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The Cardiothoracic Surgery Network: Randomized Clinical Trials In the Operating Room

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In 2006, the National Heart, Lung and Blood Institute (NHLBI) announced the formation of a new clinical research network entitled, "The Network for Cardiothoracic Surgical Investigations in Cardiovascular Medicine."(1) Numerous academic cardiac surgery groups in the United States and Canada submitted applications. There were additional applications from clinical research organizations to serve as the network's Data Coordinating Center (DCC). Seven clinical sites in the United States and 1 in Canada were selected for participation in the Network, along with a DCC (see appendix). Notification of awards was made in July, 2007 and Network activity began soon thereafter. The Network has recently expanded to include additional enrolling sites (Appendix).

The goal of the Cardiothoracic Surgery Network (CTSN) is to establish a cooperative network of cardiac surgery programs to promulgate the use of evidence-based medicine in surgical practice. The Network is intended to conduct important, randomized clinical trials and observational studies, disseminate the results, and thereby translate the findings into clinical practice. The program is expected to support and maintain the necessary infrastructure to develop, coordinate, and conduct several collaborative clinical studies and interventional protocols designed to improve cardiovascular disease outcomes. Participating sites are required to provide adequate patient populations, foster a culture of clinical research and support the infrastructure necessary for successful patient enrollment and study completion. The network DCC provides the organizational expertise for conduct of the trials across the sites, while managing network operations. The purpose of this short report is to publize the organizational administration and projects currently under study.

There is a Steering Committee (SC) that includes the Principal Investigator (PI) from each of the 8 clinical sites, the DCC PI, appointed co-chairs, and NHLBI Program Officers. Two external committees appointed by the NHLBI are the Protocol Review Committee (PRC) and the Data and Safety Monitoring Board (DSMB). There is also an Event Adjudication

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Committee. Core labs are established, as needed, for specific trials and are subcontracted by the DCC. Examples include echocardiography, cardiopulmonary exercise testing, and ambulatory rhythm monitoring. Subcommittees of the SC manage Network policies and functions, such as budget and publications.

Development of Trial Protocols

At the inaugural meeting of the SC in October, 2007, the PIs reviewed multiple proposals for network trials. There was consensus around the issue of optimal management of patients with ischemic heart disease and mitral regurgitation (MR). Another area of consensus focused on concomitant atrial fibrillation (AF) ablation procedures for patients undergoing mitral valve surgery (MVS).

Committees were then established to develop the clinical trial protocols. These protocol development committees (PDCs) typically meet weekly by teleconference. Protocols are refined through bi-weekly Steering Committee teleconferences and quarterly in-person Steering Committee meetings that include co-Investigators. Study coordinators, key members of the research teams who are responsible for patient screening, enrollment and data collection, also meet regularly by teleconference and participate in the quarterly Steering Committee meetings.

Network protocols progress through many steps in development and refinement through the PDCs. Iterative drafts of the protocol are brought to the full SC for approval. Once approved, the protocol is reviewed and amended, as needed, by the independent PRC. For a protocol that involves a drug or medical device, such as a tissue ablation device for AF procedures, additional approval by the US Food and Drug Administration (FDA) is required. After Network DSMB review, the study protocol requires approval by the DCC's Institutional Review Board (IRB). Each clinical site then submits the protocol to its own IRB for approval. Throughout the many steps in this process, NHLBI Program Officers are engaged and provide final approval for the studies.

Surgical Interventions for Moderate Ischemic Mitral Regurgitation

This trial is designed to study 300 patients with coronary artery disease and moderate ischemic mitral regurgitation (IMR). The patients are randomized 1:1 to coronary bypass grafting (CABG) plus mitral valve repair using an undersized annuloplasty ring or to CABG alone. The primary endpoint is the degree of left ventricular remodeling as assessed by a change in left ventricular end-systolic volume index (LVESVI) at 12 months. Additional secondary endpoints include various clinical outcomes at 6, 12, and 24 months, other echocardiographic outcomes, functional status, quality of life (QOL), and neurocognitive outcomes.

The target population is patients with moderate IMR referred for CABG. CTSN investigators identified a lack of consensus as to optimal therapy for moderate IMR and the degree to which CABG alone will improve MR and ventricular function. IMR is not a structural valve problem. It is characterized by geometric alterations of the left ventricle that may be global or regional. Although both regional and global changes may respond to

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revascularization, the degree to which revascularization alone can stabilize or reverse associated MR is unpredictable (2-7).

For IMR patients treated with coronary artery bypass grafting (CABG) alone, the unadjusted incidence of death is increased with moderate IMR, and is increased even in the presence of only mild IMR compared to patients with no IMR (8). Patients with IMR may also suffer other significant adverse events, such as progressive heart failure and the need for re-intervention.

