Advances in the Treatment of ACS and Collaborative Research

Written by Mary Mosley

Ischemic heart disease is a global public health problem and the leading cause of death in all countries except for sub-Saharan Africa, stated Robert A. Harrington, MD, PhD, Stanford University, Palo Alto, California, USA, in his Louis F. Bishop Lecture. The substantial advances in the treatment of acute coronary syndromes (ACSs) achieved over the past 25 years have improved care and reduced morbidity and mortality. Global collaborative research programs, innovative research strategies, and training of young clinical investigators will form the backbone of a robust future of cardiovascular (CV) research.

ADVANCES IN TREATING NSTE ACS

The need to distinguish non–ST-segment elevation (NSTE) ACS from ST-segment elevation (STE) ACS was underscored by the GUSTO II trial, which investigated the role of antithrombin therapy in ACS. NSTE accounts for 85% of ACS-related deaths, and the risk of future events with NSTE surpasses that with STE at 30 days. Most ACS-related hospital admissions are for NSTE (1.24 million of 1.57 million). Patients with NSTEMI are older and more are women, and they are sicker with more diabetes and cardiac and noncardiac comorbidities.

Clinical practice guidelines (CPGs) have provided an organized way to approach the care of NSTEMI patients and a process for a methodologic review of the literature and an unbiased presentation to practitioners. Peterson and colleagues were the first to show that adherence to CPGs improved outcomes, with a 2% absolute decrease in mortality in the hospitals with the most vs least adherence. However, <25% of CPGs recommendations are level A [Tricoci P et al. *JAMA*. 2009], indicating the need for more evidence.

CPGs now recommend the use of risk scores to stratify patients with NSTE. Troponin I was identified as a more sensitive marker than creatine kinase MB to diagnose a myocardial infarction (MI), with a linear relationship between its level and degree of short-term risk. The TIMI risk score provided a simple tool for bedside use. The GRACE ACS risk model provided an easy computer program for use at point-of-care and assesses risk in-hospital and at 6 months for death and death plus MI.

Antithrombotics became the cornerstone of NSTE treatment through the seminal work of Theroux and colleagues who showed the benefit of aspirin and heparin. Through clinical trials with some 49 000 patients, glycoprotein IIb/IIIa inhibitors became an important antiplatelet treatment included in the CPGs; however, the modest reduction in MI in ACS patients must be balanced against the bleeding risk. Newby and colleagues showed that the benefit with glycoprotein IIb/IIIa inhibitors is exclusively in patients who are troponin positive, which is the first observation of personalized treatment in ACS, stated Dr Harrington.

The next important advance was adenosine diphosphate receptor inhibitors, such as clopidogrel, added to aspirin, which substantially reduced CV death and MI but increased the risk of major bleeding. Clopidogrel provided a 20% benefit over aspirin alone in patients with NSTE-ACS studied in the CURE trial. This led to the recommendation for adding clopidogrel to aspirin for ACS [Hamm CW et al. *Eur Heart J*. 2011]. This theme has continued with the development of newer, more potent, and less variable agents. Prasugrel in the TRITION-TIMI 38 trial and ticagrelor in the PLATO trial have both shown superior efficacy for reducing ischemic events relative to clopidogrel, with a price to be paid in terms of increased bleeding. The search continues for improving outcomes with an intravenous adenosine diphosphate inhibitor, cangrelor, which was shown to improve outcomes in the setting of percutaneous coronary intervention; the primary composite outcome of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours was significantly lower with cangrelor (3.8%) vs control (placebo or clopidogrel; 4.7%; $P = .0007$) [Steg PG et al. *Lancet*. 2013].

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In terms of strategy regarding patients presenting with angina symptoms, an early invasive approach was shown to be effective in high-risk patients with about a 28% relative reduction in the TIMACS trial [Mehta SR et al. *N Engl J Med*. 2009] and is now used in about 80% to 90% of these patients, stated Dr Harrington. There was no benefit and perhaps harm in low- and intermediate-risk patients. However, substantial risk continues to accrue after early revascularization, and the risk of late mortality is >50% at 7 years [Chan MY et al. *Circulation*. 2009].

Some progress has been made in reducing this long-term risk. The IMPROVE-IT trial [NCT00202878] is the most recent example, which showed that the aggressive reduction in low-density lipoprotein cholesterol (LDL-C) from 70 mg/dL to 50 mg/dL reduced the composite primary outcome of CV death, MI, unstable angina requiring hospitalization, coronary revascularization, or stroke. Notably, this risk reduction in IMPROVE-IT matched the predicted risk reduction based on the anticipated LDL-C lowering in the trial and the Cholesterol Treatment Trialists' meta-analysis [Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010]. However, it took 10 years and a complex, expensive clinical trial to achieve this answer, stated Dr Harrington. He suggested that the use of randomized registry trials, ie, the integration of a randomized study within a clinical registry first demonstrated by the TASTE trial [Fröbert O et al. *N Engl J Med*. 2013], will be a more efficient way to answer such clinical questions.

GLOBAL ACADEMIC COLLABORATION

The partnerships among academic research organizations to conduct large-scale clinical trials and a guiding set of principles for working within the industry are important legacies of the GUSTO trial. These principles include an independent executive committee, independent access to data, publication rights and oversight of analyses, a reasonable duration of confidentiality, and intellectual property protection. A new paradigm for collaboration has been suggested that recognizes the overlapping needs of relevant groups [Roe MT et al. *Am Heart J*. 2015. In press]. Academic research organizations and mentorship are needed to train the next generation of clinical investigators. Dr Harrington stressed the need for greater diversity within global collaboration.

Dr Harrington then changed gears to talk about the role of informatics to answer clinical questions by interrogating large networks of data and said that the innovative ecosystem in Silicon Valley is being explored for ideas. Stanford University, Duke University, and Google are collaborating on the Baseline study, an epidemiologic research project that is using mobile technology, imaging, and Google's informatics capabilities to understand the transition from a healthy to a diseased state.

The Cardiovascular Genome-Phenome Study led by the American Heart Association is using informatics to explore the combined data sets from the Framingham Heart Study and Jackson Heart Study along with imaging and specimens collected within these studies to understand the genetic and epigenetic determinants of disease, phenotypes, and response to treatment across ethnicities. A collaboration between the NIH and the Patient-Centered Clinical Research Network to determine the optimal aspirin dose is an example of a seamless, pragmatic trial with the potential to be a model for conducting large clinical trials in a simpler and less costly fashion by randomizing data from multiple patient networks.

Observational studies are now being conducted via smartphone applications, such as the *MyHeart Counts* research application through Apple's research kit, and the next step is determining how to layer a randomized trial on top of such approaches, stated Dr Harrington. Within 2 weeks of its debut, 24 000 patients had downloaded *MyHeart Counts* and provided informed consent.