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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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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Abstract

Background—Patients with moderate ischemic mitral regurgitation have demonstrably poorer outcome compared to coronary artery disease patients without mitral regurgitation. The optimal
treatment of this condition has become increasingly controversial and a randomized trial evaluating current practices is warranted.

**Methods and Results**—We describe the design and initial execution of the Cardiothoracic Surgical Trials Network moderate ischemic mitral regurgitation trial. This is an ongoing prospective, multi-center, 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.

**Conclusion**—The results of the Cardiothoracic Surgical Trials Network ischemic mitral regurgitation trials will provide long-awaited information on controversial therapies for a morbid disease process.

**Introduction**

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 post-infarction 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 (CAD) in the corresponding territory. Structural or organic mitral regurgitation (MR), on the other hand, connotes a distinct pathology of the mitral valve, most commonly myxomatous degeneration, mitral valve prolapse, and Barlow’s disease. Each of these pathologic entities may lead to chronic non-ischemic MR.

The presence of IMR is a significant predictor of adverse short and long term outcomes in patients with coronary artery disease, particularly following acute myocardial infarction [3–6]. When treated with coronary artery bypass graft (CABG) surgery alone, the unadjusted incidence of death is significantly increased even in the presence of only mild IMR (8.4% at 1 year) compared to patients with no IMR (3.8% at 1 year). The mortality risk increases with increasing severity of MR, and is 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 (MV) repair/replacement (MVR/R), or with CABG alone [8–10]. Operative mortality for CABG as well as for CABG combined with mitral valve repair has declined steadily nationwide over the past five years [11], but the additional aortic cross clamp time and cardiopulmonary bypass time associated with the performance of MV repair increases the risk of the combined procedure [12,13]. This approach does not allow for a purely off-pump procedure. Therefore, selection of the appropriate patients is imperative to ensure that the trade-off of the additional risk of mitral valve repair is necessary and provides additional short and/or long term benefit.

Proponents for treating mild-to-moderate ischemic MR with revascularization alone argue that revascularization improves regional contractility and restores MV-papillary muscle continuity, thus normalizing MV function [14, 15]. On the other hand, proponents for a more aggressive treatment strategy cite the negative consequences of ongoing MR. Myocardial revascularization alone may be insufficient to restore normal ventricular
physiology once MR develops. Correction of MR may prevent progressive adverse remodeling and may 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], where 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 MR, 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 ACC/AHA guidelines for both CABG Surgery and the Management of Patients with Valvular Heart Disease both 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].

In February 2004, the National Heart, Lung, and Blood Institute's (NHLBI) Advisory Council proposed that the Institute evaluate the status of and future directions in cardiac surgery. The NHLBI convened a working group on future directions in cardiac surgery which called for the formation of a Cardiotoracic Surgical Clinical Trials Network (CTSN) designed to develop a culture of rigorous clinical evaluative research within the field of cardiac surgery. The Network 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 of both the NHLBI working group and the CTSN Investigators for initial investigation [18].

**Trial Objectives**

The CTSN Surgical Interventions for Moderate Ischemic MR Trial seeks to evaluate the safety and efficacy of mitral valve repair for moderate IMR. Specifically, the trial compares mitral valve repair combined with coronary artery bypass grafting to coronary artery bypass grafting alone in this patient population. The primary aim of the trial is to evaluate the impact of these two surgical approaches on left ventricular remodeling as assessed by end systolic volume index (ESVI). Secondary aims of this trial include assessment of the impact of these two surgical interventions on the severity of the MR, 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 (eAppendix A). Patients deemed eligible are randomly assigned in a 1:1 allocation to CABG combined with MV repair or CABG alone. (See Figure 1) The enrollment period is estimated to be 36 months, and all patients will be followed for 24 months following randomization. A minimum of 2 years of follow-up is intended, although the primary endpoint will be assessed at 1 year.
Neither patients nor investigators are blinded to the treatment assignment due to the nature of treatment intervention. The investigators, however, are blinded to all data from other clinical sites, with the exception of information required for IRB reporting purposes. All protocol defined echocardiograms are analyzed by a centralized core laboratory, and all core lab personnel are blinded to clinical characteristics and outcomes. Serious and protocol defined adverse events are adjudicated by an independent Event Adjudication Committee. Trial oversight is provided by an independent Data and Safety Monitoring Board (DSMB) appointed by the NHLBI.

