

Editorial

A Perspective on Cardiovascular Research: A Practitioner's Responsibility to the Disseminated Outcomes

Jin Kyung Kim*

Division of Cardiology, Department of Medicine, University of California – Irvine, Irvine, California, USA

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed nations [1,2]. Undoubtedly, the need for understanding pathophysiology of and advancing therapy for the myriad of disabling and/or fatal cardiovascular conditions is immense. This need is in part reflected by the sheer extent of ongoing basic science, translational and clinical research in the field, leading to the explosion of published discoveries that impact our knowledge and the way we care for patients with CVD. There is currently more than 270 scientific journals dedicated to topics of cardiology and cardiovascular medicine, and the number is increasing. This is not even including journals with broader aims that may often publish articles with findings related to cardiovascular topics. Within the last two decades, the number of randomized clinical trials in cardiology has increased by more than 40% [3]. To date, there are 17641 clinical trials registered to study topics related to the heart at *clinicaltrials.gov*. The 2013 fiscal year budget for the National Heart Lung Blood Institute (NHLBI) at the National Institutes of Health (NIH), a major component of which is spent on direct research support, reached approximately \$ 3 billion. These exemplify the tremendous effort by the biomedical community and the public driving the progress of cardiovascular research at an exponential speed to the cutting-edge, evidence-based medicine practiced today.

At the face of such an unparalleled pace of scientific growth in cardiology, it is perhaps pertinent to take a moment and learn to be cognizant of potential pitfalls of that very "evidence" we are trained to base our medical practice, pitfalls that may (and did in a few recent times) have significant consequences in the way cardiology is practiced. William Harvey, the 17th-century English physician who was the first to describe the role of the heart in the body's circulatory system, said, "All we know is still infinitely less than all that remains unknown" [4]. Despite the discoveries made since the times of Dr. Harvey, his statement remains true to this day, some 385 years later. It is humbling. And yet, in awe of the sheer amount of knowledge gained from the modern research, one is often too apt to forget specific limitations of that knowledge. These limitations are not necessarily minor at times. They derive from many convoluted facets that stretch on the pathway from

Corresponding author

Jin Kyung Kim, M.D., Ph.D. University of California, Irvine Medical Center, 101 The City Drive, City Tower, Suite 400, Orange, CA 92868, USA, Tel: 714-456-3380; Fax: 714-456-8895; E-mail: jkim13@uci.edu

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the laboratory bench to patients – no scientific studies, whether basic or clinical, are perfect, thereby rendering the conclusions drawn from the very imperfect studies potentially flawed or at least limited in their application. Insensitivity to such a reality can harbor potentially injurious consequences.

A notable recent example is found in the history of drug-eluting stent (DES) in coronary artery revascularization. As remarkable as the success of cardiac catheterization and percutaneous coronary interventions (PCI) has been - just 12 catheterization laboratories in 1950s, to the seminal first percutaneous transluminal coronary angioplasty by Andreas Gruntzig in 1977, to more than 600,000 PCI performed per year to date in US - long-term results of PCI with initial bare metal stents was still inferior when compared to those of the surgical approach. This was mainly thought to be due to the high rate of revascularization and repeat intervention of in-stent restenosis. Thus came the development of DES in an attempt to curtail the stent restenosis rate. When the result of the first major clinical trial of DES, the RAVEL study, was published in 2002, it reported "no angiographic evidence of restenosis and no need for repeated interventions" [5]. This conclusion, received with much fanfare by the cardiology community, opened the floodgate of indiscriminate use of the stent. The clearly stated limitations of the study was glossed over, only to discover in a short time later that the implantation of DES in "all-comers" result in outcomes quite different than those reported from carefully controlled, *limited* settings of the initial clinical trials. We now know that the restenosis rate of DES is not zero. The repeat revascularization rate, though lower than that of bare metal stents, depends on many factors, chiefly among them the complexity of the lesion, just as in the case with the use of bare metal stents. Incidence of life-threatening stent thrombosis is not negligible. Today, the long-term safety of DES is still not completely abated, and the placement of DES subjects the patient to at least 12 months of dual antiplatelet therapy in order to avoid stent thrombosis [6]. Thus, it is vital that evidence-based medicine be practiced in a truly *evidence-based* manner by recognizing all the limitations and differences of the trial-derived findings.

The practice of perspicacity is all the more important when conclusions from trials are directly incorporated into guidelines, with implications of a sanctioned shift in patient management, as was the case with the study of estrogen in the cardiovascular system. Historical observations have long held that younger women in general are at lower risk of CVD when compared to men of similar age. Since the monumental Framingham Heart Study report associating menopause with the risk of CVD, [7] numerous population-based studies and basic science data have converged to a concept of cardioprotection conferred by endogenous estrogen. Replacing it with hormone therapy in postmenopausal women, then, was thought to extend the protective effect and lower the risk of CVD. In order to confirm this long-held belief and the salutary benefits of estrogen reported from observational studies, the Women's Health Initiative (WHI) was launched by the National Institutes of Health. One of the main components of WHI was randomized, controlled, prospective trials to assess the role of estrogen plus progesterone or estrogen-alone replacement therapy in prevention of chronic diseases, including coronary heart disease. The initial findings of the trials were a mix of different negative and positive risk-benefit profiles on cancer, hip fracture, venous thromboembolism, stroke, and coronary heart disease in the estrogen/progesterone and estrogen-alone treatment groups [8,9]. The increased risks of breast cancer and thromboembolism in the initial report of the estrogen/progesterone treatment group were highlighted in the media, while significant other health benefits drew relatively little notice. Coronary heart disease risk was considered increased in the estrogen/progesterone group and neutral in the estrogen-alone group. The published findings drew confounded reactions from those well-aware of the positive biological evidence for estrogen's overall cardioprotective effects. Strong criticisms ensued from many clinicians and researchers alike, as subsequent examinations revealed the trial design and data to be suboptimal to definitively answer the efficacy of hormone replacement as a primary prevention therapy of coronary heart disease in younger perimenopausal patients. In fact, further analyses of the trial data support that estrogen-based hormone therapy does provide cardioprotective effects in younger women who would most benefit from the replacement therapy in extending the protection by endogenous estrogen. Despite the controversy associated with the heavily questioned initial findings, the results of WHI have been swiftly incorporated into the recommendations and guidelines of professional societies, which now warn against the use of the hormone therapy in postmenopausal women (with an exception of treating severe vasomotor symptoms of very low risk patients). This adaption of the WHI's "bottom-line" conclusions unfortunately undercuts the insight gained from years of careful investigative works that clearly differentiate the effects of hormone therapy on younger perimenopausal women from those on older women years post menopause with high risk factors.

There is no question that progress in cardiovascular research has been laudable. And ambitious endeavors of current and future investigators will continue to deepen our knowledge on the workings of the human heart and shape the success of novel therapies to come. It is then imperative that we handle the newfound gains responsibly and sensibly - by taking the data at face value, being familiar with limitations and pitfalls of relevant research outcomes, and avoiding oversimplification or overgeneralization when translating research findings to clinical applications.

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