Keynote Lecture Series

Repair or replace for severe ischemic mitral regurgitation: prospective randomized multicenter data

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Ischemic mitral regurgitation (IMR) is a subset of functional mitral regurgitation (MR) that has the potential to impact an increasing number of patients in the future. This is in the context of a worldwide population, which continues to live longer with improved survival after myocardial infarction. Substantial data have accumulated over the past few decades demonstrating the negative effects of IMR. Further, significant research has been done to define the optimal surgical approach and several studies have compared mitral repair versus replacement for patients with severe mitral regurgitation (SMR). Studies supporting performance of mitral repair cite superior operative morbidity and mortality rates, while proponents of mitral replacement cite improved long-term durability and correction of MR. Lack of clinically robust Level I randomized controlled trial data have curtailed attempts to better define appropriate surgical treatment allocation over the past few decades. Recently, however, the Cardiothoracic Surgical Trials Network (CTSN) conducted the first randomized controlled trial, funded by the National Heart, Lung, and Blood Institute, the National Institute for Neurological Diseases and Stroke and the Canadian Institute for Health Research, to compare the performance of mitral repair versus replacement for SMR. Herein, the present review describes the design, results and implications of the CTSN SMR trial and its efforts to identify the most efficacious surgical approach to SMR. This review also describes CTSN investigation to predict the recurrence of MR after mitral repair.

Keywords: Ischemic; mitral regurgitation (MR); repair; replacement

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Ischemic mitral regurgitation (IMR) has historically been associated with poor surgical outcomes. A complication of myocardial ischemia, IMR is a subset of functional mitral regurgitation (MR) that has the potential to impact an increasing number of patients in the future due to the world's ageing population and improved survival after myocardial infarction. Substantial data have accumulated over the past few decades demonstrating the negative effects of IMR (1,2). While a spectrum of severity (mild, moderate and severe) exists for IMR, even mild forms of MR after myocardial infarction have been associated with significantly increased cardiovascular mortality (17%) compared to patients without MR (2).

The mechanisms underlying IMR are primarily related to the effects of left ventricular (LV) remodeling after myocardial infarction. The two most significant processes of LV remodeling underlying the development of MR affect (I) the papillary muscles and (II) the mitral annulus. Following myocardial ischemia, remodeling changes occurring in the inferior and posterior aspects of the LV may result in displacement of the papillary muscles away from the mitral annulus, resulting in restricted mitral valve leaflet motion due to tethering. Concomitantly, global LV dilation resulting from altered cardiac myocyte dysfunction after infarction may cause annular enlargement of the mitral valve. This results in reduced central coaptation of

the anterior and posterior mitral valve leaflets. The negative influence of the LV remodeling process through these two primary mechanisms may result in IMR that is further compounded by LV dysfunction and the decrease in force generated by an infarcted LV to close the mitral leaflets and overcome the effects of leaflet tethering.

The treatment of IMR has been an issue of continued debate for several decades. Myocardial revascularization alone has proven insufficient for cases of moderate to severe mitral regurgitation (SMR), with evidence of an equivalent degree of MR persisting in up to 77% of cases (3). The surgical treatment of the mitral valve for moderate to SMR has evolved with repair favored over replacement due to lower perioperative mortality (4,5). The downside of repair is the high recurrence rate associated with reduction annuloplasty alone. While innumerable approaches to mitral repair exist (6-12), the benefits of a chordal sparing technique when performing mitral replacement have been well documented (13). As a result, substantial research has been done to define the optimal surgical approach and several studies have compared mitral repair and replacement for patients with SMR (4,13-16). Studies supporting performance of mitral repair cite superior operative morbidity and mortality rates, while proponents of mitral replacement cite improved long-term durability and correction of MR. Contributing to the controversy regarding the optimal surgical treatment allocation for SMR has historically been a lack of high-level evidence, limited to retrospective analyses often with heterogeneous patient populations and the reporting of short-term outcomes. In lieu of these limitations, professional societal recommendations and practice guidelines have identified SMR as a Class I indication for surgical treatment (17,18). However, recommendations for a proper surgical approach (repair versus replacement) remain less definitive.