Patient Population

The patient population for this trial consists of patients with clinically significant CAD and an indication for CABG associated with moderate IMR. The ischemic etiology and degree of MR is assessed by transthoracic echocardiography (TTE) within 30 days prior to randomization, as determined by the clinical site echocardiographer. All clinical site labs are accredited by the echocardiography core lab with regard to both image acquisition and interpretation prior to site activation and patient enrollment. Patients are eligible to participate regardless of the presence or absence of symptoms attributable to MR. Furthermore, in order to increase the generalizability of the results of this trial, since the timing of referral for surgical intervention in patients with moderate ischemic MR is quite variable in the community, the trial was designed in the absence of a “run-in” period that would otherwise have optimized medical therapy prior to the qualifying TTE. As such, patients can be included in the trial even if subsequent TTEs following the qualifying TTE, but prior to randomization, demonstrate a decrease in the severity of MR with optimal medical therapy. Patients who have echocardiographic documentation of severe IMR by TTE at any time are candidates for a separate CTSN trial comparing MV repair to replacement.

Echocardiographic Assessment of the Degree of MR

This trial is designed to evaluate a patient population within the clinical spectrum of moderate ischemic MR, identified transthoracic echocardiography. The initial mitral valve inclusion criteria were to have an effective regurgitant orifice (ERO) area of 0.2 cm\(^2\) to 0.39 cm\(^2\) [7, 11, 18] and a structurally normal mitral valve. It became clear, however, early in the course of screening patients for enrollment that the ERO\(_a\) criterion was overly restrictive and led to the exclusion of patients with other semi-quantitative echocardiographic measures of moderate MR. Review of trial screening logs indicated that failure to meet the original ERO criterion, despite the consensus opinion of the surgical principal investigator and the site echocardiographer that the MR was moderate, was the major cause of screening failure. Therefore, the echocardiographic inclusion criteria were broadened to more closely reflect the consensus of surgeons and cardiologist to ensure that enrolled patients more closely resembled those referred in clinical practice. Specifically, inclusion was redefined as moderate IMR with (a) an effective regurgitant orifice (ERO) area of 0.2 cm\(^2\) to 0.39 cm\(^2\), or (b) an ERO area < 0.2 cm\(^2\) and additional evidence of more than mild MR as suggested by such integrative criteria as the density of the MR velocity profile, pulmonary vein systolic flow abnormalities, left atrial jet area, etc. [7, 11, 18, 20] (see Table 1)
Eligibility Criteria

Criteria for inclusion in this trial, beyond the echocardiographic identification of moderate ischemic MR, are intentionally broad, focusing on targeting patients with coronary anatomy amenable to bypass grafting and a clinical indication for revascularization. Patients are excluded from participation if they have evidence of concomitant structural MV disease, prior mitral valve intervention, or planned concomitant intra-operative procedures with the exception of Maze procedures or closure of a patent foramen ovale (PFO) or atrial septal defect (ASD). The key eligibility criteria for the trial are listed in Table 2.

Randomization

Randomization is blocked and stratified by clinical center. Randomization is performed intra-operatively, following sternotomy and before cannulation of the aorta, in order to minimize the likelihood of enrolling patients in the study with unexpected surgical contraindications to MV repair. The timing of randomization was chosen to ensure that both cannulation for cardiopulmonary bypass is possible, and that patients with structural MV pathology identified by intra-operative transesophageal echocardiography (TEE) not appreciated on the original transthoracic study are excluded prior to randomization. The randomization process is controlled centrally and performed through a Web-based data collection system that automates the delivery of randomization codes. The treatment assignment is sent to the site coordinator electronically, in a secure fashion, and electronic verification of the treatment assignment is required before proceeding with the treatment intervention. Thereafter, primary efficacy will be analyzed by intention-to-treat; that is, the patients will be grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned.

