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)

Supplemental material is available online.

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 years¹¹; 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

FIGURE 1. Study design flow chart. MR, Mitral regurgitation; CABG, coronary artery bypass grafting; LVESVI, left ventricular systolic volume index; LOS, length of stay; LVEF, left ventricular ejection fraction; AE's, adverse events.

oversight is provided by an independent data and safety monitoring board appointed by the NHLBI.

Patient Population

The patient population for this trial consists of patients with clinically significant coronary artery disease and an indication for CABG associated with moderate IMR. The ischemic etiology and degree of mitral regurgitation is assessed by transthoracic echocardiography (TTE) within 30 days before randomization, as determined by the clinical site echocardiographer. All clinical site laboratories are accredited by the echocardiography core lab with regard to both image acquisition and interpretation before site activation and patient enrollment. Patients are eligible to participate regardless of the presence or absence of symptoms attributable to mitral regurgitation. Furthermore, to increase the generalizability of the results of this trial, because the timing of referral for surgical intervention in patients with moderate IMR 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 before the qualifying TTE. As such, patients can be included in the trial even if subsequent TTEs after the qualifying TTE, but before randomization, demonstrate a decrease in the severity of mitral regurgitation 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 mitral valve repair and replacement.

Echocardiographic Assessment of the Degree of Mitral Regurgitation

This trial is designed to evaluate a patient population within the clinical spectrum of moderate IMR, as identified by TTE. The initial mitral valve inclusion criteria were an effective regurgitant orifice (ERO) 0.2 cm^2 to 0.39 cm^2 in area^{7,11,18} and a structurally normal mitral valve. It became clear early in the course of screening patients for enrollment, however, that the ERO area criterion was overly restrictive and led to the exclusion of patients with other semiquantitative echocardiographic measures of moderate mitral regurgitation. Review of trial screening logs indicated that failure to meet the original ERO area criterion, despite the consensus opinion of the surgical principal investigator and the site echocardiographer that the mitral regurgitation was moderate, was the major cause of screening failure. The echocardiographic inclusion criteria were therefore broadened to reflect more closely the consensus of surgeons and cardiologists in an effort to ensure that enrolled patients more closely resembled those referred in clinical practice. Specifically, inclusion was redefined as moderate IMR with (1) an ERO area of 0.2 cm^2 to 0.39 cm^2 or (2) an ERO area less than 0.2 cm^2 and additional evidence of more than mild mitral regurgitation, as suggested by such integrative criteria as the density of the mitral regurgitation velocity profile, pulmonary vein systolic flow abnormalities, and left atrial jet area (Tables 1 and 2).^{7,11,18,20}

Eligibility Criteria

Criteria for inclusion in this trial, beyond the echocardiographic identification of moderate IMR, are intentionally broad, focusing on targeting patients with coronary anatomy amenable to CABG and a clinical indication for revascularization. Patients are excluded from participation if they have evidence of concomitant structural mitral valve disease, previous mitral valve intervention, or planned concomitant intraoperative procedures, with the exception of maze procedures or closure of a patent foramen ovale or an atrial septal defect. The key eligibility criteria for the trial are listed in Table 3.

Randomization

Randomization is blocked and stratified by clinical center. Randomization is performed intraoperatively, after the sternotomy but before cannulation of the aorta, to minimize

TABLE 1. Integrative method criteria for echocardiographic assessment of degree of mitral regurgitation: Echocardiographic color Doppler and quantitative criteria

	Mild	Moderate	Severe
Color flow jet area	<20% of LA area	20%–39% of LA area	Large central jet (usually >10 cm ² or >40% of LA area) or variable size wall-impinging jet swirling in LA
Quantitative parameters			
Vena contracta width (cm)	<0.30	0.30–0.69	≥0.70
Effective regurgitant orifice area (cm ²)	<0.20	0.20–0.39	≥0.40

LA, Left atrium.

the likelihood of enrolling patients in the study with unexpected surgical contraindications to mitral valve repair. The timing of randomization was chosen to ensure both that cannulation for cardiopulmonary bypass is possible and that patients with structural mitral valve pathology identified by intraoperative transesophageal echocardiography (TEE) not detected on the original TTE study are excluded before 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 is to be analyzed by intention to treat; that is, the patients are grouped by their assignment at randomization regardless of whether they actually receive the treatment to which they are initially assigned.

