Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

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As emphasized by the Bipartisan Policy Center, health care expenditures are anticipated to reach 20% of US gross domestic product by 2020 and are a major threat to the sustainability of the health care system and to the economic productivity and stability of the country. Although death rates attributable to cardiovascular disease (CVD) have declined by almost one-third over the last 1½ decades, CVD remains the leading cause of death and the burden of CVD remains unacceptably high, especially considering the aging of the population.[1] The economic effects of the burden of CVD are profound because managing CVD constitutes 16% of overall national health care expenditures.[1] Given these sobering statistics, it is "mission critical" to examine how progress has been made in addressing CVD and to determine what steps need to be taken to further improve individual and societal cardiovascular health and economic well-being.

This is a highly relevant week for such reflection, given the current theme issue of *JAMA* on CVD and the occurrence of the 2012 Annual Scientific Sessions of the American Heart Association (AHA), where attendees from around the globe will gather in Los Angeles to discuss the latest findings in cardiovascular science. This meeting will include more than 4400 original abstracts, 376 invited scientific sessions, and the first public presentation of 27 late-breaking clinical trials.[2]

The National Center for Advancing Translational Sciences (NCATS) is dedicated to catalyzing innovative methods and technologies to enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.[3] Randomized controlled trials (RCTs) are a cornerstone of modern clinical science and a critical tool for the clinical/translational investigator to evaluate the benefits and risks of promising scientific advances.

Adaptive Design of RCTs

Despite remarkable expenditures in research and development during the last several decades, there is a disturbingly low return on this investment, with only 25 to 30 new molecular entities approved for commercial use annually by the US Food and Drug Administration (FDA); only a small fraction are indicated specifically to manage problems in patients with CVD.[4] Adaptations to RCTs are prespecified prior to initiation of the RCT and can occur at 1 or more of the following levels: (1) enrollment characteristics; (2) treatments being studied; or (3) the primary end point.[4,5]

Perhaps the most exciting opportunity for CVD researchers is to capitalize on the advances in systems and computational biology that can inform first-in-human, proof-of-concept, and phase 2 dose-ranging trials in ways that were not previously possible.[4] Examples include using biomarkers, genetic observations, and definitions of pathophenotypes to adapt the treatments being investigated. This is particularly relevant to new treatments being explored for managing dyslipidemia (eg, PCSK9 inhibition), diabetes, ischemic heart disease, and heart failure—all topics that are among the 19 studies presented in the Clinical Science: Special Reports sessions at the AHA meeting.[2] As emphasized by the FDA in a draft guidance document, adaptive designs are encouraged during the learning or exploratory phase of development of new treatments.[6] However, adaptations to RCTs can introduce threats to the overall study type I (α) error and raise concerns about possible investigator bias and uncertainty about the population for which an intervention is most applicable. Despite a lack of widespread acceptance of this approach in confirmatory or registration pathway trials,[4,6] at least 1 drug for CVD treatment was studied using an adaptive design in pivotal trials.[7]

Innovations in RCTs

Quality of RCTs. In addition to design issues, the quality of RCTs must be addressed. Inadequate attention to the conduct of an RCT can jeopardize the ability to interpret it, as well as its suitability for informing clinical practice. A hallmark of most interventions in CVD is that the treatment effect in both absolute and relative terms is typically modest and incremental beyond comparator therapies. Coupled with a declining rate of CVD events,[1] trials designed to establish therapeutic efficacy in CVD require large sample sizes, threatening the collective ability to conduct the RCTs to establish the value of new therapeutic interventions.

The intention of pioneering investigators in the GISSI and ISIS study groups was to carry out large, simple trials designed to answer a straightforward question about the value of a therapeutic strategy on important health outcomes, particularly mortality. Large, simple trials were useful for evaluating fibrinolytics, β-blockers, antithrombotics, statins, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. As large trials became a popular (and accepted) way to evaluate new therapies, the original intent of simplicity was lost while large sample

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sizes were maintained, leading to increasingly complex trials requiring collaborations among thousands of investigators, frequently across dozens of countries. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuing costs.

Issues related to international differences in outcomes, the ethics of the globalization of research, and deviation from good clinical practice, as well as methodological issues such as how to handle missing data and complete ascertainment of vital status, have contributed to the call for innovations in the conduct of RCTs in CVD. Since assessing the effects of interventions on human health requires researchers to study large populations, it is imperative to acquire population-level data to understand which patient characteristics predict benefit or risk with various interventions. The tools of informatics, social networking, electronic medical records (EMRs), crowd sourcing, and other social media can all be applied to address the challenges posed by the need to conduct large RCTs.

