Special Report

Saving and Improving Lives in the Information Age
Presidential Address at the American Heart Association
2014 Scientific Sessions

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Good afternoon, and welcome to the Scientific Sessions. On behalf of all of the American Heart Association’s (AHA) clinicians, scientists, lay volunteers, and staff, I extend a warm welcome and offer my thanks for your efforts to understand, prevent, and treat cardiovascular diseases. We are inspired by your dedication to saving and improving lives.

The burden of these diseases is something we all share, no matter where we live or work. So let us make the most of our opportunities to learn from one another throughout the Scientific Sessions. For these next 4 days, Chicago is home to the latest in cardiovascular and stroke research. Chicago is also home to significant cardiovascular history. Ninety years ago, Chicago resident Dr James B. Herrick joined Dr Paul Dudley White and 4 other pioneering physicians at Chicago’s Drake Hotel to create the AHA. They started this lifesaving organization just 4 miles away from where we are sitting right now. Yet, it was worlds away when we consider what we can offer patients today.

We now have tools at our disposal that we could barely imagine only a few years ago. New diagnostic and therapeutic options are being discovered at a pace unseen in human history. We have an unprecedented opportunity to harness these advances to save and improve lives, and that is what I would like to talk to you about.

But first, I would like to share a quick illustration of just how much our tools have changed. This 28-pound box is the actual ECG machine Paul Dudley White used in his office decades ago. It was considered state of the art back then. With the help of technology, I could record my patient’s electrocardiogram at a US hospital in just a few seconds. This proves the concept that remote acquisition of ECGs is possible.

How do we best take advantage of the rapidly changing technologies and the seemingly endless array of big data engulfing us and translate this information into practical applications for the everyday care of our patients around the world? This is a critical question. Heart disease and stroke remain the leading causes of death in the world, taking >17 million lives annually. That figure is expected to surpass 23 million by 2030.

Leading cardiology organizations around the world have set bold goals to deal with the burden of cardiovascular diseases. We all know that we can save and improve lives with evidence-based treatments and a focus on prevention. We also know, however, that even our very best efforts at implementing them more widely will not be sufficient. Yet, the solution is within our grasp, which is why we are all here. We have come to Chicago to discuss how scientific research can most rapidly uncover and implement innovative new therapies.

I believe that to accelerate the pace of discovery, we need more than just “science as usual”; we need disruptive innovation. Disruptive innovation is a concept introduced by Harvard Business School professor Clayton Christiansen. It occurs when a new development has an unexpected and profound impact on how we live and work. For example, landlines gave way to cell phones, which gave birth to the smartphone, which is an all-in-one tool—like a modern-day Swiss Army knife—for patients and members of the healthcare community alike.

Here is an example from my own practice. A 67-year-old patient was referred to me for evaluation of recurrent palpitations that were not diagnosed despite multiple prior 12-lead ECGs using the modern version of a machine like Paul Dudley White’s, ambulatory monitoring sessions, and exercise tests. I prescribed a heart rhythm monitoring device like the one on the smartphone I demonstrated a moment ago. He recorded several tracings at home and at work and then e-mailed them to me. They showed recurrent episodes of atrial fibrillation. And so, very quickly and with the help of technology, I could formulate a therapeutic plan.

My patient is 1 of ≈33.5 million people around the world affected by atrial fibrillation, which increases their risk of stroke 5-fold and drastically increases healthcare costs.
The number of patients with atrial fibrillation is expected to grow dramatically because it occurs with greater prevalence in elderly people, a rapidly growing segment of our population. For more than half a century, we have treated atrial fibrillation with the standard oral anticoagulant warfarin. The story behind the development of warfarin is actually a wonderful illustration of disruptive innovation.

In February 1933, a farmer in Wisconsin noticed that his cows developed a severe and often fatal bleeding problem after eating sweet clover hay. Looking for answers, one snowy Saturday, he loaded his truck with hay from his barn, drove 240 miles to Madison, WI, and ended up meeting agricultural biochemist Paul Link. Researchers in Dr Link’s laboratory already knew about coumarin, a naturally occurring aromatic hydrocarbon found on the shaft of sweet clover hay. They discovered that when the hay became wet, a fermentation reaction fused 2 molecules of coumarin, and the resulting compound was the source of the bleeding. They named it dicumarol and advised the farmer not to feed his cows any more wet hay.