Endpoint Definitions

The primary endpoint for the trial is the degree of left ventricular remodeling, assessed by the left ventricular end systolic volume index (LVESVI) measured by TTE at 12 months following randomization. The principal secondary endpoint is a composite of Major Adverse Cardiac Events (MACE), defined by a non-weighted composite score composed of the following components: death, stroke, worsening heart failure (≥ NYHA Class), HF hospitalization, and MV re-intervention. Additional secondary endpoints include all-cause mortality, functional status assessed by peak VO$_2$ uptake during cardiopulmonary exercise testing, Quality of Life (SF-36, Duke Activity Status Index [DASI], and Minnesota Living with Heart Failure [MLHF] questionnaire) and health care costs.

Treatment Intervention

Procedural Technique

All patients enrolled in this trial undergo coronary artery bypass grafting as per individual surgeon technical preference, with the exception of cardiopulmonary bypass support, which is required for all patients in the trial. For those patients randomly assigned to MV repair in addition to CABG, the repair is performed using standard techniques, but the protocol
mandates the use of a complete ring and downsizing by 2 sizes whenever possible. The other elements of operative and perioperative clinical care are not prescribed by protocol.

**Surgeon Certification**

In order to minimize the effect of variation in operator expertise for the purposes of this clinical trial, all surgeons operating on patients enrolled in the trial must meet a minimum threshold of experience and be certified by the site Principal Investigator. Protocol specified surgical certification requires that the surgical investigator performs a minimum of 10 MV repair procedures per year, averaged over 2 years. A certified clinical site surgeon must participate in the MV procedure of a patient enrolled at that site if the primary surgeon is not certified.

**Follow-up**

Post-randomization data collection occurs at predetermined study visits as well as at event-driven visits. Planned study visits include the first postoperative day and months 6, 12, and 24 postoperatively. Blood, urine, and tissue sample collection is performed intra-operatively and additional blood and urine collections are made 6 and 12 months post randomization. Physical examination, New York Heart Association Classification, Angina Class, echocardiogram, and quality of life assessments are performed at postoperative months 6, 12, and 24. Cardiopulmonary exercise testing is performed (if possible) at baseline and at 6 and 12 months. Neurocognitive testing is performed at baseline and 12 months postoperatively. Direct cost data are obtained quarterly for all randomized patients. A minimum of 2 years of follow-up is intended, although the primary endpoint is determined at 1 year.

**Sample Size**

For calculation of sample size, we assumed that the mean baseline LVESVI in the target population to be 80 ml/m² (normal LVESVI ~ 25ml/m²). For patients randomized to receive CABG only, we anticipate a 5% reduction in LVESVI, or an absolute change of 4 ml/m². A clinically important additional reduction of 12 ml/m², or a total reduction of 20% (16 ml/m²) is estimated for patients who undergo MV repair in addition to CABG. Assuming that baseline and 12 month LVESVI in both arms follows a gamma distribution with common standard deviation of 35 ml/m², a total of 300 patients, randomized with equal probability to each arm, provides approximately 90% power to detect this additional difference of 12 ml/m² in LVESVI.

**Primary Analysis**

The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed Wilcoxon Rank-Sum test. The choice of the Wilcoxon Rank-Sum test for the primary analysis is motivated by the expectation of a relatively substantial amount of non-ignorable missing data, primarily due to patient death; one-year incidence of mortality is expected to range from 10–15%, and potentially differ between randomization arms.
Additional Analyses

The details of the bypass operation performed (number of grafts placed, quality of grafts and target vessels) and assessment of regional and global LV function at 6, 12 and 24 months will allow examination of the success of the revascularization component of the procedure. The interaction between the pre-operative plan for revascularization, any variation from the plan, the resulting change in global and regional LV function, and associated change in the severity of IMR will thus be evaluated. This analysis may identify patient subsets that differ in meeting the primary and secondary endpoints, and are perhaps more responsive to revascularization alone.

Discussion

The cardiac surgery community has not been recognized historically for the conduct of large scale, multicenter, comparative effectiveness or translational clinical trials. The decision to investigate the surgical treatment options for ischemic MR has provided the opportunity to identify investigational issues that will be relevant to all future surgical clinical research.