Recently, the Cardiothoracic Surgical Trials Network (CTSN) conducted the first randomized controlled trial, funded by the National Heart, Lung, and Blood Institute, the National Institute for Neurological Diseases and Stroke and the Canadian Institute for Health Research, to compare the performance of mitral repair versus replacement for SMR (19). Herein, the present review describes the design, results and implications of the CTSN SMR trial and its efforts to identify the most efficacious surgical approach to SMR.

CTSN SMR trial: study design

The CTSN SMR Trial was designed to evaluate the safety and efficacy of mitral repair versus replacement for SMR. The primary outcome of interest was the degree of LV remodeling as assessed by changes in LV end-systolic volume index (LVESVI) at 12 months after mitral repair or replacement by transthoracic echocardiography. Secondary outcomes included differences in survival, functional status, quality of life, length of stay, hospital readmission, recurrent MR, LV ejection fraction, adverse events and costs. The study represents a parallel design, prospective, multi-institution, randomized (1:1) clinical trial. Participating centers represented highly experienced CTSN centers, performing large volumes of mitral operations. All patients were followed up for 24 months after randomization and end points were measured at 30 days as well as 6, 12 and 24 months.

In addition to the randomization process, patient inclusion and exclusion criteria were designed to minimize heterogeneity between treatment groups (15). Eligible patients for enrollment included those with SMR with or without a need for concomitant coronary artery bypass grafting. SMR was assessed by transthoracic echocardiography as per the judgment of the designated echocardiographer at each clinical site. In general, SMR was defined by echocardiographic evidence of an effective regurgitant orifice area (EROa) greater than or equal to 0.4 cm^2. Other inclusion criteria included eligibility status for either mitral repair or replacement operations as well as candidacy for surgical myocardial revascularization if necessary. The most significant exclusion criterion included those with MR due to structural mitral valve disease.

Surgical treatment groups consisted of either mitral repair or replacement with or without coronary artery bypass graft (CABG) surgery where appropriate. Regardless of technique, all procedures were performed via full or partial sternotomy or via a right thoracotomy with the use of cardiopulmonary bypass. All mitral replacements were performed with complete chordal sparing. All mitral repair operations were performed with undersized complete rigid or semi-rigid annuloplasty rings with or without the need for CABG and subvalvular procedures to address the presence of chordal tethering. The technique for CABG was not prescribed, however left internal thoracic artery conduit choice was encouraged.

CTSN SMR trial: results and implications

Through the recruitment of a multi-institution study population from 22 clinical centers, the CTSN SMR Trial

data represent generalizable results for patients with SMR with respect to the impact of mitral valve repair versus replacement on LV remodeling, mortality, morbidity and quality of life over a 24-month follow-up period.

The principal findings of this study were the demonstration of improved patient outcomes and cardiac function over baseline following the performance of surgical treatment for SMR. Specifically, these data demonstrate that performance of either mitral repair or replacement results in significantly improved LV remodeling and LVESVI, reduced incidence of recurrent MR (MR=3-5), reduced NYHA functional class and increased patient quality of life. These results are fundamental to shaping the future approach to the medical and surgical management of SMR as they directly address the critical question of whether or not to surgically address the mitral valve beyond myocardial revascularization and conservative medical management. These data are also the first to report among existing literature that *any* operation (repair or replacement) significantly improves LVESVI over baseline with the demonstration of a mean improvement in LVESVI from a baseline of 6.5 and 7.3 at 12 months for mitral repair and replacement respectively. The overall rate of worsening heart failure was also low (4%) and was not significantly different between MV repair (5.6%) and replacement (6%) groups. These results are consistent with reported series that have documented the benefits of either treatment approach to correct SMR over and above that of surgical myocardial revascularization alone (3,20-24). However, these results provide a critical extension of prospective, randomized results to existing observational literature that has reported on the purported benefits of one mitral valve technique over the other. While the large majority of former observational series have documented no difference in short- and long-term outcomes related to heart failure symptoms as a function of mitral repair or replacement (4,5,14,16,25), these data further strengthen the argument for performance of either mitral technique with select differences in short-term results.

