could we do this worldwide? Because evidence matters, we need to find a way!

So far, we've been looking at evidence in my favorite briar patches of clinical trials and outcomes research. But some of you are pursuing careers in epidemiology, health services or health policy research, trying to benefit populations. The AHA thinks about that kind of research too, especially when we set organizational goals. You may know that in 2000, we set a goal of reducing deaths from coronary heart disease and stroke in the U.S. by 25% by 2010. Our metrics were age-adjusted death rates provided by our partners at the CDC. We worked especially hard to foster evidence-based therapies via guidelines, performance measures and quality improvement initiatives. One of the most impactful QI initiatives has been Get With the Guidelines, which continues to help healthcare providers improve the acute care and prevention they deliver, now in nearly 2,500 hospitals in the U.S. and proudly in partnership with hundreds more worldwide. Altogether, we did very well, accelerating the decline in deaths that had begun decades before. While we also had some success in reducing disparities in care, substantial health inequities still persisted at the end of that decade, and we took that into account as we moved toward the next ten years.

In 2010, we announced our next goal: "by 2020, to improve the cardiovascular health of ALL Americans by 20 percent, while reducing deaths from cardiovascular diseases and stroke by 20 percent." With the phrase, "ALL Americans," we committed to examining everything through a health equity lens, and we expanded our reach to address ALL cardiovascular diseases as well as stroke. We started off well, but the decline in deaths began plateauing around 2014 and there's

been an increase in age-adjusted stroke deaths over the last four years. The unfortunate reality is that our progress has stalled.

We'd like to hear from you on this. On a scale of 1-to-10 – with 10 being the highest – how much does the flattening of the death rate worry you?

Statistics show pockets of success, such as with our old foe coronary heart disease. Deaths from coronary heart disease have declined more than 20% over this period, and the decline is seen across racial and ethnic subgroups. While we haven't come close to full equity, there is progress. Heart failure, on the other hand, seems to be responsible for at least part of the plateauing. And we don't have a solution for the problem with stroke, although recent advances in acute treatment hold promise.

Population data, another important form of evidence, tells us that improvements in cardiovascular health are strongly related to education, income and ZIP code – even more than genetic code. This recent study reported that low-income counties in the U.S. had less improvement in cardiovascular health than high-income counties. In an upcoming AHA Presidential Advisory points out a major health divide between urban America and the 60 million people living in rural communities. So when we look at the entire landscape, we see opportunities to make a difference. This has nothing to do with ideology. This is about truth. Because evidence matters.

Evidence also matters in issues such as diversity in the workforce. Investigators who choose the science they do are often more sensitive to the needs of others like themselves, and those of us who train and hire them need to find and nurture individuals reflecting our diverse population.

Over the last 30 years, I've mentored and trained hundreds of individuals. As a department and health system leader the last 7 years, I've become quite concerned with the lack of diversity in cardiovascular medicine.

A particular type of student I've recently begun mentoring is one I especially relate to – the first-generation college student. Not only was I the first person in my family to attend college, I think I was the first in my neighborhood. I can relate to the struggles these students face - everything from imposter syndrome to not understanding career opportunities that might be readily available. First-generation medical students face many of the same issues. I've become personally committed to helping, and I hope those of you who've walked this sometimes-lonely path will share your time and expertise with these students and trainees. Sharing your story is a way of making another kind of evidence matter.

Another part of my personal narrative shapes my professional outlook. It stems from the fact that I was raised by a hard-working single mother. My only sibling is a sister. I have four daughters, two granddaughters, and a wife who has a master's degree and directs the Physician Assistant graduate program at Stanford.

Unfortunately, I lost my mother far too young. She was 42 when she succumbed to sudden cardiac death. However, I'm fortunate and proud to be joined here today by many of the intelligent and talented women who mean so much to me.

The point is, the insight and support of a variety of women have helped shape me throughout my life and career. Yet within the world of cardiology, the male-female ratio is out of whack. Fewer than 20% of U.S. cardiologists are women. Stunningly, twelve states have fewer than 10 women cardiologists! Numbers are similarly imbalanced in many other countries as well.

