ORIGINAL ARTICLE

Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation

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ABSTRACT

BACKGROUND

In a randomized trial comparing mitral-valve repair with mitral-valve replacement in patients with severe ischemic mitral regurgitation, we found no significant difference in the left ventricular end-systolic volume index (LVESVI), survival, or adverse events at 1 year after surgery. However, patients in the repair group had significantly more recurrences of moderate or severe mitral regurgitation. We now report the 2-year outcomes of this trial.

METHODS

We randomly assigned 251 patients to mitral-valve repair or replacement. Patients were followed for 2 years, and clinical and echocardiographic outcomes were assessed.

RESULTS

Among surviving patients, the mean (±SD) 2-year LVESVI was 52.6±27.7 ml per square meter of body-surface area with mitral-valve repair and 60.6±39.0 ml per square meter with mitral-valve replacement (mean changes from baseline, −9.0 ml per square meter and −6.5 ml per square meter, respectively). Two-year mortality was 19.0% in the repair group and 23.2% in the replacement group (hazard ratio in the repair group, 0.79; 95% confidence interval, 0.46 to 1.35; P=0.39). The rank-based assessment of LVESVI at 2 years (incorporating deaths) showed no significant between-group difference (z score=−1.32, P=0.19). The rate of recurrence of moderate or severe mitral regurgitation over 2 years was higher in the repair group than in the replacement group (58.8% vs. 3.8%, P<0.001). There were no significant between-group differences in rates of serious adverse events and overall readmissions, but patients in the repair group had more serious adverse events related to heart failure (P=0.05) and cardiovascular readmissions (P=0.01). On the Minnesota Living with Heart Failure questionnaire, there was a trend toward greater improvement in the replacement group (P=0.07).

CONCLUSIONS

In patients undergoing mitral-valve repair or replacement for severe ischemic mitral regurgitation, we observed no significant between-group difference in left ventricular reverse remodeling or survival at 2 years. Mitral regurgitation recurred more frequently in the repair group, resulting in more heart-failure–related adverse events and cardiovascular admissions. (Funded by the National Institutes of Health and Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT00807040.)

ISCHEMIC MITRAL REGURGITATION IS A SE-rious consequence of coronary artery disease that carries a substantial risk of death from cardiovascular causes in proportion to its severity.[1,2] Ischemic mitral regurgitation is anatomically characterized by remodeling or distortion of left ventricular geometry that ultimately results in papillary-muscle displacement, leaflet tethering, and impaired coaptation. For the subgroup of patients with severe ischemic mitral regurgitation, the prognosis is grave, with rates of death ranging from 15 to 40% at 1 year.[2-4]

For patients with severe ischemic mitral regurgitation, the benefit of surgical revascularization is undisputed, provided that the patient has suitable coronary targets affected by high-grade proximal lesions that compromise ischemic but viable myocardium. Expert consensus favors simultaneous correction of mitral regurgitation, although the question of which surgical strategy is the most effective remains controversial.[5,6] Support for mitral-valve repair with a restrictive annuloplasty has been based on its relatively lower perioperative morbidity and mortality, as well as the presumed benefits of preserving the subvalvular apparatus to maintain left ventricular systolic function.[7-10] However, this procedure can result in functional mitral stenosis[11] and has been associated with a high rate of recurrent mitral regurgitation.[12-16] Chordal-sparing mitral-valve replacement, on the other hand, is believed to provide more durable correction of mitral regurgitation with favorable ventricular remodeling,[17] albeit in association with a higher risk of perioperative death,[10,18] long-term thromboembolism, endocarditis, and structural valve deterioration.

The Cardiothoracic Surgical Trials Network recently addressed the tradeoff between lower perioperative risk with restrictive mitral-valve repair and better long-term correction of mitral regurgitation with chordal-sparing replacement by conducting a multicenter, randomized trial comparing these two approaches in patients with severe ischemic mitral regurgitation.[1] This trial showed no significant between-group differences in left ventricular reverse remodeling (as measured by the left ventricular end-systolic volume index [LVESVI]), survival, or clinical outcome at 1 year, although there was a significantly higher rate of recurrent moderate or severe mitral regurgitation in the repair group. We present here the 2-year echocardiographic and clinical outcomes of patients in that trial.