The randomization of enrolled subjects into mitral repair versus replacement treatment groups resulted in several noteworthy comparisons. First, non-inferiority was demonstrated between the performances of mitral repair *vs*. replacement with or without concomitant coronary revascularization with respect to the study's primary endpoint of LVESVI at 12 and 24 months post-surgery as measured by transthoracic echocardiogram (TTE). Based on these findings, the null hypothesis was accepted that post-surgical LV remodeling as assessed by LVESVI is no different between mitral repair and replacement for SMR and remains improved overall. Second, while no significant differences in operative mortality were observed between treatment cohorts, the 1.6% mortality rate for mitral repair and 4.0% mortality rate for mitral replacement compare favorably to current national estimates. Recent data from the Society of Thoracic Surgeons reports nationwide mortality rates following performance of mitral repair + CABG of approximately 5% (4.8% in-hospital mortality and 5.3% operative mortality) compared to 8% (7.8% in-hospital mortality and 8.5% operative mortality) for mitral replacement + CABG (26). Thus, the documented improvements in mortality in these analyses likely reflect the experience of participating surgeons and hospitals committed to the surgical treatment of mitral disease. Perhaps more important than operative mortality, however, were the observed trends in survival between mitral repair and replacement treatment groups. While no significant differences were observed in patient survival between treatment groups overall, there was a non-statistically significant trend toward earlier mortality for patients randomized to mitral replacement compared to repair (mean survival days: 75 versus 163). Taken together with the reported equivalent major adverse cardiac event ± death rates, incidence of postoperative stroke or need for reoperation following mitral procedure, these data do not appear to demonstrate superiority of one surgical treatment approach over the other with respect to early postoperative morbidity or mortality. Nevertheless, select observational and single-institutional series, many of which are limited to short-term outcome measures, have reported differences in outcomes between these two treatment options with respect long-term freedom from MR, improved functional status and patient quality of life (4,16,27-31).

Beyond surgical mortality, a divergence in outcomes between these treatment options was revealed in regard to the impact of mitral repair versus replacement on the incidence of recurrent SMR. One of the most surprising findings in these data was the revelation that mitral repair demonstrated a 32.6% rate of recurrent moderate and rarely severe SMR (Grade 4 MR=27.6% and Grade 5 MR=4.3%) compared to the much lower rate of 2.3% among those undergoing mitral replacement at 12 months follow-up. These rates were more than expected based on reported literature that have documented much lower rates for the performance of mitral repair (5). Perhaps more importantly, however, was the revelation that despite these differences, the findings did not translate into worsened LVESVI, heart

failure symptoms or rates of hospital readmission for heart failure among randomized study cohorts. Interestingly, the reported incidence of recurrent MR occurring at 6 months did not become more severe at 12 months. Repair group patients without recurrent MR demonstrated greater improvement in LVESVI (i.e., lower) than those with moderate or SMR recurrence (47±23 *vs.* 64±24 mL/m^2, P<0.001).

Limitations should be noted for the CTSN SMR Trial. First, no subgroup analyses were performed based upon the underlying mechanism of IMR. Second, these data report on short- and mid-term results and do not, at present, provide results related to long-term durability or survival following mitral repair or replacement. This will be important to report in the future as previous retrospective reports have demonstrated good (85%) 5-year survival following mitral repair for MR (16). These data do not provide results for patients with poor preoperative risk owing to pulmonary hypertension or severe renal or hepatic disease as such patients were excluded from enrollment. Ideally, clinical trials are powered to provide definitive data for all study endpoints. However, to do so in the present trial would have required sample sizes of several thousand patients due to the relatively low incidence of certain secondary endpoints, including mortality. This would not have been feasible within the 5-year term of the CTSN.

In summary, the CTSN SMR Trial represents the largest prospective randomized clinical trial to date that addresses the relative benefits of mitral repair and replacement in patients with severe IMR within a multi-institution cohort of patients. These data demonstrate the safety and efficacy of current surgical approaches to the mitral valve to address SMR in the modern era. Overall, the results of this study suggest that regardless of surgical technique, either mitral replacement or repair is effective for the surgical treatment of IMR. Chordal sparing mitral replacement in the short-term has significantly reduced rates of recurrent MR. However, the long-term implications of valve repair and replacement remain unclear.