It is clear that one element for success is the creation of a culture of surgical investigation that is dissociated from the treatment paradigms that have been developed in the absence of evidence from randomized clinical trials. The second element of success is a shared vision of cardiac surgical investigation with the cardiology community at each site, within each region, and nationally. The effort must begin with engaged and committed surgical leadership at each clinical site, coupled with diplomatic and persistent engagement of the cardiology community. The nature of a patient referral for surgery generally confers the expectation on the part of each participant that a specific procedure will be performed. Although expectations must be adjudicated at the local level, patients, surgical investigators and their referring physicians must eventually be willing to embrace participation in a randomized trial to provide greater insight into best practices. No single formula works to achieve this goal, yet lessons have been learned through the CT Surgery Network that will help future trials.

One important lesson concerns enrollment. The core CTSN clinical sites were activated for enrollment as of April 2009. Initially, the accrual rate was substantially less than estimated by historical rates of combined CABG/mitral valve procedures at the clinical sites. An extensive evaluation of the protocol, the structure of the Network, and site performance characteristics was undertaken, including multidisciplinary visits to each site. This evaluation disclosed several obstacles and inefficiencies that were amenable to improvement by protocol modification and establishing the clear expectation that each site develop a culture of clinical research to include surgeons and cardiologists in collaboration.

It became clear that the historical prevalence of IMR had been significantly overestimated through historical reliance on contrast ventriculography and qualitative TTE and TEE estimates of the degree of MR. A review of the Duke Cardiovascular Database revealed that patients often change MR severity grade when evaluated by TEE in the operating room. In a series of 430 patients having both pre-operative TTE and intra-operative TEE, 19% of
patients with mild MR documented preoperatively were found to have moderate MR in the operating room. In patients who had moderate MR preoperatively, 14% were found to have severe MR in the operating room. The clinical decision-making in these patients was undoubtedly driven by the intra-operative TEE findings, but such patients would not be eligible for this trial. The more common occurrence of a reduction in the severity of MR on intra-operative TEE (37% of preoperative moderate MR determined intra-operatively to be mild) does not prevent enrollment in the protocol as designed since the qualifying echo is the pre-operative TTE study. The Protocol Development Committee (PDC), in collaboration with the Echo Core Lab leadership therefore recommended that the determination of degree of MR be made by the site echocardiographer using the TTE and all the primary and secondary criteria outlined above.

Site visits with surgeons, cardiologists, and institutional leadership, as well as reviews of screening logs, and meetings of the CTSN steering committee provided new insights into the interaction among patients, referring cardiologists, site cardiologists and surgeons that influence trial conduct and enrollment. It became clear that the cardiovascular community has developed paradigms for the management of patients with IMR that are not evidence-based but could affect patient recruitment.

Treatment of patients with CAD and IMR has generally related to a qualitative assessment of the severity of MR, the presence of heart failure symptoms, and the correlation of CAD with myocardial ischemia, viability and function. In the setting of moderate IMR, treatment paradigms are easily biased and may in some instances lead to a premature recommendation for MV surgery that can preclude randomization into the trial once the expectation for repair has been established in the patient’s mind. The generalizability of the study results may also be negatively impacted if only patients with IMR towards the lower end of the moderate scale were enrolled. Similar concerns have been raised regarding patient recruitment in trials of percutaneous PFO closure. Network cardiologists and surgeons realized that joint evidence-based decision-making and clinical equipoise would be required to enable patient enrollment.

The dynamic nature of ischemic MR was also found to be a major impediment to patient enrollment. Clinically indicated TTEs, performed with variable image acquisition, were frequently found to demonstrate suitable IMR severity, but failed to capture either the primary endpoint measure (LVESV) or the ERO area. Subsequent research TTEs, performed under the conditions of optimal medical therapy for ischemia and following diuresis, frequently then failed to meet the criteria for MR severity. Thus, although such patients have the appropriate substrate for enrollment in the trial and underwent treatment for ischemic MR of the severity seen on presentation, they were not eligible for randomization. This finding led to site-specific improvements in the quality of clinical TTEs, thus enabling capture of the key elements of IMR in patients at initial presentation.

A systematic review of screening failures also revealed several limiting exclusion criteria, including prior cardiac surgery, planned concomitant surgical correction of atrial fibrillation, and a rigid threshold defining exclusion for pulmonary hypertension regardless of relation to
the degree of MR. Revisions to the eligibility criteria were approved by the DSMB in May, 2009.