METHODS

STUDY DESIGN AND TRIAL OVERSIGHT

The study design has been described previously.[1,19] The trial was conducted by the Cardiothoracic Surgical Trials Network and was funded by the National Institutes of Health (NIH) and the Canadian Institutes of Health Research. The trial included 22 clinical centers with a coordinating center, an independent event-adjudication committee, and an NIH-appointed data and safety monitoring board that oversaw trial progress. The institutional review board at each study center approved the protocol, which is available with the full text of this article at NEJM.org. The investigators vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol.

PATIENTS AND INTERVENTIONS

We enrolled adults with chronic severe ischemic mitral regurgitation and coronary artery disease who were eligible for surgical repair or replacement of mitral valves, with or without coronary-artery bypass grafting (CABG). We assessed severe ischemic mitral regurgitation using resting transthoracic echocardiography and integrative criteria[20] that were verified by an independent core laboratory. (Details are provided in the Supplementary Appendix, available at NEJM.org.) All patients provided written informed consent.

Eligible patients were randomly assigned to undergo either mitral-valve repair or chordal-sparing replacement. Randomization was stratified according to center and blocked to ensure ongoing equivalence of group size. Mitral-valve repair was performed with the use of an approved complete rigid or semirigid annuloplasty ring, which was downsized to correct for annular dilatation. Mitral-valve replacement included complete preservation of the subvalvular apparatus. The technique of preservation, type of prosthetic valve, and technique of suture placement were at the discretion of the surgeon. Each treating cardiologist prescribed guideline-directed medical treatment, including aspirin, lipid-lowering agents, beta-blockers, renin–angiotensin–aldosterone antagonists, and cardiac-resynchronization therapy.

STUDY END POINTS

All patients were followed for 2 years, and end points were assessed at 30 days and at 6, 12, and 24 months. All study investigators were unaware of the overall outcome data. The primary end point was the degree of left ventricular reverse remodeling, which was defined as the LVESVI at 1 year after randomization, as assessed by means of transthoracic echocardiography, as reported previously.[1] Secondary end points included left ventricular size and function at other time points and rates of death, major adverse cardiac or cerebrovascular events (a composite outcome that included death, stroke, subsequent mitral-valve surgery, heart-failure hospitalization, or an increase in New York Heart Association [NYHA] class by one or more classes), serious adverse events, recurrent mitral regurgitation, and rehospitalization, as well as quality of life.

STATISTICAL ANALYSIS

The trial was designed to have a power of 90% to detect a difference of 15 ml per square meter of body-surface area in the LVESVI from baseline to 1 year, as reported previously.[1] We assumed a baseline LVESVI of 100 ml per square meter, improvements of 20 ml per square meter in the repair group and 35 ml per square meter in the replacement group, and a similar rate of death at 1 year of 10 to 20% in the two groups.[21-23] The primary null hypothesis was that there would be no between-group difference in the LVESVI at 1 year.[1]

