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Severe Ischemic Mitral Regurgitation: Is it Better to Repair or Replace the Valve?

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Abstract:
BACKGROUND Ischemic mitral regurgitation (MR), which develops as a complication of myocardial infarction and adverse left ventricular remodeling, is associated with significant mortality risk over time. Practice guidelines recommend repair or replacement for severe, ischemic MR, but there remains a lack of conclusive evidence to indicate which of these interventions is superior. The choice between these surgical options is characterized by the trade-off between reduced operative morbidity and mortality with repair versus better long-term correction of ischemic MR with replacement. The long-term benefits of repair versus replacement remain unknown, which has led to uncertainty and significant variation in surgical practice.
METHODS The severe MR (SMR) randomized trial was designed to evaluate the safety and effectiveness of mitral valve repair versus replacement in patients with severe ischemic MR. This trial is being conducted as part of the NIH and CIHR supported Cardiothoracic Surgical Trials Network (CTSN) in 22 clinical centers. The primary endpoint for the trial is the degree of left ventricular remodeling, as assessed by Left Ventricular End Systolic Volume Index (LVESVI) at 12 mos post-surgery by TTE (integrative method). Secondary endpoints include mortality, MACE, adverse events, recurrent MR, QoL, and hospitalizations (24 mos).
RESULTS The patient population consists of 251 patients with severe ischemic MR (often with tethering as a major mechanism) with and without need for CABG (table). The mean baseline LVESVI was 63.4 (±26.8). The average follow-up time of the cohort is 19 months as of 6/18/13 and all patients have recently completed their one-year endpoint assessment. Primary and secondary endpoint data will be presented.
CONCLUSIONS The approach to managing ischemic MR remains controversial. The results of the trial will help delineate the appropriate therapeutic approach for this growing patient population.

Baseline Characteristics

	MV Replacement (N=125)	MV Repair (N=126)
Male	78 (62%)	77 (61%)
Age	67.9 ±9.0	69.0 ±10.2
LVEF (%)	40.0 ±11.4	42.4 ±11.4
Crea (mg/dL)	1.3 ±1.0	1.3 ±0.7
NYHA		
Class I & II	47 (38%)	53 (42%)
Class III & IV	76 (61%)	69 (55%)
MLHF	50.0 ±27.4	46.1 ±27.2
Angina Scale (CSCC)		
None	56%	45%
III & IV	17%	25%
SF-12 (Physical)	37.2 ±7.2	37.3 ±8.1

Clinical Trial:
Hypothesis and Purpose:The overall objective of this study is to evaluate the safety and effectiveness of mitral valve repair versus mitral valve replacement for patients with severe ischemic mitral regurgitation (MR). Specifically, this study compares mitral valve repair with annuloplasty and a sub-valvular procedure for severe tethering to mitral valve replacement and complete preservation of the sub-valvular apparatus. The primary aim of this trial is to evaluate the impact of these two surgical approaches on left ventricular remodeling. The null hypothesis is that there is no difference in the post surgical LVESVI between patients randomized to undergo mitral valve repair compared to patients randomized to undergo MV replacement. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level two-tailed Wilcoxon Rank-Sum test. Secondary aims of this trial include assessment of the impact of these two surgical interventions on cardiac performance, mortality, adverse events, quality of life, functional status, severity of MR, and health resource use.
Study Design and Methods: This is a parallel groups, prospective, multi-center, randomized controlled clinical trial. The trial will be conducted in highly experienced clinical centers participating in the NIH/CIHR-supported CT Surgery Network. The estimated enrollment period is 24 months (n=250) and all patients will be followed for 24 months post-randomization. Endpoints will be measured at 30 days, 6, 12, and 24 months.
Sample Size: The sample size is 250 patients.
Population Studied:
Characterization of Patient Population