Following this intensive two month period of self-evaluation and modifications to the protocol, a new target accrual rate (12.4 patients per month) was established. The current enrollment rate meets expectations. In addition, criteria were established within the Network for the incorporation of ancillary and satellite sites; 12 additional sites have been activated. At the time of manuscript preparation, the MMR trial has enrolled 144 patients, or 48% percent of the target study population.

The process of creating and implementing an effective investigational network to address significant cardiac surgical problems has been enlightening. The design of the current trial, and our experience in conducting it, has revealed limitations in the application of observational data to patient care. The absence of robust randomized trial evidence regarding the treatment of ischemic MR has severely limited the ability of surgeons and cardiologists to determine the best options for these patients.

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Disclosures

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References


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Infection Event Adjudication Committee: Rachel Miller (Chair); Shirish Huprikar, Marilyn Levi
Figure 1.
Study Design Flow Chart
**Table 1**

Integrative Method Criteria for Echo Assessment of Degree of MR

1a. Echo Color Doppler Criteria

<table>
<thead>
<tr>
<th>Color Flow Jet Area</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color Flow Jet Area</td>
<td>&lt; 20% of LA area</td>
<td>20% to 39% of LA area</td>
<td>Large central jet (usually &gt; 10 cm² or &gt; 40% of LA area) or variable size wall - Impinging jet swirling in LA</td>
</tr>
<tr>
<td>Quantitative Parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC width (cm)</td>
<td>&lt; 0.3</td>
<td>0.3 – 0.69</td>
<td>≥0.7</td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>&lt; 0.20</td>
<td>0.20 – 0.29 0.30 – 0.39</td>
<td>≥0.40</td>
</tr>
</tbody>
</table>

1b. Echo Supportive Criteria

<table>
<thead>
<tr>
<th>Structural Doppler Parameters</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA size</td>
<td>Normal</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>LV size</td>
<td>Normal</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Mitral leaflets or support apparatus</td>
<td>Normal or abnormal</td>
<td>Normal or abnormal</td>
<td>Abnormal/ Flail leaflet/Ruptured papillary muscle</td>
</tr>
<tr>
<td>Mitral inflow - PW</td>
<td>A wave dominant</td>
<td>Variable</td>
<td>E wave dominant (E usually 1.2 m/s)</td>
</tr>
<tr>
<td>Jet density - CW</td>
<td>Incomplete or faint</td>
<td>Dense</td>
<td>Dense</td>
</tr>
<tr>
<td>Jet contour – CW</td>
<td>Parabolic</td>
<td>Usually parabolic</td>
<td>Early peaking-triangular</td>
</tr>
<tr>
<td>Pulmonary vein flow</td>
<td>Systolic dominance</td>
<td>Systolic blunting</td>
<td>Systolic flow reversal</td>
</tr>
</tbody>
</table>

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### Table 2

**Selected Eligibility Criteria**

<table>
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<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>1. Moderate MR in the judgment of the clinical site echocardiographer, assessed by TTE using the integrative method</td>
</tr>
<tr>
<td>2. Coronary artery disease amenable to coronary artery bypass grafting and a clinical indication for revascularization</td>
</tr>
<tr>
<td>3. Age ≥18 years</td>
</tr>
<tr>
<td>4. Able to sign Informed Consent and Release of Medical Information forms</td>
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<thead>
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<th>Key Exclusion Criteria</th>
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<tr>
<td>1. Any evidence of structural (chordal or leaflet) mitral valve disease</td>
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<td>2. Inability to derive ERO and ESVI by transthoracic echocardiography</td>
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<td>3. Planned concomitant intra-operative procedures (with exception of closure of PFO or ASD, or Maze procedure)</td>
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<td>4. Prior surgical or percutaneous MV intervention</td>
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<td>5. Contraindication to cardiopulmonary bypass</td>
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<td>6. Clinical signs of cardiogenic shock at the time of randomization</td>
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<td>7. Treatment with chronic intravenous inotropic therapy at the time of randomization</td>
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<td>8. ST segment elevation MI requiring intervention within 7 days prior to randomization</td>
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