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

Louis P. Perrault, MD, PhD,^a Alan J. Moskowitz, MD,^b Irving L. Kron, MD,^c Michael A. Acker, MD,^d Marissa A. Miller, DVM, MPH,^e Keith A. Horvath, MD,^f Vinod H. Thourani, MD,^g Michael Argenziano, MD,^h David A. D'Alessandro, MD,ⁱ Eugene H. Blackstone, MD,^j Claudia S. Moy, PhD,^k Joseph P. Mathew, MD, MHSc,^l Judy Hung, MD,^m Timothy J. Gardner, MD,ⁿ and Michael K. Parides, PhD^b

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

From the Department of Surgery,^a Montreal Heart Institute, University of Montréal, Montréal, Québec, Canada; International Center for Health Outcomes and Innovation Research (InCHOIR) in the Department of Health Evidence and Policy,^b Mount Sinai School of Medicine, New York, NY; Division of Thoracic and Cardiovascular Surgery,^c University of Virginia School of Medicine, Charlottesville, Va; Division of Cardiovascular Surgery,^d University of Pennsylvania, Philadelphia, Pa; Division of Cardiovascular Sciences,^e National Heart, Lung, and Blood Institute, Bethesda, Md; NIH Heart Center at Suburban Hospital,^f Bethesda, Md; Division of Cardiothoracic Surgery,^g Emory University Hospital Midtown, Atlanta, Ga; Division of Cardiothoracic Surgery,^h Columbia University Medical Center, New York, NY; Department of Cardiovascular and Thoracic Surgery,ⁱ Montefiore-Einstein Heart Center, New York, NY; Department of Thoracic and Cardiovascular Surgery,^j Cleveland Clinic, Cleveland, Ohio; National Institute of Neurological Disorders and Stroke,^k Bethesda, Md; Department of Anesthesiology,^l Duke University Medical Center Durham, NC; Division of Cardiology,^m Massachusetts General Hospital, Boston, Mass; and Center for Heart & Vascular Health,ⁿ Christiana Care Health System, Newark, Del.

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Address for reprints: Michael K. Parides, PhD, InCHOIR, Department of Health Evidence and Policy, Mount Sinai School of Medicine, NY (E-mail: michael.parides@mssm.edu).

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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 extra-ventricular Dacron patches and balloons¹⁴; external infarct plication sutures¹⁵; reduction of leaflet tethering by cutting a limited number of secondary chordae^{16,17}; edge-to-edge suture creating a double orifice valve¹⁸; LV restoration procedure with improvement of papillary muscle orientation¹⁹; 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,

FIGURE 1. Severe mitral regurgitation trial design schematic. *MR*, Mitral regurgitation; *CABG*, coronary artery bypass grafting; *LVESVI*, left ventricular end-systolic volume index; *QoL*, quality of life; *LOS*, length of stay; *LVEF*, left ventricular ejection fraction; *AEs*, adverse events.

unexpected adverse events for institutional review board reporting purposes. Trial oversight is provided by an independent data safety and monitoring board.

CHARACTERIZATION OF PATIENT POPULATION

The patient population for this trial consists of patients with severe ischemic MR (often with tethering as a major mechanism) with and without the need for concomitant coronary artery bypass surgery (Table 1). The degree of MR is assessed by transthoracic echocardiogram, in the judgment of the clinical site echocardiographer. Subsequently, all echocardiograms are overread by the echocardiography core laboratory. If site investigators have questions about the degree or etiology of MR (ie, the presence and contribution of structural valve disease), echocardiograms can be transmitted, via a secure Web-based system, for feedback from the core laboratory before patient randomization.