The patient population for this trial consists of patients with severe ischemic mitral regurgitation with and without the need for concomitant coronary artery bypass surgery. All patients who meet the eligibility criteria may be included in the study regardless of gender, race or ethnicity.
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 (Zoghbi W. et al. J. American Society of Echocardiography. 2003:16:777-802). Quantitative guidelines as proposed would be: ERO ≥ 0.4 cmsq. If ERO < 0.4, then the degree of mitral regurgitation will be guided by other color Doppler quantitative methods (jet area/left atrial area ratio, vena contracta, supportive criteria in an integrated fashion.
2. Eligible for surgical repair and replacement of mitral valve
3. Age ≥ 18 years
4. Able to sign Informed Consent and Release of Medical Information forms
5. Coronary artery disease with or without the need for coronary revascularization
Selected Exclusion Criteria
1. Any evidence of structural (chordal or leaflet) mitral valve disease or ruptured papillary muscle
2. Prior mitral valve repair
3. Severe irreversible pulmonary hypertension in the judgment of the investigator
4. Contraindications to CPB
5. Inability to derive ERO and ESVI by transthoracic echocardiography
6. Planned concomitant intra-operative procedures (with the exception of tricuspid valve repair, closure of patent foramen ovale [PFO] or atrial septal defect [ASD], or Maze procedure)
7. Clinical signs of cardiogenic shock at the time of randomization
8. Treatment with chronic intravenous inotropic therapy at the time of randomization
9. ST segment elevation MI requiring intervention within 7 days prior to randomization
10. Congenital heart disease (except PFO or ASD)
11. Evidence of cirrhosis or hepatic synthetic failure
12. Excessive surgical risk (in the judgment of the surgical investigator)
Intervention(s):
Mitral Valve Replacement Group
Mitral valve replacement will include complete preservation of the subvalvar apparatus. The technique of preservation, choice of prosthetic valve, and technique of suture placement will be dependent on the surgeon's preference. The prosthetic valve will be tested for paravalvular leaks using the left ventricular saline infusion test.
Mitral Valve Repair with Annuloplasty Group
The annuloplasty ring will be chosen by the surgeon. The ring is sized to the anterior leaflet and intertrigonal distance. A semi-rigid or rigid annuloplasty ring will be used and. If tethering is present, a subvalvar procedure may be performed.
Power Calculations: The sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing mitral valve repair. 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 the standard deviation for the change in both arms is 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 in LVESVI between patients randomized to mitral valve repair and patients randomized to mitral valve replacement. Power is based on a 0.05 level two-tailed Wilcoxon Rank-Sum test. The sample size takes account of a single interim analyses to be performed in addition to the final analysis.
Primary End Points: The primary endpoint for the trial is the degree of left ventricular remodeling, as assessed by change in Left Ventricular End Systolic Volume Index (LVESVI) between randomization and 12 months post-surgical intervention, measured with transthoracic echocardiography.
Secondary End Points: This trial assesses several secondary endpoints. The principal secondary endpoint for the trial is all-cause mortality. This endpoint provides complementary clinical information to the primary physiological endpoint for assessing the overall benefits of treatment.
Additional secondary endpoints for the trial are as follows:
Functional Status, Neurocognition and Hospitalizations
o MACE (death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, mitral valve re-intervention)
o NYHA Classification
o Peak VO2 (assessed by a cardio-pulmonary stress test)
o Angina class
o Neurocognitive outcomes
o LOS for the index hospitalization and discharge location
o Re-admission rates (within 30 days and long term for all, cardiovascular, and heart failure re-admissions) and days alive out of hospital (as a percent of survival)
Physiologic Measures
o Echo (Quantification of MR (Effective Regurgitant Orifice Area [ERO]), Quantification of mitral valve area, MV and subvalvular assessments, LV size, function and geometry (including, but not limited to LVEF, LVESVI, LV sphericity), RV size and function, LA dimension, MV tethering, Intracardiac pressures, Regional wall motion)
o Adequacy of revascularization
Quality of Life and Economic Measures
o Minnesota Living with Heart Failure (MLHF) score
o SF-12
o EuroQoL
o DASI
o Cost and cost effectiveness
Safety
o Incidence of serious adverse events
o Reoperation for MR and freedom from re-operation in general
Peri-operative Measures
o Operative time, cardiopulmonary bypass (CPB) and cross clamp time
o Blood loss and transfusion
Outcome(s)[Statistical Plan or Main Results]:
Methods of Analysis