Available evidence addressing treatment decisions for IMR patients is limited to observational studies and case series, in which correction for significant and substantial imbalances in baseline patient characteristics and selection bias may be lacking. Furthermore, ACC/AHA guidelines for CABG and Valve Disease do not provide a decision algorithm for IMR. The indication for mitral valve operation in the patient who undergoes CABG with mild to moderate MR is still unclear, although there are data to indicate benefit of mitral valve repair in some patients with moderate IMR. (9) What is clear from many reports of patients with coronary artery disease and IMR is that their prognosis is poorer compared to patients with CAD alone regardless of treatment, and that a randomized clinical trial should prove helpful to clinicians managing such patients.

Patients with primary structural mitral valve defects are excluded as are patients in cardiogenic shock. Inclusion in this trial requires a patient to meet specific echocardiographic criteria. On transthoracic examination, the quantitative parameter for MR to qualify as moderate is an effective regurgitant orifice area (ERO) between 0.2 and 0.39 cm^2. If the ERO is < 0.2 cm^2, the degree of regurgitation can be judged as moderate using other quantitative and integrative criteria. as recommended by the American Society of Echocardiography(ASE) (10).

Evaluation of Outcomes Following Mitral Valve Repair or Replacement in Severe Chronic Mitral Regurgitation

The objective of this study is to evaluate the safety and efficacy of mitral valve repair versus valve replacement for patients with severe ischemic mitral regurgitation (MR). 250 patients with coronary artery disease and severe ischemic mitral regurgitation are being randomized 1:1 to mitral valve repair or replacement with or without surgical revascularization. The primary endpoint is change in LVESVI at 12 months. Additional secondary endpoints include clinical outcomes at 6, 12, and 24 months, other echocardiographic outcomes, functional status, quality of life (QOL) assessment, and neurocognitive outcomes. Severe MR is defined echocardiographically by an ERO > 0.4cm2 or by using the integrative criteria recommended by the ASE (10).

Severe IMR is associated with very poor health outcomes in cardiac patients. As a complication of myocardial infarction, IMR has a poor prognosis with a 5-year survival of only about 30% in the presence of severe mitral regurgitation (11). Several studies have compared replacement to repair in patients with severe MR, but uncertainty persists regarding the optimal surgical approach for these patients. As with the management of

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patients with moderate IMR, available evidence is limited to observational studies and case series. There are several reports of effective early valve repair followed by late repair failure and recurrence of severe MR. Given the increasing prevalence of this high-mortality condition and apparent equipoise among surgeons as to preferred operative treatment, (6,7,12,13) the SC concluded that a randomized study was needed. This trial of valve repair versus replacement is addressing the effectiveness of valve repair that includes, when necessary, a sub-valvular procedure to deal with severe tethering versus mitral valve replacement with complete preservation of the sub-valvular apparatus.

Surgical Ablation versus No Surgical Ablation for Patients with Persistent Atrial Fibrillation Undergoing Mitral Valve Surgery

This trial is designed to enroll 260 patients with chronic AF and mitral valve disease requiring surgery. The patients will randomized in 1:1 fashion to mitral valve surgery (MVS) with an ablation procedure plus left atrial appendage (LAA) ligation or MVS with LAA ligation alone. Patients in the ablation treatment group will be further randomized to pulmonary vein isolation (PVI) alone or to PVI and a bi-atrial lesion set. The primary endpoint is freedom from AF at both 6 and 12 months. Additional secondary endpoints include clinical outcomes at 6, 12, and 24 months, functional status, and QOL assessment.

New tissue ablation technologies have resulted in many more attempts at AF ablation during heart surgery. These devices have facilitated the performance of ablative lesions and have reduced operative times substantially. Most current procedures include pulmonary vein isolation (PVI) with or without additional lesions sets in the left atrium; in most cases, the right atrium is left untreated. These simpler ablation procedures compared to the complex Cox-Maze II operation have led to an increase in surgical ablations performed over the last 5 years. MVS patients represent the majority of those treated.

Although surgical PVI is the most common approach currently, there is evidence that more extensive lesion sets may increase ablation effectiveness. In the electrophysiology laboratory, higher rates of freedom from AF correlate with a greater volume of ablated left atrial tissue. Based on these reports, an ablation procedure that includes a connecting lesion to the mitral annulus and right atrial lesions may be more effective than simple PVI alone.

Ablation procedure success generally is defined by freedom from AF at 12 months. Assessment of the absence of AF, however, can be challenging, with the accuracy of AF detection dependent upon the tracking methods used. The primary end point of this study will be freedom from AF using 3-day continuous monitoring at 6 and 12 months post-ablation. In addition, weekly rhythm strips will be collected to assess AF load. This strategy of intense rhythm monitoring using 2 different techniques will enable the investigators to compare the effectiveness of these 2 methods of AF ablation, providing important guidance for the design of future trials.

Prior to undertaking a large-scale, pivotal trial to assess the clinical benefit of surgical ablation for AF in MVS patients, the Network is undertaking this proof-of-concept trial to demonstrate the sustained effectiveness of surgical ablation and to guide the choice of

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ablation procedure. Since the left atrium is already opened for MVS, the ablation procedure will add little time and risk. If ablation is effective over MVS alone, subsequent trials can compare specific lesion sets and ablation devices.