TABLE 1. Selected inclusion criteria

1. Chronic severe ischemic mitral regurgitation (often with tethering as a major mechanism) in the judgment of the clinical site echocardiographer, assessed by transthoracic echocardiogram. Assessment of mitral regurgitation will be performed using an integrative method.
2. Eligible for surgical repair and replacement of mitral valve
3. Coronary artery disease with or without the need for coronary revascularization

Initially, the entry criteria established the degree of MR based on assessment of effective regurgitant orifice area (EROa) alone with severe MR defined as an EROa of 0.4 cm² or more. However, screening efforts identified patients with multiple quantitative echocardiographic indicators of severe MR, who had an EROa of less than 0.4 cm², who were unable to be enrolled. In this ischemic population, this was primarily observed in patients with eccentricity of MR jets. As a result, the assessment of MR was modified to the integrative method. If the EROa in a patient is found to be less than 0.4 cm², then additional assessments of the degree of MR are guided by other color Doppler quantitative methods (jet area/left atrial area ratio, vena contracta) and supportive criteria in an integrated fashion (Appendix 2).

Because patients with MR owing to structural disease have a different prognosis from that of those who have ischemic MR, such patients are excluded from entry. In addition, patients with poor operative risk owing to pulmonary hypertension, severe renal disease, and hepatic disease are also excluded from randomization. Selected exclusion criteria are depicted in Table 2.

PRIMARY END POINT AND ANALYSIS

The primary end point for the trial is the degree of LV remodeling, as assessed by LVESVI at 12 months after intervention by transthoracic echocardiogram. The null hypothesis is that there is no difference in the postoperative LVESVI between patients randomized to undergo mitral valve repair compared with patients randomized to undergo mitral valve replacement.

The primary null hypothesis will be tested in an intent-to-treat analysis using 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 owing to patient mortality. One-year incidence of mortality is expected to range from 15% to 20% and potentially differ between randomization arms. Some patients, expected to be few, may also be missing echocardiographic assessment for reasons directly related to the severity of their illness. These missing data cannot be considered ignorable, and imputation requires strong untestable assumptions.

A number of additional secondary analyses are planned to supplement the primary analysis and aid interpretation

TABLE 2. Selected exclusion criteria

Selected exclusion criteria

1. Any evidence of structural mitral valve disease or ruptured papillary muscle
2. Inability to derive effective regurgitant orifice area and end-systolic volume index by transthoracic echocardiography
3. Planned concomitant intraoperative procedures (except tricuspid valve repair, patent foramen ovale closure, atrial septal defect closure, or maze procedure)
4. Prior mitral valve repair
5. Contraindications to cardiopulmonary bypass
6. Clinical signs of cardiogenic shock at the time of randomization
7. Treatment with chronic intravenous inotropic therapy at the time of randomization
8. Severe irreversible pulmonary hypertension in the judgment of the investigator
9. ST-segment elevation myocardial infarction requiring intervention within 7 days before randomization
10. Congenital heart disease (except patent foramen ovale or atrial septal defect)
11. Chronic renal insufficiency defined by creatine ≥ 2.5 or chronic renal replacement therapy
12. Evidence of cirrhosis or hepatic synthetic failure
13. Excessive surgical risk (in the judgment of the surgical investigator)
14. Recent history of psychiatric disease that may impair compliance with protocol

of the trial's results. These include repeating the primary analysis on the ranked differences of LVESVI from randomization to 12 months and extending the Wilcoxon rank sum test to adjust for baseline LVESVI (ie, a "nonparametric analysis of covariance"). Because this is a randomized trial, no baseline differences are expected. A secondary analysis of the primary end point will also be performed by jointly modeling LVESVI and time to death using a model suggested by Xu and Zeger.²³ This model uses a latent variable approach, whereby conditional on this latent variable LVESVI and time to death are assumed to be independent.

