Design, rationale, and initiation of the Surgical Interventions for Moderate Ischemic Mitral Regurgitation Trial: A report from the Cardiothoracic Surgical Trials Network

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Objective: Patients with coronary artery disease complicated by moderate ischemic mitral regurgitation have demonstrably poorer outcome than do patients with coronary artery disease but without mitral regurgitation. The optimal treatment of this condition has become increasingly controversial, and a randomized trial evaluating current practices is warranted.

Methods: We describe the design and initial execution of the Cardiothoracic Surgical Trials Network Surgical Interventions for Moderate Ischemic Mitral Regurgitation Trial.

Results: This is an ongoing prospective, multicenter, randomized, controlled clinical trial designed to test the safety and efficacy of mitral repair in addition to coronary artery bypass grafting in the treatment of moderate ischemic mitral regurgitation.

Conclusions: The results of the Cardiothoracic Surgical Trials Network Surgical Interventions for Moderate Ischemic Mitral Regurgitation Trial will provide long-awaited information on controversial therapies for this morbid disease process. (J Thorac Cardiovasc Surg 2012;143:111-7)

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Functional ischemic mitral regurgitation (IMR) can be defined as mitral valve regurgitation in the setting of ischemic heart disease without evidence of structural pathology of the valve apparatus. It results from postinfarction left ventricular dysfunction and dilatation (remodeling), papillary muscle displacement with leaflet tethering, and progressive annular dilatation.[1,2] It is often associated with a regional wall motion abnormality and coronary artery disease in the corresponding territory. Structural or organic mitral regurgitation, on the other hand, connotes a distinct pathology of the mitral valve, most commonly myxomatous degeneration, mitral valve prolapse, or Barlow disease. Each of these pathologic entities may lead to chronic nonischemic mitral regurgitation.

The presence of IMR is a significant predictor of adverse short- and long-term outcomes in patients with coronary artery disease, particularly after acute myocardial infarction.[3-6] When coronary artery disease is treated with coronary artery bypass grafting (CABG) alone, the unadjusted incidence of death has been found to be significantly increased even in the presence of only mild IMR (8.4% at 1 year) relative to patients with no IMR (3.8% at 1 year). The mortality risk increases with increasing severity of mitral regurgitation and has been found to be twice as great in patients with moderate IMR treated with CABG alone (16.9% at 1 year).[7] The surgical treatment of IMR has become increasingly controversial, with approximately equal numbers of patients treated with either combined CABG and mitral valve repair or replacement or with CABG alone.[8-10] Operative mortality for CABG as well as for CABG combined with mitral valve repair has declined steadily nationwide during the past 5 years[11]; however, the additional

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CTSN = Cardiothoracic Surgical Trials Network
ERO = effective regurgitant orifice
IMR = ischemic mitral regurgitation
LVESVI = left ventricular end-systolic volume index
NHLBI = National Heart, Lung, and Blood Institute
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

aortic crossclamp time and cardiopulmonary bypass time associated with the performance of mitral valve repair increase the risk of the combined procedure.[12,13] This approach does not allow a purely off-pump procedure. Selection of the appropriate patients is thus imperative to ensure that the trade-off of the additional risk of mitral valve repair is necessary and provides additional short- or long-term benefit.

Proponents of treating mild to moderate IMR with revascularization alone argue that revascularization improves regional contractility and restores mitral valve papillary muscle continuity, thus normalizing mitral valve function.[14,15] On the other hand, proponents of a more aggressive treatment strategy cite the negative consequences of ongoing mitral regurgitation. Myocardial revascularization alone may be insufficient to restore normal ventricular physiology once mitral regurgitation has developed. Correction of mitral regurgitation may prevent progressive adverse remodeling, improve cardiac function, and attenuate the risk of heart failure.

Available evidence addressing treatment decisions for IMR is limited to small, single-center, randomized trials, observational studies, and case series,[7-11,13,15] in which correction for significant and substantial imbalances in baseline patient characteristics is problematic, making it difficult to develop a clear understanding of appropriate treatment options. These studies are also limited by variable definitions of the severity and etiology of mitral regurgitation, variable surgical repair techniques, potential publication bias, limited patient follow-up, and lack of information on key secondary outcomes such as quality of life.[12] Importantly, the recently published American College of Cardiology and American Heart Association guidelines both for CABG and for the management of patients with valvular heart disease avoid addressing the decision algorithm for IMR.[16,17] The only consensus established from literature review is that the preferred treatment is unknown and should be individualized and that a randomized clinical trial to generate necessary evidence on which to base clinical decisions is essential.[7,11,18,19]

TRIAL DETAILS

In February 2004, the National Heart, Lung, and Blood Institute (NHLBI) advisory council proposed that the NHLBI evaluate the status of cardiac surgery and its future directions. The NHLBI convened a working group on future directions in cardiac surgery, which called for the formation of the Cardiothoracic Surgical Trials Network (CTSN), which was designed to develop a culture of rigorous clinical evaluative research within the field of cardiac surgery. The CTSN includes integration of both cardiologists and surgeons in the ownership of and responsibility for trials bridging the integrated specialties. Moderate IMR was the top priority for initial investigation of both the NHLBI working group and the CTSN investigators.[18]

Trial Objectives

The CTSN Surgical Interventions for Moderate Ischemic Mitral Regurgitation Trial seeks to evaluate the safety and efficacy of mitral valve repair for moderate IMR. Specifically, the trial compares mitral valve repair combined with CABG to CABG alone in this patient population. The primary aim of the trial is to evaluate the effects of these 2 surgical approaches on left ventricular remodeling, as assessed by left ventricular end-systolic volume index (LVESVI). Secondary aims of this trial include assessment of the effects of these 2 surgical interventions on the severity of the mitral regurgitation, regional and global cardiac performance, mortality, adverse events, quality of life, functional status, neurocognitive function, and health resource use.

Trial Design

This is a prospective, multicenter, randomized clinical trial conducted at the clinical centers participating in the CTSN (Appendix E1). Patients deemed eligible are randomly assigned in a 1:1 allocation to CABG combined with mitral valve repair or CABG alone (Figure 1). The enrollment period is estimated to be 36 months, and all patients will be followed up for 24 months after randomization. A minimum of 2 years of follow-up is intended, although the primary end point will be assessed at 1 year.

Neither patients nor investigators are blinded to the treatment assignment because of the nature of treatment intervention. The investigators are, however, blinded to all data from other clinical sites, with the exception of information required for institutional review board reporting purposes. All protocol-defined echocardiograms are analyzed by a centralized core laboratory, and all core laboratory personnel are blinded to clinical characteristics and outcomes. Serious and protocol-defined adverse events are adjudicated by an independent event adjudication committee. Trial