CTSN Observational Studies

1. Management Practices and the Risk of Infections Following Cardiac Surgery

The objective of this short-term observational study is the identification of modifiable management practices and patient characteristics that are predictive of postoperative infections. In addition, the study is designed to delineate practice variations that may be associated with higher infection rates. Patients will be followed for 60 days after the index cardiac surgical intervention and the enrollment period will continue until a minimum of 200 patients with major infections are accrued. This study is expected to require up to a 6 month enrollment period.

Hospital-acquired infections represent the main non-cardiac complication after heart surgery. They are associated with substantial morbidity and higher mortality. In addition, infectious complications result in greater economic burden. This observational study will allow for an assessment of how major infections and the management practices associated with their occurrence, affect patient outcomes as well as hospital resource use and inpatient costs.

2. Planning Grant to Compare Hybrid Revascularization with Percutaneous Coronary Intervention for Patients with Multivessel Coronary Artery Disease

This multi-center observational study is funded separately by NHLBI as an NIH Challenge Grant in Health and Science Research (14). It was awarded in September, 2009, to a consortium of CTSN investigators and several other cardiac surgery groups. The objective of this study is to explore relevant aspects of hybrid coronary revascularization (HCR) and to compare HCR to multivessel percutaneous coronary intervention (PCI) in order to design a pivotal comparative effectiveness trial of this emerging therapeutic strategy. HCR involves the surgical placement, generally without use of cardiopulmonary bypass, of a left internal mammary artery bypass graft to an obstructed left anterior descending artery, along with concomitant PCI to other obstructed coronary arteries. A specific aim of this observational study includes characterization of the patients currently undergoing HCR in order to address the feasibility of recruitment of this target population into a clinical trial. In addition, this study will track event rates in multivessel coronary revascularization patients undergoing HCR or PCI. Management practices for HCR and PCI procedures will be observed, along with concomitant medical therapies and the variations within and among participating institutions, with the goal of developing a definitive clinical trial subsequent to this observational period.

There will be two patient cohorts enrolled in this study. The first group will be identified during the initial 3 month period when undergoing coronary angiography. The second group will be enrolled over a 12 month period when they undergo a HCR or multivessel PCI procedure. All enrolled patients will be followed for a minimum of 18 months. To date, there has been no randomized trial comparing HCR to either CABG or PCI. Preliminary

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observational data suggest that HCR has the potential to disseminate widely and become the third major interventional alternative for patients with multi-vessel CAD. Without sound data from a randomized clinical trial, there may be insufficient evidence to guide application of this potentially important procedure for a major patient population.

Summary

At the midpoint in its initial 5-year funding period, the CTSN has successfully undertaken several multicenter randomized trials involving patients undergoing heart surgery. There has been enrollment of more than 100 patients during the first year in the randomized trials involving mitral valve surgery. Patients with persistent AF having MVS are now being enrolled in a trial examining the effectiveness of concurrent AF ablation procedures. Both of the observational studies, just described, have commenced. The HCR project comparing hybrid revascularization to PCI, undertaken through supplemental funding as an NIH Challenge Grant, has allowed the CTSN to engage additional cardiac surgery centers in this innovative research study.

The enrollment of patients who are undergoing major cardiac surgery in trials that involve randomization to different operative techniques historically has been challenging. Skeptics claim that randomized trials of surgery patients are impossible to complete successfully. Others question whether cardiac surgeons can accept the concept of equipoise or are willing to address uncertainty about optimal treatment with their patients. This early experience with CTSN refutes such skepticism. Patient enrollment, however, remains challenging. Commitment to patient screening and enrollment in these trials must be made by all physicians who care for eligible patients, including the cardiologists at the clinical centers. The principal requirement, however, remains the acceptance by the operating surgeon that equipoise is present and that evidence of procedural effectiveness based on outcomes must be pursued. Additional information regarding the CTSN can be found at http://www.ctsurgerynet.org/

Appendix

PARTICIPAPNTS IN THE NETWORK FOR CARDIOTHORACIC SURGICAL INVESTIGATIONS

Core Clinical Centers (Principal Investigator)

Cleveland Clinical Foundation (Eugene H. Blackstone, MD)

Columbia University Medical Center (Michael Argenziano, MD)

Duke University (Peter K. Smith, MD)

Emory University (John D. Puskas, MD)

Montefiore Medical Center - Albert Einstein College of Medicine (Robert E. Michler, MD)

Montreal Heart Institute (Louis P. Perrault, MD)

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University of Virginia Health Systems (Irving L. Kron, MD)

Affiliated and Ancillary Clinical Centers (Principal Investigator)

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East Carolina Heart Institute (T. Bruce Ferguson, MD)

Hôpital du Sacré-Coeur de Montréal (Pierre Pagé, MD)

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Canadian Institute of Health Research (Ilana Gombos, PhD)

National Institute of Neurological Diseases and Stroke (Claudia Moy, PhD)

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