SAMPLE SIZE ESTIMATION

Sample size estimates to ensure the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing mitral valve repair were based on data derived from the clinical literature.²⁴⁻²⁶ We assume that the mean baseline LVESVI in the target population is 100 mL/m². For patients randomized to receive mitral valve repair, we anticipate a 20% reduction in LVESVI, or an absolute change of 20 mL/m². We believe a meaningful effect worth detecting is an additional 15% (15 mL/m²), or a total reduction of 35% or 35 mL/m² for patients undergoing mitral valve replacement. 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 250 patients, randomized with equal probability to each arm, provides approximately 90%

power to detect a difference of 15 mL/m². Power is based on a .05 level 2-tailed Wilcoxon rank sum test. The sample size takes account of a single interim analysis to be performed in addition to the final analysis.

INTERIM ANALYSIS

We will perform a single interim analysis with respect to the primary end point to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of this analysis is at .5 on the information scale, that is, after half of the patients (125) reach the primary end point. We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look. The resulting critical values to be used for each analysis are 2.963 at the first interim analysis and 1.969 at the final analysis. In addition to the ethical concern of continuing a trial that shows a clear benefit in favor of one treatment, there is also a corresponding ethical concern of continuing a trial that has little chance of ever showing a benefit of one treatment compared with the other. The trial's conditional power, under the original alternative hypothesis, will be computed at the interim look, which will allow the data safety and monitoring board to use this to determine whether randomization, if not completed, should be halted for futility.

CHARACTERIZATION OF TREATMENT INTERVENTIONS

In designing this trial, the investigators spent considerable time specifying the guidelines that define the surgical technique. These specifications include designation that all procedures must be performed with full or partial sternotomy or with a right thoracotomy with cardiopulmonary bypass according to local standards. Exposure of the mitral valve is accomplished by either the left atrial (Waterston groove) or biatrial approach. *Mitral valve replacement* is accomplished with complete chorda sparing. The technique for subvalvular preservation, the type of prosthesis (mechanical or bioprosthesis), and technique of suture placement are selected by the surgeon, at his or her preference. *Mitral valve repair* is accomplished using an undersized annuloplasty ring. The ring size is determined by the surface area of the anterior mitral leaflet as measured by the intertrigonal distance and anterior leaflet height. A subvalvular procedure can be performed if tethering is present. Secondary mitral valve replacement can be performed at the surgeon's discretion if residual MR is significant after LV saline infusion testing or at transesophageal echocardiography after cardiopulmonary bypass. *Coronary artery bypass grafting* is performed using standard techniques and 2-stage venous cannulation. Conduit selection and harvesting methods are not prescribed, although use of the left internal thoracic artery is recommended when a graft to the left anterior descending coronary artery is indicated. Complete

revascularization should be accomplished, within the judgment of the surgical investigator.

SECONDARY END POINTS

Mortality

All-cause mortality is a particularly important secondary end point. Given that this trial's primary end point is an echocardiographic assessment (LVESVI), it will be important to supplement the finding of a treatment effect (or lack of one) for the primary end point with a corresponding effect on a clinical end point such as all-cause mortality. The trial is not powered to detect small mortality differences; however, an observed difference in mortality, consistent in direction with that observed for LVESVI, will serve to validate the trial's findings. The proportion of deaths between randomization groups, both at 12 and 24 months, will be compared by a χ^2 test. Time to death will be described by Kaplan-Meier curves and differences between randomization groups assessed via the log-rank test.

Quality of Life, Functional Status, and Neurocognition

Several measures of quality of life will be used to capture both overall quality of life and disease-specific quality of life. Overall quality of life will be captured with the short form health survey (SF-12) and EuroQol, whereas disease-specific quality of life will be measured with the Minnesota Living with Heart Failure Score and the Duke Activity Status Index. Measurements with these instruments will occur at 30 days and at 6, 12, and 24 months. Functional status will be captured through measurement of cardiopulmonary stress testing, as clinically tolerated, New York Heart Association heart failure class, and the Canadian Cardiovascular Society angina class at 6 and 12 months after randomization. Neurocognitive performance at 12 months will be assessed using the following battery of tests: Hopkins Verbal Learning Test,²⁷ Trail Making Tests A and B,²⁸ Medical College of Georgia Complex Figures,²⁹ Boston Naming Test,³⁰ Digit Span,³¹ and Digit Symbol Substitution Test.³¹

