HHS Public Access

Author manuscript

J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2015 December 22.

Published in final edited form as:

J Thorac Cardiovasc Surg. 2011 August ; 142(2): 265–266. doi:10.1016/j.jtcvs.2011.02.035.

Building an Infrastructure for Clinical Trials in Cardiac Surgery

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By any standard, cardiac surgery has been a spectacularly dynamic field of medicine. The introduction of major surgical innovations, and ongoing incremental change, in such areas as coronary artery bypass grafting (CABG), cardiac valve replacement and repair, myocardial protection, mechanical circulatory support, aortic reconstruction and the treatment of arrhythmias, have extended survival and improved quality of life for many patients suffering from cardiac disease. A rapid pace of innovation requires a rigorous infrastructure for clinical evaluation that provides timely assessments of the value of new treatments.

This need is underscored by the significant prevalence and cost associated with cardiovascular diseases. In fact, medical care for cardiovascular diseases accounted for 6 of the 20 most expensive conditions billed to Medicare in 2006, totaling $103 billion. Cardiac surgery is an important part of the therapeutic armamentarium and its application to targeted populations has evolved considerably over the past several years. Surgical investigators have championed less invasive methods of caring for increasingly older and sicker patients with a variety of diseases and high expectations for robust outcomes. Evaluating the benefits of surgery in the modern era requires careful consideration of risk and cost-benefit trade-offs.

Many surgical procedures have undergone extensive clinical trials. CABG surgery is arguably one of the most widely studied surgical procedures ever, with several large-scale randomized trials starting in the 1970s, and, continuing, most recently, with the STICH trial, which randomized approximately 2000 patients with ischemic cardiomyopathy. Yet, a National Heart, Lung, and Blood Institute (NHLBI) working group in 2004 concluded that there were substantial impediments to clinical trials of cardiac surgical procedures and that the field lacked the necessary organizational infrastructure to accomplish the task (1).

The NHLBI, in collaboration with the National Institute for Neurological Diseases and Stroke (NINDS) and the Canadian Institutes for Health Research (CIHR), created the Cardiothoracic Surgery Trials Network (CTSN) in the fall of 2007 to fill this lacuna. The

mission of the Network is to design, conduct, and analyze multiple, collaborative clinical trials that evaluate surgical interventions, and related management approaches, for the treatment of cardiovascular disease in adult patients. The Network has developed a portfolio of trials that evaluate clinically meaningful questions and address important public health issues.

Comparative Effectiveness Trials

In recent years, there has been increasing recognition that the evidence base underlying much of clinical practice is inadequate, a deficiency which is also true for cardiac surgery. A recent review of ACC/AHA guidelines, for instance, found that only 11% of recommendations were based on high-quality evidence (2). This limitation implies that a substantial number of commonly used procedures lack an appropriate evidence base for effective clinical decision-making. This realization has been a driving force for the selection of randomized trials by the Network.

One area of focus is *ischemic mitral regurgitation* (MR), which is estimated to affect 2.8 million Americans. In this issue of the Journal, investigators discuss the design of the *severe* ischemic MR trial, which evaluates the safety and efficacy of mitral valve repair versus mitral valve replacement in patients with severe MR identified echocardiographically by an integrative method (3), and the *moderate* ischemic MR trial, which evaluates the safety and efficacy of CABG plus mitral valve repair versus CABG alone (4). Another critical area is the treatment of *atrial fibrillation* (AF), including surgical ablation, which the Institute of Medicine (IOM) recently ranked within the first quartile of the 100 priorities for comparative effectiveness research (5). The Network's AF trial, also described in this issue, compares left atrial appendage (LAA) closure plus surgical ablation to LAA closure alone for (long-standing) persistent AF in patients undergoing mitral valve surgery. Nested within this trial is a comparison of 2 different lesion sets in the ablation group (pulmonary vein isolation alone versus a biatrial lesion set), which will provide preliminary data to guide development of a follow-up trial. In addition, Network investigators received challenge grant funding to develop a randomized trial comparing *hybrid revascularization* procedures to multi-vessel PCI with drug eluting stents in patients with multi-vessel coronary artery disease (CAD) involving the left anterior descending (LAD) artery. This funding supports an observational study to collect preliminary data on patient eligibility and outcomes following PCI and hybrid procedures utilizing left internal thoracic artery-LAD bypass, as well as to support development of a finalized protocol for a pivotal trial.

Quality Improvement Studies

Hospital-acquired *infections* represent the major non-cardiac complication after heart surgery, which are associated with substantial morbidity, higher mortality, prolonged hospitalizations and increased rate of re-admissions. While prior studies have examined the relationship between patient characteristics (e.g., co-morbid conditions) and hospital-acquired infections post-cardiac surgery, the literature has not sufficiently examined the relationship between treatment/management practices (e.g., line management, ventilator management, etc) and postoperative infection risk. Knowledge about this relationship is

critical to developing interventions to avert infections. The Network recently enrolled over 5200 patients in a prospective cohort study that assesses major infections (such as deep surgical site infection, endocarditis, mediastinitis, and pneumonia) and minor infections (such as superficial surgical site infections and symptomatic UTIs) after cardiac surgery. This study analyses management practices that may put patients at high risk for infections, and should provide insights to help guide the development of more effective strategies for reducing these debilitating and costly complications.

Trials in the Pipeline

In addition to comparative effectiveness trials and quality improvement studies, the Network is developing smaller trials of novel interventions, notably stem cell therapy. The management of advanced heart failure has increasingly become the domain of both cardiologists and surgeons, with transplantation and left ventricular assist device (LVAD) therapy. Both therapies provide significant survival benefits, but transplantation is limited by the supply of donor organs and LVAD therapy is still plagued by adverse events, although these are decreasing with newer generation devices and improvements in patient management. These risks could be minimized further if the duration of support could be limited by inducing myocardial recovery which could lead to explantation, in which case LVAD use would become a short-term therapeutic rescue. One promising avenue to improve performance is by the intramyocardial injection of *mesenchymal precursor cells (MPCs)*, which may engraft and provide a renewable source of functional cardiomyocytes and a network of new blood vessels, and promote the release of factors capable of paracrine signaling. The Network, in collaboration with the Cardiac Cell Therapy Research Network, is completing the protocol for a Phase II trial that will evaluate the safety, and explore the efficacy, of direct myocardial injection of two different doses of MPCs in LVAD recipients awaiting cardiac transplantation. Another promising cell type is *cardiac progenitor cells (CPCs)*. The Network is currently developing a proof-of-concept study to explore the safety, efficacy and feasibility of intra-coronary injections of autologous CPCs following cardiac transplantation. This trial will provide important exploratory information regarding the effects of CPCs on myocardial function following transplant (with the ultimate objective of modulating tolerance and reducing the incidence of allograft rejection), and the ability of CPCs to engraft and differentiate within the scaffold of the transplanted heart. Finally, Network investigators are exploring the development of a randomized trial to evaluate the effectiveness and safety of *endovascular stent graft* treatment of patients with acute, uncomplicated *Type B, aortic dissection* at high risk for complications.

Some Concluding Observations

These trials and observational studies constitute the first phase of the Network's activities. Much has been learned by the surgical investigators, data coordinating center, and Institute leadership. Notable insights include the importance of establishing a dedicated culture of research at each investigative site, cultivating a collaborative relationship with the cardiology community, and recognizing the need to define equipoise in randomized trials, especially when choosing between (or among) available surgical and medical options. The value of these attributes cannot be overestimated. It is anticipated that the research of the

Network will offer important insights and lay the foundation for larger randomized trials to further strengthen the evidence base that should guide clinical decision-making.

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