The primary outcome of this trial is the degree of left ventricular remodeling at 12 months post surgical intervention, assessed by Left Ventricular End Systolic Volume Index (LVESVI). The null hypothesis is that there is no difference in the post surgical LVESVI between patients randomized to undergo mitral valve repair compared to patients randomized to undergo MV replacement. 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 15-20%, 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 we are hesitant to impute such data using models whose assumptions would not be testable. Absent these concerns, the primary analysis would be by analysis of covariance.
The Wilcoxon Rank-Sum test allows a straightforward incorporation of patients with non-ignorable missing data into the analysis; thereby, avoiding the potential bias of relying on a complete case analysis or on an analysis that assumes the missing data mechanism is missing at random (MAR). For the analysis, patients who die will be assigned ranks lower than the lowest observed rank, in ascending order based on the time of death (earliest to latest). Patients whose missing data are determined by independent adjudicators to be due to severity of illness will be given the next lowest set of tied ranks. We expect relatively few patients to be missing 12 month LVESVI due to withdrawal or refusal. Patients with missing data not due to severity of illness or mortality will have their 12 month LVESVI imputed via multiple imputation (Rubin) assuming that the data are MAR, i.e., the missing nature of the variable is independent of the value of the variable given the observed data. The specific imputation model to be used will be determined prior to examination of any outcome data, but will include measured LVESVI at six months.
The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for change in LVESVI for each patient with missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. The imputation models will reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data.
After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment effect. We propose to use 15 datasets (an odd number to allow use of one of the datasets to represent the median analytic result). An illustration of the use of this general imputation approach for rank based methods is provided in Mogg and Mehrotra (Statistics in Medicine, 2007). For simplicity our primary analysis will not be stratified by clinical center, although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.
Interim Analysis
We plan to perform a single interim analysis with respect to the primary endpoint to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of this analysis is at 0.5 on the information scale, i.e., after one-half of patients (125 reach the primary endpoint. The utility of performing this analysis will depend on the rate of accrual of patients into the trial. We assume an accrual rate of approximately sixteen to seventeen (16-17) patients per month, or slightly more than two (2) patients per center per month. As the decision to terminate early would likely occur after most, if not all, patients were randomized, the principal benefit of early termination would be prompt dissemination of results, and no further randomization into an inferior treatment. A group sequential procedure will be used to allow for flexibility in the number and timing of interim analyses should the DSMB choose to modify the proposed plan, or should accrual mitigate the usefulness of an interim look. 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, 1.969 at the final analysis.
Author Disclosure Information: M.A. Acker: Consultant/Advisory Board; Modest; Thoratec Inc.. M.K. Parides: None. L.P. Perrault: None. A.J. Moskowitz: None. P. Voisine: None. P.K. Smith: None. A.C. Gelijns: None. J.W. Hung: None. E. Blackstone: None. J. Puskas: None. M. Argenziano: None. J.S. Gammie: None. M. Mack: None. D.D. Ascheim: Consultant/Advisory Board; Modest; Backbeat Medical, Inc., Velomedix. E. Bagiella: None. T. Ferguson: None. K. Horvath: None. N.L. Geller: None. M.A. Miller: None. J.Y. Woo: None. D.A. D'Alessandro: None. G. Ailawadi: Research Grant; Significant; Astra Zeneca (investigation of aneurysms). Speakers Bureau; Modest; St. Jude speaker, Atricure proctor. Consultant/Advisory Board; Modest; Abbott, Edwards. F. Dagenais: None. T.J. Gardner: None. P.T. O'Gara: None. R. Michler: None. I.L. Kron: None.

Application Information (Complete):
*Is this a Late Breaking Clinical Trial (1st presentation of completed trial), a Clinical Trial Update or High Impact Information from Clinical Registries? : Late Breaking Clinical Trial
*Is this a study testing a treatment/intervention to improve health outcomes?: Yes
*Is this a First in Man therapeutic trial?: No
*Multi-Center study?: Yes
*Number of Sites: : 22
*Final Enrollment Month: April
*Final Enrollment Year: 2012
*Final Data Availability (Month): June
*Final Data Availability (Year): 2013
*Results being presented elsewhere?: No
*Disclosure: There are no unlabeled/unapproved uses of drugs or products.
*Description : The CTSN SMR trial was designed to evaluate the safety and effectiveness of mitral valve repair versus replacement in patients with severe ischemic MR.

Principal Investigator (Complete):
First Name: : Annetine
Last Name: : Gelijns

Payment (Complete): Your credit card order has been processed on Monday 24 June 2013 at 3:07 PM.
Additional Info (Complete):
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If there is an ACRONYM for your trial/study, please type it in the space provided. If no, please enter No in the space provided. : CTSN SMR
Has this research received full or partial funding from the American Heart Association?: No

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