CTSN: predicting recurrent MR after mitral repair

Based upon the higher recurrent MR rates reported within the CTSN SMR Trial, a fundamental question emerged as to whether a subgroup of patients could be identified who would benefit most from undergoing MV repair compared to replacement. To investigate this question, a follow-up analysis of the CTSN trial was presented at the 94th Annual Meeting of the American Association for Thoracic Surgery (AATS) in Toronto, Ontario. The primary objective of this analysis was to determine whether it is possible to predict the likelihood of recurrent MR after repair based upon preoperative clinical and echocardiographic data (32).

This study analyzed 116 patients who underwent MV repair (96% of patients with SMR and 4% with moderate IMR at enrollment). On comparison of baseline characteristics stratified by patients who survived without MR recurrence to those who experienced moderate to SMR recurrence or death, patients who experienced an adverse outcome were older, had a higher frequency of basal aneurysm/dyskinesis and a lower frequency of NYHA Class III and IV. Similarly, a comparison of patients without MR recurrence to those with recurrent MR revealed that recurrence was associated with a higher frequency of basal aneurysm/dyskinesis, history of ventricular arrhythmias and lower frequency of New York Heart Association (NYHA) Class III and IV. Importantly, six patients underwent MV replacement before leaving the OR because repair did not sufficiently correct the MR.

With respect to mitral repair outcomes over time, several interesting patterns were observed. First, after taking into account a minority of patients who developed ring dehiscence after repair (n=4) and those with uncorrected MR in the OR who required replacement (n=6), rates of recurrent moderate and SMR over the study period included the following (for moderate and severe MR respectively): 23.8% and 9.9% at 30 days, 25.3% and 10.5% at 6 months, 29% and 10.8% at 12 months and 38.0% and 10.1% at 24 months. Mortality for these patients was 14.7% at one year, and 19.8 % at 2 years. As a result, a total of 76 patients experienced moderate/SMR or death over time (53 MR recurrences, 10 deaths and 13 combined MR recurrences and deaths). Thus, in order to predict which patients undergoing MV repair would have an increased likelihood of recurrent MR, the authors performed parsimonious multivariable regression of analyses of factors demonstrating significant univariate measures of association with MR recurrence. These results demonstrated that no significant, independent associations between baseline echocardiographic measures of MV geometric tethering and moderate/severe recurrent MR. However, the presence of basal aneurysm/dyskinesis was strongly associated with this outcome.

Based on this secondary analysis of the CTSN SMR Trial data, several conclusions were drawn. First, moderate and severe recurrent IMR after a restrictive annuloplasty ring

appears to occur early and affects the majority of patients by 2 years. Most recurrent MR after MV repair was moderate, with little progression to SMR, and the severity of MR was dynamic in that some moderate MR patients subsequently developed mild MR. Basal aneurysm/dyskinesis was independently associated with the likelihood of recurrent moderate or SMR. These results hold promise for the ability to predict which patients will develop recurrent IMR and thus those who may be better served with performance of either MV replacement or more complex repair techniques that directly address leaflet tethering.

Conclusions

Level 1 randomized controlled data now exists to address the question of the most efficacious surgical approach to severe IMR. Severe IMR remains a significant clinical challenge in the modern surgical era that can be corrected with surgical mitral repair using restrictive annuloplasty or complete chordal sparing replacement techniques. Both surgical approaches improve LV remodeling with reduced LVESI at 12 months and are associated with similar 1-year mortality. Higher rates of recurrent MR after MV annuloplasty are more common among patients with preoperative evidence of basilar LV aneurysms and/or dyskinesis. For these patients, either MV replacement or repair techniques that address leaflet tethering may provide a more durable, long-term result. Multi-institution clinical trial collaborations are essential in the modern surgical era to most appropriately address areas of clinical equipoise in order to improve patient outcomes and provide generalizable consensus guidelines and treatment recommendations.

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Footnote

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