Because the researchers recognized the potential benefit of drugs to inhibit the coagulation system, they synthesized various derivatives, including one that proved to be an even more potent anticoagulant. They named this derivative after the laboratory’s sponsor, the Wisconsin Alumni Research Foundation, and the original substance, coumarin. And that is how we got the name warfarin. So, an effort to save dairy cows led to an innovative drug with dramatic implications for patients. The effectiveness of this therapy in preventing stroke in patients with atrial fibrillation was confirmed decades later.

However, as you know, there are difficulties in administering warfarin: food and drug interactions, the need for frequent monitoring, and dose adjustments to optimize anticoagulation. Investigators have long searched for potential replacements, leading to large phase 3 trials comparing warfarin with novel oral anticoagulants, including the direct thrombin antagonist dabigatran and the specific factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Each of these compounds blocks the catalytic center of specific proteins in the coagulation system and went through a lengthy development process.

This starts with the initial drug discovery phase, followed by the preclinical phase and then a series of clinical trials. A typical development program takes 15 years, with 10,000 compounds originally screened for 1 compound that makes it to regulatory approval. And all this costs about US $1 billion. Clearly, this is a system in need of disruptive innovation.

I am very familiar with this process because I have been a Thrombolysis in Myocardial Infarction (TIMI) Study Group investigator for 3 decades, evaluating multiple new therapeutic agents. I led the team that studied the effect of edoxaban on stroke and systemic embolic events in the ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation) study, which Dr Robert Giugliano presented during the Scientific Sessions in 2013. We published our findings simultaneously in the New England Journal of Medicine. We studied 21,000 patients and then pooled our data with the results of the prior trials of novel oral anticoagulants. In that analysis of 72,000 patients, we found that the new drugs are similar to warfarin in preventing ischemic stroke. Of great importance to patients, their use is also associated with a 50% reduction in hemorrhagic stroke. These new drugs have important implications in clinical practice. On the plus side, there is no need for therapeutic drug monitoring or frequent dose adjustment. On the other hand, these medications are quite costly. And approved antidotes are not yet available, although they are being developed and data on some are being presented at this meeting.

Now, let us think about the 2 pathways by which oral anticoagulants for atrial fibrillation were introduced into clinical medicine (Figure 1). Warfarin came to us by serendipity. The novel oral anticoagulants were developed through a targeted and expensive approach. Obviously, we cannot rely on either method to find effective new therapies. We need innovative and new approaches that do not require chance delivery of tainted hay or billion-dollar projects that span 2 decades. How might we improve the discovery and preclinical phase of drug development, as well as the clinical trials by which we assess new treatments?

It would be useful to focus drug discovery on a systems medicine approach. Here, one synthesizes a network of information from genetic, molecular, and cellular studies and constructs a model that predicts an individual patient’s response to treatment, streamlining future testing. We may then extend the observations to subgroups who have a similar profile and ultimately pool that information to develop a picture of how a population of patients might need a range of customized treatments.

An important discovery by Professor S. Yamanaka, from Japan, represents another innovation that takes us closer to individualized therapy. He found that human skin fibroblasts can be reprogrammed to induced pluripotent stem cells, known as iPS cells, which can then differentiate into specific cell types, including cardiomyocytes. Today, a skin cell can be harvested from a patient with a given disease phenotype. The resultant iPS cells can then differentiate into disease-specific cardiomyocytes. Drug screens can be performed on those cells

![Oral Anticoagulation for AFIB](image)

Figure 1. Comparison of the discovery and development of warfarin and novel oral anticoagulants (NOACs). Warfarin was discovered through a process of serendipity and was developed through a series of relatively inexpensive trials in which it was compared with placebo. NOACs were the result of a targeted discovery process and were developed through a series of expensive trials in which they were compared with warfarin. See text for further discussion. AFIB indicates atrial fibrillation.
to identify the most effective regimen for patients with specific disease characteristics.\textsuperscript{28,29}

Another intriguing innovation is a novel bioengineering platform referred to as “organs on a chip.”\textsuperscript{30,31} In a “heart on a chip” model, neonatal rat cardiomyocytes are layered on a deformable thin elastic film, or chip. When the myocytes contract, they cause the film to bend. The chip is placed in a microfluid test chamber where drugs can be infused and electric currents can be delivered to stimulate the cells. In a proof-of-concept experiment, a dose-response curve for isoproterenol affecting twitch stress is shown. You will hear more about this concept from Dr Donald Ingber, this year’s Conner Lecturer, whose presentation will also explore the use of iPS–derived human cardiomyocytes with a specific disease phenotype.