Adverse Events, Hospitalization, and Economic End Points

Serious and protocol-defined adverse events are measured prospectively and differences between treatment groups will be assessed using Poisson regression. In addition, major adverse cardiac events are being assessed. These events are a nonweighted composite end point composed of death, stroke, worsening heart failure (+1 New York Heart Association class), hospitalization for congestive heart failure, and mitral valve reintervention. The proportion of patients experiencing a major cardiac event will be compared by χ^2 test at 12 and 24 months. Economic end points are important as well. Hospital resource use will be captured by measuring overall length of stay and intensive care unit

days during the index hospitalization, as well as readmission rates for all causes and specifically for heart failure. Days alive out of the hospital will be compared between treatment groups accounting as a percent of survival. Hospital costs will be calculated from hospital charges using the institution-specific ratio of cost to charges. The incremental cost-effectiveness ratio in units of dollars per quality-adjusted life years will be calculated when the differences in health outcomes are associated with a difference in cost.

DISCUSSION

Patients with severe ischemic MR constitute a large and growing population with a dismal prognosis. Both mitral valve repair and replacement procedures are widely used to treat this problem. Yet, there is considerable controversy over the relative benefits of these 2 treatment approaches and no definitive trials to guide treatment decisions. The CTSN identified this as a high-priority concern and chose to address it as one of its first randomized trials. The CTSN's severe MR trial, which is in essence a comparative effectiveness trial, is designed to provide insights into a range of outcomes that are relevant to clinicians and patients for making treatment decisions and should expand the methodology for conducting surgical trials.

Ideally, clinical trials should be powered to make definitive statements about all of the relevant clinical end points. However, providing adequate power for all of the relevant clinical end points, including mortality, in the severe MR trial would have required a sample size in the range of several thousand patients. It would not have been feasible to enroll and complete follow-up for all patients and analyze and disseminate the results of such a trial within the 5-year term of the CTSN. As such, the CTSN investigators chose LV remodeling as the primary end point. Specific guidelines were created for ensuring rigorous and standardized measurement of this end point, and an independent core laboratory was established to overread all echocardiograms in this trial and provide real time consultation to investigators during the enrollment process. Mortality is the most important secondary end point and will provide corroborating evidence needed to interpret the differences observed in ventricular remodeling.

A critical dimension for making treatment decisions is information about the expectations for quality of life after surgery. Particularly relevant to this target population are the impact of treatment on congestive heart failure and angina pectoris symptoms. To measure treatment effects on congestive heart failure symptoms and functional status, the trial is measuring New York Heart Association classification, Minnesota Living with Heart Failure Score, the Duke Activity Status index, and peak volume of oxygen use. Given that one of the concerns about mitral valve repair is that it might not be as effective as replacement in controlling MR, it is important that the impact of heart failure on quality of life and functional status be measured longitudinally throughout the

follow-up period of the trial. The fact that the trial includes general measures of quality of life (ie, the SF-12 and Euro-Qol) will allow us to interpret the observed disease-specific symptoms in the broader context of physical and mental quality of life experienced by patients. These health status measures will also be used to calculate quality-adjusted life-years for the cost-effectiveness analysis.

Another critical concern of patients undergoing cardiac surgery is the impact of surgery on brain functioning. This trial, therefore, has been designed to carefully measure cognitive functioning and neurologic events over the 2-year time period. An independent neurocognitive core laboratory was established to train investigators in neurocognitive testing, score all test results, and provide quality assurance relative to this measure throughout the trial. The investigators are also exploring alternative methods for analyzing neurocognitive data, which have the potential to address some of the controversies regarding analysis in this field.

