Optimal surgical management of severe ischemic mitral regurgitation: To repair or to replace?

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Background: Ischemic mitral regurgitation, a complication of myocardial infarction and coronary artery disease more generally, is associated with a high mortality rate and is estimated to affect 2.8 million Americans. With 1-year mortality rates as high as 40%, recent practice guidelines of professional societies recommend repair or replacement, but there remains a lack of conclusive evidence supporting either intervention. The choice between therapeutic options is characterized by the trade-off between reduced operative morbidity and mortality with repair versus a better long-term correction of mitral insufficiency with replacement. The long-term benefits of repair versus replacement remain unknown, which has led to significant variation in surgical practice.

Methods and Results: This article describes the design of a prospective randomized clinical trial to evaluate the safety and effectiveness of mitral valve repair and replacement in patients with severe ischemic mitral regurgitation. This trial is being conducted as part of the Cardiothoracic Surgical Trials Network. This article addresses challenges in selecting a feasible primary end point, characterizing the target population (including the degree of mitral regurgitation) and analytical challenges in this high mortality disease.

Conclusions: The article concludes by discussing the importance of information on functional status, survival, neurocognition, quality of life, and cardiac physiology in therapeutic decision making. (J Thorac Cardiovasc Surg 2012;143:1396-403)

Ischemic mitral regurgitation (MR), especially severe ischemic MR, has long been associated with poor health outcomes in patients with cardiac disease. Also known as functional MR, ischemic MR is a complication of myocardial infarction (MI) and has been estimated to affect 1.6 to 2.8 million people in the United States in 2004.[1] As the population ages and the survival after MI increases, so will the number of people with ischemic MR.[2] Ischemic MR is associated with a shortened survival. Even mild ischemic MR after MI dramatically increases cardiovascular mortality, with a 17% increase at 3.5 years compared with that of patients with similar degrees of ischemia but without MR (29% vs 12%; $P < .001$).[3] In a population with mixed levels of severity of ischemic MR, overall mortality was 62% versus 39% in patients without MR ($P < .001$) at 5 years.[4] When the ischemic MR was severe, the 1-year mortality rate has been reported as being as high as 40%.[5]

Post-MI changes in ventricular structure and function can produce MR through 2 distinct processes. Locally, inferior and posterior remodeling can cause displacement of the papillary muscles away from the mitral valve annulus, producing leaflet tethering and restriction of motion. This inhibits the leaflets' ability to close effectively at the level of the annulus. Globally, annular enlargement owing to left ventricular (LV) dilatation causes central malcoaptation at the level of the annulus. This is compounded by LV dysfunction, which decreases the force available to close the leaflets in opposition to the increased tethering forces noted above.[1,6,7]

Revascularization does not often significantly reduce moderate to severe MR; one study reported that moderate to severe MR persisted in 77% of patients.[8] Mitral valve

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Abbreviations and Acronyms

CTSN = Cardiothoracic Surgical Trials Network
EROa = effective regurgitant orifice area
LV = left ventricular
LVESVI = left ventricular end-systolic volume index
MI = myocardial infarction
MR = mitral regurgitation
NHLBI = National Heart, Lung, and Blood Institute
PI = Principal Investigator
SF-12 = short form health survey (12 items)

replacement was the preferred approach in early studies. However, suboptimal results were demonstrated, in part because the subvalvular apparatus was not being preserved. Although repair and replacement both appear to eliminate MR immediately postoperatively, large retrospective studies have suggested that repair has lower perioperative mortality.[9,10]

The surgical approach to mitral valve repair has evolved over time. Therapy directed to reducing the annular size alone has a demonstrated 6-month recurrence of severe MR of 28% to 30%.[11,12] The long-term recurrence rates are in the 72% range.[11] Significant mitral annulus undersizing has been attempted; however, these long-term results are still not optimal.[13] Several new rings are available that attempt to reshape the annulus. However, the major concern remains that reduction annuloplasty alone does not address the subvalvular changes or the tethering mechanism. Alternative surgical options have been explored, including extraventricular Dacron patches and balloons[14]; external infarct plication sutures[15]; reduction of leaflet tethering by cutting a limited number of secondary chordae[16,17]; edge-to-edge suture creating a double orifice valve[18]; LV restoration procedure with improvement of papillary muscle orientation[19]; and suture relocation of the posterior papillary.[20]

Several studies thus have compared replacement and repair in patients with severe MR, but considerable controversy remains regarding the optimal surgical approach for these patients. Available evidence is limited to observational studies and case series, where correction for significant and substantial imbalances in baseline patient characteristics (ie, risk factors) is suboptimal. These studies are also limited by short-term outcome measures, inclusion of patients with different types of mitral valve disease, and lack of information on important secondary outcomes, such as quality of life. Consequently, recent practice guidelines of professional societies recommend class I surgical treatment of patients with symptomatic severe MR but do not indicate whether to repair or replace the mitral valve inasmuch as the long-term benefits of these alternative procedures are unknown.[21,22] The choice between therapeutic options is characterized by a perceived trade-off between reduced operative morbidity and mortality, with repair versus a potentially better long-term correction of mitral insufficiency with replacement. This uncertainty has led to significant variations in surgical practice. Given the prevalence of this high-mortality condition, a randomized trial that would address the relative benefits of repair versus replacement in patients with severe ischemic MR could have a significant impact on patient management and health outcomes.

This article describes the design of such a trial that is currently being conducted as part of the Cardiothoracic Surgical Trials Network (CTSN; Appendix 1) and funded by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute for Neurological Diseases and Stroke, and the Canadian Institute for Health Research. In particular, the article addresses challenges in selecting a feasible primary end point, characterizing the target population (including the degree of MR), and analytical challenges in this high mortality disease. This article concludes by discussing important insights that are expected to emerge from this trial, which has already accrued over 50% of required sample size.

STUDY DESIGN

The primary aim of the trial is to evaluate the impact of replacement versus repair on LV remodeling, as assessed by LV end-systolic volume index (LVESVI) at 12 months after surgery. This is a parallel design, prospective, multicenter, randomized (1:1) clinical trial comparing mitral valve repair and mitral valve replacement (Figure 1). The trial is conducted in highly experienced clinical centers participating in the Cardiothoracic Surgery Clinical Trials Network.

The randomization procedure is being performed intraoperatively, after the first incision and before cannulation of the aorta. After verification of entry criteria, random treatment assignment is generated by the trial's electronic data capture system. The randomization is stratified by clinical center and uses a random permuted block design with blocks of size 2, 4, and 6 to ensure balance in the number of patients assigned to each treatment.

For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated. All patients are to be followed up for 24 months after randomization, and end points are measured at 30 days and 6, 12, and 24 months. The nature of the treatments precludes masking of patients and their treating clinicians to treatment assignment; however, all echocardiograms are being analyzed by an independent core laboratory. Investigators will also be blinded to all data from other clinical sites with the exception of serious,