At AHA, our new Go Red for Women Science and Medicine Committee has set goals for the inclusion of women in all science activities, including the development of enhanced grant submission and peer review processes to identify and eliminate potential biases against women. While our science committees currently are 42% female, we're committed to getting to 50% by 2021. And, of more immediate interest, there are no all-male panels -- NO MANELS! -- at these Scientific Sessions!

For us to realize gender equity in cardiovascular medicine, men in power must recognize this disparity and do something about it! Let's not leave talent behind. Evidence -- and the people producing it -- matter!

Dr. Eugene Stead, a giant of American medicine and former chair of medicine at Duke, once noted that "chronic, multifactorial disease problems can be studied, but not by the methods of the present or past. If one wishes to create useful information … computer technology must be exploited." He said that back in 1973! Today we have the computing power and methods to fulfill his vision.

Cardiovascular medicine now exists in the world of "big data," where it is estimated that medical data DOUBLES every 73 days! This requires us to think differently about the design of clinical trials, and to develop new tools. The ADAPTABLE trial is a great example of doing a trial differently. We've used innovative technologies to screen the electronic health records of hundreds of thousands of patients to answer a critically important clinical question – what is the optimal dose of aspirin for patients with coronary artery disease. 15,000 patients, linked to the protocol by 40 U.S. health systems, have volunteered to help. This approach to link patients with this trial is

much more efficient than using hundreds of individual sites. Remarkable! And it's another step forward in study design similar to the advances by the Swedish investigators who created the Randomized Registry Trial. We look forward to the next innovation, perhaps by someone in this audience.

I believe we've only scratched the surface of optimizing the generation of evidence. We have available to us huge amounts of data -- from basic science information to EHRs to public and population health data sets, including information on the environment, housing, income, racial-and-ethnic diversity, and more. Cloud computing enables the AHA's Institute for Precision Cardiovascular Medicine to make sense of data like this, using advanced methods like AI and machine learning. The Institute also provides funding for the data scientists who make this happen. But these approaches need to be held to the same level of scientific scrutiny as drugs and devices. Evidence matters, and it can lead to a better future. Here are a few other examples:

Project Baseline involves deep subject phenotyping and long-term follow-up to understand what defines human health and to discover what signals transitions from health to disease. It's a contemporary version of the Framingham Heart Study, but with up to 8 terabytes of data being collected on each of 10,000 participants, we can search for early predictors, amenable to correction, in time to make a difference.

The ability to engage is also useful for studying a large population. In the Apple Heart Study, my colleagues at Stanford used the Apple Watch to enroll more than 400,000 subjects in only 8 months to demonstrate that atrial fibrillation can be detected in a large, asymptomatic population, using a sensor in a device already being worn. The next step is determining whether these new approaches can actually bring value to patients and the healthcare system.

AHA is fully invested in using big data resources, technology tools and novel computational methods to better understand issues related to heart disease in women. The AHA has partnered with Verily and Project Baseline to create "Research Goes Red," a technology platform to enroll and engage a million women to contribute their health data for investigation into heart and brain health. With the input of these women we'll design a competitive research portfolio that addresses their needs and concerns.

Different as they are, these examples share a common theme – vast amounts of data alone don't provide answers, but the evidence gleaned from analyzing data matters.

As we come to the end, let's go back to where we began, with one more message for early career investigators and clinicians.

This is the most exciting time ever to be engaged in science and its application to clinical medicine and public policy. Sure, we have challenges. But every generation has challenges. What makes our opportunity so wicked spectacular is that we have unprecedented ways to gather data and to generate insights at a scale and speed our predecessors dreamed about. I believe in our future because I believe in everyone, everywhere who is creating it. Together, we will provide the curiosity to raise the right questions, the passion to find the answers, the willingness to publish and speak the truth to decision-makers, and we'll do it through an equity lens.

So let's build one last word cloud along these lines. Amongst all the possibilities, what excites you most about the future of cardiovascular medicine?

Lastly, the message I want you to take home from this speech is that "evidence matters."

In all aspects of treating and preventing cardiovascular disease and stroke, in all nations around the globe, we must prioritize gathering the highest-quality evidence, and we must rely on

that evidence for the decisions we make. A world of longer, healthier lives will be the ultimate evidence of our success.

Thank you.