Behavioral Change. Approximately half of the decline in US deaths from coronary heart disease from 1980 through 2000 is considered to be attributable to use of evidence-based medical therapies and approximately half to changes in health policies and reductions in major risk factors.[8] As emphasized by the AHA, population-based strategies at primordial and primary prevention of CVD are critical to reducing the societal burden of CVD. Now that a definition of ideal cardiovascular health has been provided, the stage is set for actively pursuing investigation of interventions that are most likely to promote behavioral change and achieve ideal cardiovascular health. The alignment of efforts of governmental agencies (Million Hearts initiative), strategic alliances of professional societies, and the opportunity for funding such patient-oriented research (Patient-Centered Outcomes Research Institute) are the perfect combination to address the research gaps in studies of behavioral change. This is mission critical to bending the curve of health care costs. Interventions to be tested might include media/educational campaigns, labeling/consumer information, taxation/subsidies/economic incentives, and school/workplace/community approaches. Quantitative, qualitative, and mixed-methods research on interventions are likely to be needed to orchestrate the desired changes in behavior while balancing the perspectives of societal goals and individual choice.

Nontraditional funding sources such as third-party payers also need to be pursued. For example, the MI FREEE trial[9] demonstrated how a health policy (waiving of medication co-payment) that affects and is intertwined with patient behavior (medication adherence) can be studied in an RCT and provided information showing how that policy can affect clinical outcomes.

Comparative Effectiveness Research (CER). Among its top 100 priority areas for studies, the Institute of Medicine (IOM) Committee on CER listed investigations on health care delivery systems as its highest priority, with CVD and peripheral vascular disease the fourth highest.[10] An ideal opportunity to satisfy both these priority areas would be to embed randomization in the EMR—the point-of-care contact between clinician and patient—and to use the EMR as the case report form for data collection. Consideration should also be given to introducing randomization into registries that are sponsored by professional societies. Such systematic, evidence-based process improvement approaches are critical components of the Learning Healthcare System described by the IOM.

Innovations in Regulatory Science

These innovations to RCTs need to occur in concert with ongoing efforts by the FDA to promote innovations in regulatory science. Academic and industry stakeholders need to collaborate with the FDA to establish common definitions of end points and case report form data elements and the appropriate use of biomarkers and genetic testing in RCTs. Researchers also need to learn how to deal with the regulatory challenges of establishing new approval methods when generic drugs used in managing CVD are found to be effective for "off-label" indications. Similarly, researchers and clinicians need to consider innovative approaches when observational data raise the hypothesis that approved drugs used broadly in the population may need to be reevaluated in new RCTs to define appropriate use.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Antman reported receiving travel support from the AHA; reported that he is a senior investigator in the TIMI study group, which receives grant support to the Department of Medicine at Brigham and Women's Hospital from the National Institutes of Health, Merck, Bristol-Myers Squibb, sanofi-aventis, Millennium, Nuvelo, AstraZeneca, CV Therapeutics, Inotek, Eli Lilly, Daiichi Sankyo, Schering-Plough, Integrated Therapeutics, Bayer, Ortho, Sanofi-Synthelabo Recherche, GlaxoSmithKline, Amgen, Beckman Coulter, Biosite, Roche, Pfizer, Accumetrics, and Novartis; and was past chair of the American College of Cardiology/AHA Task Force on Practice Guidelines. Dr Harrington reported serving on the advisory boards of Bristol-Myers Squibb/Pfizer, Gilead, Portola, Merck, Johnson & Johnson, Pfizer, Regado, Novartis, Baxter, Genentech, and CSL Behring; being a consultant for Merck, Novartis, sanofi-aventis, AstraZeneca, Lilly, Bristol-Myers Squibb, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo Lilly, APT Nidus Center, Janssen, Johnson & Johnson, Momenta, Cortex, and Orexigen; receiving grants to his institution from Novartis, Merck, Portola, sanofi-aventis, The Medicines Company, Bristol-Myers Squibb, AstraZeneca, CSL Behring, Baxter, and GlaxoSmithKline; and receiving payment for lectures from AstraZeneca and WebMD. The details of his relationships with industry prior to July 1, 2012, are available at http://dcri.org.
Additional Information: Dr Antman is the chair and Dr Harrington is the vice-chair of the AHA Committee on Scientific Sessions Program.

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