The severe ischemic MR trial has already enrolled over half of the required patient population. The enrollment rate has increased substantially over time, and completion of enrollment is clearly within sight. The broad spectrum of end points being captured in this trial should address the current dilemmas in choosing an optimal surgical approach for this patient group and provide invaluable information for clinicians and patients alike making this treatment decision.

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APPENDIX 1. Cardiothoracic Surgical Trials Network (CTSN)

National Heart, Lung, and Blood Institute: Marissa A. Miller, Wendy C. Taddei-Peters, Dennis Buxton, Ron Caulder, Nancy L. Geller, David Gordon, Neal O. Jeffries, Albert Lee
National Institute of Neurological Disorders and Stroke: Claudia S. Moy

Canadian Institutes of Health Research: Ilana Kogan Gombos, Jennifer Ralph

Network Chairs: *Christiana Care Health System*, Timothy J. Gardner (Chair); *Brigham and Women's Hospital*, Patrick T. O'Gara, (Co-Chair)

Data Coordinating Center: International Center for Health Outcomes and Innovation Research (InCHOIR) in the Department of Health Evidence and Policy, Mount Sinai School of Medicine, New York, NY, Annetine C. Gelijns, Michael K. Parides, Deborah D. Ascheim, Alan J. Moskowitz, Ellen Moquete, Eric A. Rose, Melissa Chase, Yingchun Chen, Rosemarie Gagliardi, Alejandra Guerchicoff, Lopa Gupta, Alexander Iribarne, Edlira Kumbarce, Ron Levitan, Karen O'Sullivan, Mark J. Russo, Milerva Santos, William Slavik, Alan Weinberg, Martin Wells, Paula Williams, Carrie Wood, Xia Ye

Core Clinical Site Investigators: *Cleveland Clinic Foundation*, Eugene H. Blackstone (Principal Investigator [PI]), A. Marc Gillinov, Tomislav Mihaljevic, Richard A. Grimm, Ben Barzilai, Bruce D. Lindsay, Christine Whitman, Denise Kosty Sweeney, Roberta Palumbo; *NHLBI Clinical Research Scholars*: Gregory Pattakos, Pamela A. Clarke

Columbia University Medical Center, Michael Argenziano (PI), Mathew Williams, Lyn Goldsmith, Rebecca T. Hahn, Linda Gillam, Craig R. Smith, Yoshifumi Naka, Allan Stewart, Allan Schwartz

Duke University, Peter K. Smith (PI), Stacey Welsh, John H. Alexander, Carmelo A. Milano, Donald D. Glower, Joseph P. Mathew, J. Kevin Harrison; *NHLBI Clinical Research Scholars*: Mark F. Berry, Cyrus J. Parsa, Betty C. Tong, Judson B. Williams

East Carolina Heart Institute, T. Bruce Ferguson (PI), Alan P. Kypson, Evelio Rodriguez, Malissa Harris, Brenda Akers, Allison O'Neal

Emory University, John D. Puskas (PI), Vinod H. Thourani, Robert Guyton, Jefferson Baer, Kim Baio, Alexis Neill

Montefiore-Einstein Heart Center, New York, NY, Robert E. Michler (PI), Ricardo Bello, David A. D'Alessandro, Joseph J. DeRose, Jr, Daniel J. Goldstein, Cynthia Taub, Daniel Spevak, Roger Swayze

Montreal Heart Institute, Louis P. Perrault (PI), Arsène-Joseph Basmadjian, Denis Bouchard, Michel Carrier, Philippe Demers, Michel Pellerin, Sophie Robichaud

NIH Heart Center at Suburban Hospital, Keith A. Horvath (PI), Philip C. Corcoran, Michael P. Siegenthaler, Mandy Murphy, Margaret Iraola, Ann Greenberg

University of Pennsylvania, Michael A. Acker (PI), Y. Joseph Woo, Wilson Y. Szeto, Mary Lou Mayer

University of Virginia, Irving L. Kron (PI), Gorav Ailawadi, Karen Johnston, John M. Dent, Sandra Burks, Kim Gahring

