Cardiothoracic Surgical Trials Network: Evidence-based surgery

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The Cardiothoracic Surgical Trials Network (CTSN) was created after discussion between the American Association for Thoracic Surgery Scientific Affairs and Government Relations Committee and the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The Scientific Affairs and Government Relations Committee had originally met to review funding for cardiothoracic surgeons by the NIH, including the NHLBI, because funding levels for thoracic surgeons were clearly in a downward spiral. Ratcliffe and colleagues¹ published data demonstrating that NIH funding for surgery as a whole, but especially for thoracic surgery, was quite poor. This seemed ironic given the high levels of innovation in cardiothoracic surgery, and it was a departure from history because many of the early developments in thoracic surgery were due to successful partnerships with the NHLBI.

The leadership at the NHLBI recognized the importance of these issues and convened a conference to discuss the need for funding of the future of cardiac surgery. There was clear recognition that despite success in other specialties, a specific network for clinical trials in cardiac surgery had not been established. Many of the developments in cardiac surgery were based on retrospective data. With notable exceptions, such as the Coronary Artery Surgery Study trial for coronary artery bypass grafting,² clinical trials in cardiac surgery have been infrequently performed.

The outcome of the conference was a request for proposals for the CTSN. This effort was led by Marissa Miller of the extramural NHLBI. Tim Gardner, a past president of The American Association for Thoracic Surgery, and Patrick O'Gara, president of The American College of Cardiology, were codirectors of these efforts. Multiple applications to participate were reviewed, and 8 primary centers were selected from the United States and Canada to capture the expertise and recruiting potential to successfully carry out the intended clinical trials. A Data and Clinical Coordinating Center was also selected with expertise in surgical trial design and analysis.

Cardiothoracic Surgical Trials Network.

Central Message

This editorial provides a brief synopsis of the history and development of the CTSN and a review of recent CTSN investigative activity.

Perspective

This editorial presents a review of the development of the Cardiothoracic Surgical Trials Network (CTSN), as well as a synopsis of 3 major CTSN trials, including the severe ischemic mitral regurgitation trial, the moderate ischemic mitral regurgitation trial, and the atrial fibrillation trial. The results of these trials provide critical randomized clinical data to cardiac surgeons.

Once the primary sites and the Data and Clinical Coordinating Center had been selected, an organizational meeting was held in Washington, DC. Part of the original application process was related to each center describing 2 potential clinical trials. From this pool of potential studies, there was an enthusiastic discussion about which trials should be conducted, and 3 major trials were initially chosen. These included the severe ischemic mitral regurgitation trial, the moderate ischemic mitral regurgitation trial, and a trial of atrial fibrillation ablation during concomitant mitral valve surgery. Although these trials were particularly interesting to the surgeon group at this meeting, with time it became clear that enrollment was difficult. To overcome this obstacle, significant efforts by the leadership of the CTSN as well as the Data and Clinical Coordinating Center resulted in CTSN visits to each participating center to encourage further collaboration between the surgeons and cardiologists. Fortunately these efforts were successful, and the various trials were completed.

The first 3 major CTSN trials had interesting and unexpected results. The severe ischemic mitral regurgitation

Abbreviations and Acronyms

CTSN = Cardiothoracic Surgical Trials Network
 NHLBI = National Heart, Lung and Blood Institute
 NIH = National Institutes of Health

trial, which compared mitral valve replacement with mitral valve repair, resulted in equivalent outcomes for the 2 groups with a single exception.³ There was significant recurrence of at least moderate mitral regurgitation in a third of the patients who underwent mitral valve repair (compared with those who had replacement) within the first year of surgery. Although the patients did equally well, these results clearly changed the philosophy of whether repair was the preferred treatment for severe ischemic mitral regurgitation. Mitral valve replacement is now practiced more frequently in this subgroup of patients. Further analysis and subsequent publications from the CTSN defined the subgroup of patients in which mitral regurgitation was more likely to recur.⁴ A trial for moderate ischemic mitral regurgitation demonstrated that coronary artery bypass grafting alone and with mitral repair were equivalent in left ventricular reverse remodeling, major adverse cardiac and cerebrovascular events, mortality, and quality of life in patients with moderate ischemic mitral regurgitation.⁵ Although the patients who underwent mitral valve repair had less residual mitral regurgitation, they had longer bypass times, longer stays after surgery, and more neurologic events. Finally, the atrial fibrillation ablation trial demonstrated that both pulmonary vein isolation and more complex ablation procedures resulted in significantly higher freedom from atrial fibrillation than did mitral valve surgery alone, but at a cost of higher permanent pacemaker implantation.⁶

All 3 of these major efforts resulted in publications in *The New England Journal of Medicine*, and all should change the practice of cardiac surgery. The CTSN also conducted an exploratory trial that evaluated the safety and explored the efficacy of direct myocardial injection of a single dose of mesenchymal precursor cells in left ventricular assist device recipients, either awaiting cardiac transplant or as destination therapy. This exploratory trial demonstrated that the cells were safe and suggested an efficacy signal. Finally, the CTSN conducted a prospective cohort study to examine (1) the frequency of postoperative infections and associated mortality and (2) modifiable management practices predictive of infections within 65 days from cardiac surgery. Nearly 5% of patients had major infections, which dramatically affect survival and readmissions. Practices associated with reduced infection risk included prophylaxis with second-generation cephalosporins, whereas postoperative antibiotic duration longer than 48 hours, stress hyperglycemia, intubation time of 24 to 48 hours, and ventilation for longer than 48 hours were associated with increased risk. There was a significant

but differential effect of transfusion by surgery type (excluding left ventricular assist device placement or transplant). The success of these trials and the resultant publications led to the renewal of the network.

Richard Weisel, Editor-in-Chief of *The Journal of Thoracic and Cardiovascular Surgery*, has succeeded Tim Gardner. Under his leadership, there have been several new trials that are presently enrolling. A study investigating the superiority of rate versus rhythm control for postoperative atrial fibrillation has just completed enrollment, and analysis is being performed. There is a neuroprotection trial in aortic valve surgery that has recently commenced. This trial will compare 2 different kinds of embolic protection devices versus standard cannulation techniques in preventing brain injury, including stroke and other neurocognitive events. Finally, a follow-up trial investigating stem cell therapy in patients with left ventricular assist devices has recently opened enrollment.

Although there have been previously reported randomized clinical trials in thoracic surgery, the CTSN is the first well-organized, multicenter group to compare various surgical techniques in a randomized fashion. It took a partnership of the cardiothoracic surgical community, cardiologists, and NHLBI. These efforts have also expanded from North America and will soon include a collaborative effort in Europe. In conclusion, the CTSN has accomplished much to advance the field of thoracic surgery, and we remain optimistic that these efforts will continue into the future. The CTSN has been highly successful in addressing difficult clinical questions that will improve the care of our patients. Evidence-based cardiac surgery is here to stay.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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