Now, let us consider some new technologies that can enable clinical research. We can do that simply by looking around this room. How many of us are wearing devices that track heart rate, calories burned, or other physiological parameters?\textsuperscript{32} These sensors communicate with our smartphones, which 75% of us have within 5 ft of us all the time.\textsuperscript{33} Is it possible to use these technologies to conduct clinical research across the biologic continuum, from ideal health to disease (Figure 2)? This powerful and novel research platform could allow us to evaluate therapies in ways that were not available a few short years ago.\textsuperscript{34,35} In fact, an important study is already doing just that: the Health eHeart study based out of the University of California at San Francisco.\textsuperscript{36} The plan is to enroll 1 million people worldwide to create a distributed cohort that leverages the Internet and mobile technology. Of course, data security measures are in place to protect individual privacy. Participants can link their wireless sensors to the research database and allow real-time acquisition of physiological measurements. The software interface is being written to link electronic medical records and to correlate a subject’s data with outcome events. The AHA has a scientific collaboration with the Health eHeart study. We are referring participants from our programs (eg, Go Red For Women), and in the future, we will be receiving depersonalized data, tracking participants’ progress in Health eHeart in improving their cardiovascular health. We also plan to conduct randomized trials in this new research environment. I invite you to learn more about the power of embedding randomization in observational studies at Dr Lars Wallentin’s Paul Dudley White International Lecture.

My final example is a dramatic example. The Cardiovascular Genome-Phenome Study, also known as CVGPS, was announced last year at the Scientific Sessions and is changing the landscape of clinical research.\textsuperscript{37} This study began as a collaboration between the AHA and the academic homes of the Framingham Heart Study and the Jackson Heart Study. It was inspired by our longstanding relationship with the National Heart, Lung, and Blood Institute. CVGPS will provide comprehensive genomic and phenomic information, combining data from these landmark studies and several other prominent cohort studies. Many areas of investigation will now be possible. An example is the study of phenotypic extremes. This will enable us to understand the biology of individuals affected at a very young age, those affected severely, and those who are protected from disease. Investigators will examine genetic and epigenetic determinants of differences in disease incidence, prevalence, risk, and prognosis and the response to treatments across ethnicities. Investigators in CVGPS will also provide access to a comprehensive, state-of-the-art biorepository and introduce new e-health approaches to digital data collection (Figure 3).

Now, it is my pleasure to introduce you to the very first 8 grant awardees in the CVGPS study.\textsuperscript{38} They are building the future on the power of the past and are following in the footsteps of the AHA’s founders in a bold and novel way.

Just imagine what the future would look like if we take advantage of the technologies we have discussed today and those being developed as we speak. We could envision the emerging data from clinical medicine and biomedical research being fed into a knowledge network that could offer new insights into disease.\textsuperscript{39} These insights should lead to novel clinical approaches and serve as a resource for basic research.\textsuperscript{40} The disruptive innovation exemplified by this continuously updated learning system approach takes us ever closer to the goal of precision medicine for our patients.\textsuperscript{41} Big data, like
that which will be produced in CVGPS, are so omnipresent that they can be overwhelming. However, we need to focus on what these data represent and why we are collecting them. Big data and the technologies that help us generate them are our modern-day tools for finding innovative new ways to save and improve our patients’ lives. We must also use our tools and data to inform our future advocacy and prevention strategies to create a culture of health where ideal cardiovascular health is the norm.\(^3\)\(^7\) This is a state that should be enjoyed by everyone.

Why has the AHA invested in CVGPS, and why are our researchers tackling the challenges of big data? Why are we involved in the Health eHeart study and looking deeper into ways to harness technology and data, in addition to the many other things the organization does to save and improve lives? It is simple. We do these things so people can live longer, healthier lives. So they can enjoy more of life’s precious moments, moments that truly matter.

In the languages of the attendees at this meeting is the answer. Life. …Life is why.\(^4\)\(^5\) Thank you, ladies and gentlemen.

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