Affiliate/Ancillary Sites

Hôpital du Sacré-Cœur de Montréal, Pierre Pagé (PI), Hugues Jeanmart, Philippe Demers, Claude Sauvé, Carole Sirois

Institut Universitaire de Cardiologie et de Pneumologie de Québec, Pierre Voisine (PI), François Dagenais, Eric Dumont, Gladys Dussault

Inova Fairfax Hospital, Alan M. Speir (PI), Niv Ad, Minh Dang

The Ohio State University Medical Center, Chittoor B. Sai-Sudhakar (PI), Danielle Jones

WellStar Health System, Kennestone Hospital, William A. Cooper (PI), Rajnish Prasad, Richard J. Myung, Jennifer LaCorte, Melinda Mock

Satellite Sites

Baylor Research Institute, Michael J. Mack (PI), Robert Smith, William Ryan, Jennifer Withers

Brigham and Women's Hospital, Frederick Y. Chen (PI), R. Morton Bolman III, Anne M. Burgess, Debra Conboy

Jewish and St Mary's Hospital, Mark S. Slaughter (PI), Matthew Williams, Marcus Stoddard, Heather Moody

Mission Hospital, Mark A. Groh (PI), Ben Trichon, Todd Hansen, Claudine Cuento

University of Southern California, Vaughn A. Starnes (PI), Michael Bowdish, Becky Lopez

University of Maryland, James S. Gammie (PI), Mandeep Mehra, Bartley Griffith, Dana Beach

Washington University, Ralph J. Damiano, Jr, (PI), Scott Silvestry, Marc Moon, Jennifer Lawton

Cardiopulmonary Exercise Core Laboratory: *Henry Ford Hospital*, Steven J. Keteyian, Clinton A. Brawner

Echo Core Laboratory: *Massachusetts General Hospital*, Judy Hung, Xin Zeng

Electrophysiology Core Laboratory: *University of Rochester Medical Center*, Jean-Philippe Couderc

Neurocognitive Core Laboratories: *Duke University*, Joseph P. Mathew

Protocol Review Committee: David A. Bull (Chair); Patrice Desvigne-Nickens, Executive Secretary; Dennis O. Dixon, Mark Haigney, Richard Holubkov, Alice Jacobs, Frank Miller, John M. Murkin, John Spertus, Andrew S. Wechsler

Data and Safety Monitoring Board: Frank Selke (Chair); Cheryl L. McDonald, Executive Secretary; Robert Byington, Neal Dickert, Dennis O. Dixon, John S. Ikonidis, David O. Williams, Clyde W. Yancy

Medical Monitors: James C. Fang, Wayne Richenbacher

Overall Event Adjudication Committee: Vivek Rao (Chair); Karen L. Furie, Rachel Miller, Sean Pinney, William C. Roberts

Infection Event Adjudication Committee: Rachel Miller (Chair); Shirish Huprikar, Marilyn Levi

APPENDIX 2. Integrative method criteria for echo assessment of degree of MR

Echo color Doppler criteria			
	Mild	Moderate	Severe
Color flow jet area	<20% of LA area	20% to 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			
VC width (cm)	<0.3	0.3-0.69	≥0.7
EROa (cm ²)	<0.20	0.20-0.29 0.30-0.39	≥0.40
Echo supportive criteria			
	Mild	Moderate	Severe
Structural Doppler parameters			
LA size	Normal	Normal or dilated	Usually dilated
LV 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—PW	A wave dominant	Variable	E wave dominant (E usually 1.2 m/s)
Jet density—CW	Incomplete or faint	Dense	Dense
Jet contour—CW	Parabolic	Usually parabolic	Early peaking—triangular
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

LA, Left atrium; VC, vena contracta; EROa, effective regurgitant orifice area; LV, left ventricular; PW, pulsed wave; CW, continuous wave.