End Point Definitions

The primary end point for the trial is the degree of left ventricular remodeling, as assessed by the LVESVI measured by TTE at 12 months after randomization. The principal secondary end point is a composite of major adverse cardiac events, as defined by an unweighted composite score composed of the following components: death, stroke, worsening heart failure (≥1 New York Heart Association class), hospitalization for heart failure, and mitral valve reintervention. Additional secondary end points include all-cause mortality, functional status assessed by peak volume of oxygen uptake during cardiopulmonary exercise

testing, quality of life (36-item Short Form Health Survey, Duke Activity Status Index, and Minnesota Living with Heart Failure questionnaire), and health care costs.

Treatment Intervention

Procedural technique. All patients enrolled in this trial undergo CABG according to each operating surgeon's technical preference, with the exception of cardiopulmonary bypass support, which is required for all patients in the trial. For those patients randomly assigned to undergo mitral valve repair in addition to CABG, the repair is performed with 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 the protocol.

Surgeon certification. 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 perform a minimum of 10 mitral valve repair procedures per year, averaged over 2 years. A certified clinical site surgeon must participate in the mitral valve procedure of a patient enrolled at that site if the primary surgeon is not certified.

Follow-up

Postrandomization data collection occurs at predetermined study visits as well as at event-driven visits. Planned study visits include the first postoperative day and postoperative months 6, 12, and 24. Blood, urine, and tissue

TABLE 2. Integrative method criteria for echocardiographic assessment of degree of mitral regurgitation: Echocardiographic supportive criteria

Structural Doppler parameters	Mild	Moderate	Severe
Left atrial size	Normal	Normal or dilated	Usually dilated
Left ventricular size	Normal	Normal or dilated	Usually dilated
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal, flail leaflet, ruptured papillary muscle
Mitral inflow (pulsed wave)	A wave dominant	Variable	E wave dominant (usually 1.2 m/s)
Jet density (continuous wave)	Incomplete or faint	Dense	Dense
Jet contour (continuous wave)	Parabolic	Usually parabolic	Early-peaking triangular
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

TABLE 3. Selected eligibility criteria

Inclusion criteria
1. Moderate mitral regurgitation in the judgment of the clinical site echocardiographer, as assessed by transthoracic echocardiography with the integrative method
2. Coronary artery disease amenable to coronary artery bypass grafting and a clinical indication for revascularization
3. Age ≥18 y
4. Ability to sign informed consent and release of medical information forms
Key exclusion criteria
1. Any evidence of structural (chordal or leaflet) mitral valve disease
2. Inability to derive effective regurgitant orifice and left ventricular end-systolic volume index by transthoracic echocardiography
3. Planned concomitant intraoperative procedures (with exception of maze procedure or closure of patient foramen ovale or atrial septal defect)
4. Previous surgical or percutaneous mitral valve intervention
5. Contraindication to cardiopulmonary bypass
6. Clinical signs of cardiogenic shock at the time of randomization
7. Treatment with long-term intravenous inotropic therapy at the time of randomization
8. ST-segment elevation myocardial infarction requiring intervention within 7 days before randomization

sample collections are performed intraoperatively, and additional blood and urine collections are made 6 and 12 months after randomization. Physical examination, New York Heart Association functional classification, angina class determination, echocardiography, and quality of life assessment 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 postoperative months. Direct cost data are obtained quarterly for all randomized patients. A minimum of 2 years of follow-up is intended, although the primary end point is determined at 1 year.

Sample Size

For calculation of sample size, we assumed the mean baseline LVESVI in the target population to be 80 mL/m² (normal LVESVI approximately 25 mL/m²). For patients randomized to undergo 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 mitral valve repair in addition to CABG. Assuming that baseline and 12 month LVESVI in both arms follow a gamma distribution with a common SD 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 with a .05 level 2-tailed Wilcoxon rank sum test. The choice of the Wilcoxon rank sum test for the primary analysis was motivated by the expectation of a relatively substantial amount of nonignorable missing data, primarily as a result of patient death; 1-year mortality is expected to range from 10% to 15% and may 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 left ventricular function at 6, 12, and 24 months will allow examination of the success of the revascularization component of the procedure. The interaction between the preoperative plan for revascularization, any variation from the plan, the resulting change in global and regional left ventricular function, and associated change in the severity of IMR will thus be evaluated. This analysis may identify patient subpopulations that differ in meeting the primary and secondary end points and are perhaps more responsive to revascularization alone.

DISCUSSION

The cardiac surgical 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 IMR 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; however, lessons have been learned through the CTSN 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 and mitral valve procedures at the clinical sites. An extensive evaluation of the protocol, the structure of the CTSN, 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 establishment of 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 mitral regurgitation. A review of the Duke Cardiovascular Database revealed that patients often have a change in mitral regurgitation severity grade when evaluated by TEE in the operating room. In a series of 430 patients with both preoperative TTE and intraoperative TEE, 19% of patients with mild mitral regurgitation documented preoperatively were found to have moderate mitral regurgitation in the operating room. Among patients who had moderate mitral regurgitation preoperatively, 14% were found to have severe mitral regurgitation in the operating room. The clinical decision making in these cases was undoubtedly driven by the intraoperative TEE findings; however, such patients would not be eligible for this trial. The more common occurrence of a reduction in the severity of mitral regurgitation seen on intraoperative TEE (37% of cases of preoperative moderate mitral regurgitation determined intraoperatively to be mild) does not prevent enrollment in the protocol as designed, because the qualifying echocardiogram is the preoperative TTE study. The protocol development committee, in collaboration with the echocardiographic core laboratory leadership, therefore recommended that the determination of degree of mitral regurgitation be made by the site echocardiographer from the TTE according to all the primary and secondary criteria outlined in [Tables 1 and 2](#).

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 interactions 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 coronary artery disease and IMR has generally related to a qualitative assessment of the severity of mitral regurgitation, the presence of heart failure symptoms, and the correlation of coronary artery disease 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 mitral valve 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 affected if only patients with IMR toward the lower end of the moderate scale are enrolled. Similar concerns have been raised regarding patient recruitment in trials of percutaneous patent foramen ovale closure. CTSN cardiologists and surgeons realized that joint evidence-based decision making and clinical equipoise would be required to enable patient enrollment.

The dynamic nature of IMR was also found to be a major impediment to patient enrollment. Clinically indicated TTE studies, performed with variable image acquisition, were frequently found to demonstrate suitable IMR severity but failed to capture either the primary end point measure (LVESVI) or the ERO area. Subsequent research TTE studies, performed under the conditions of optimal medical therapy for ischemia and after diuresis, frequently then failed to meet the criteria for mitral regurgitation severity. Thus although such patients had the appropriate substrate for enrollment in the trial and underwent treatment for IMR of the severity seen on presentation, they were not eligible for randomization. This finding led to site-specific improvements in the quality of clinical TTE, 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 previous cardiac surgery, planned concomitant surgical correction of atrial fibrillation, and a rigid threshold defining exclusion for pulmonary hypertension regardless of its relationship to the degree of mitral regurgitation. Revisions to the eligibility criteria were approved by the data and safety monitoring board in May 2009.

After this intensive 2-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 CTSN for the incorporation of ancillary and satellite sites, and 12 additional sites have been activated. As of this writing, the Surgical Interventions for Moderate Ischemic Mitral Regurgitation 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 this 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 IMR has severely limited the ability of surgeons and cardiologists to determine the best options for these patients.

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APPENDIX E1. CARDIOTHORACIC SURGICAL TRIALS NETWORK (CTSN)

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