We used a two-tailed Wilcoxon rank-sum test to compare the LVESVI at 2 years in an intention-to-treat analysis at a 0.05 significance level. The test accommodated nonignorable missing data with respect to the LVESVI owing to death by assigning deceased patients the worst ranks in an order that was based on the time of death. We used multiple imputation for missing data that were not due to death for the 2-year LVESVI, assuming that data were missing at random (as described in the Supplementary Appendix). We used the log-rank test to compare rates of death and major adverse cardiac or cerebrovascular events, and we calculated hazard ratios from Cox regression models to quantify relative risks. Poisson regression was used to test group differences with respect to rates of adverse events. Functional status (according to NYHA and Canadian Cardiovascular Society classifications) was compared between groups with the use of chi-square tests. To assess patients' quality of life, we used the Minnesota Living with Heart Failure questionnaire, the European Quality of Life–5 Dimensions (EQ-5D), and the physical and mental subscales of the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12). Quality of life was analyzed with the use of a mixed-effects model.
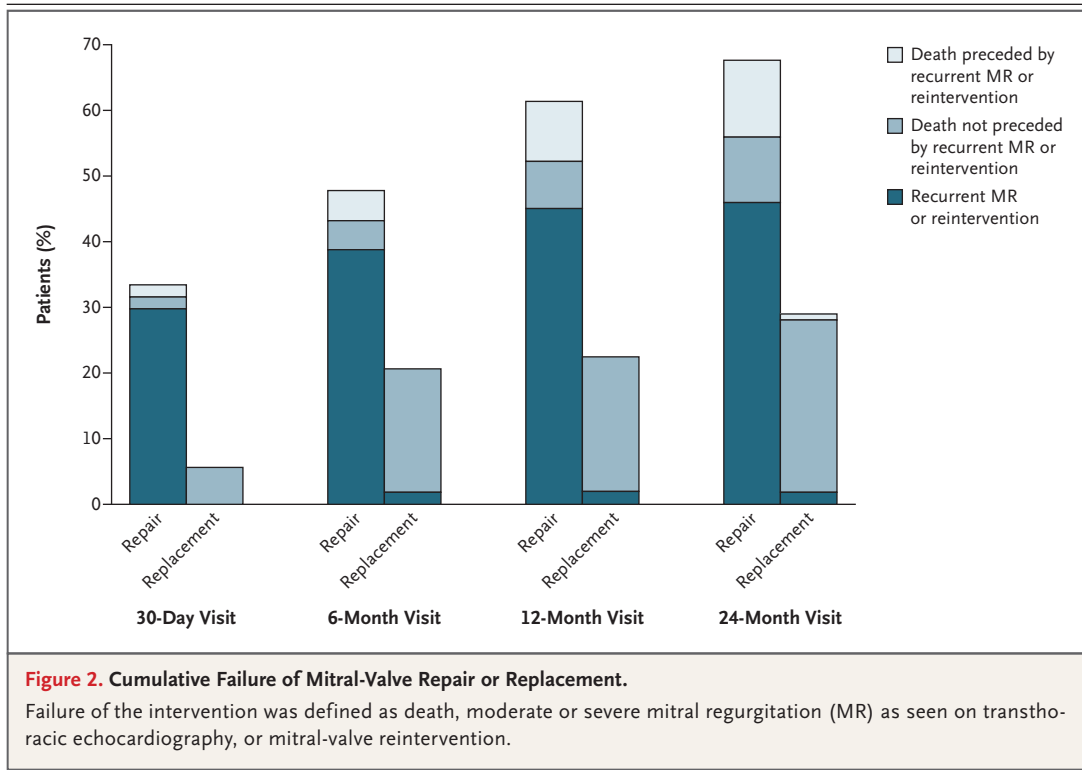
RESULTS

PATIENTS

A total of 251 patients underwent randomization, 126 to mitral-valve repair and 125 to mitral-valve replacement (Fig. S1 in the Supplementary Appendix). The two groups had similar baseline characteristics (Table S1 in the Supplementary Appendix). The mean (±SD) LVESVI was 61.1±26.2 ml per square meter in the repair group and 65.7±27.3 ml per square meter in the replacement group. Concomitant procedures were performed in 86.1% of patients. Among patients in the repair group, the average annulus size was 31.0 mm and the average ring size was 27.9 mm; 92.9% of patients received a ring measuring 30 mm or less. Subvalvular procedures were used in 11.9% of patients in the repair group. Among those receiving valve replacement, 95.4% underwent a chordal-sparing procedure. Eleven patients who were assigned to the repair group underwent replacement (includ-
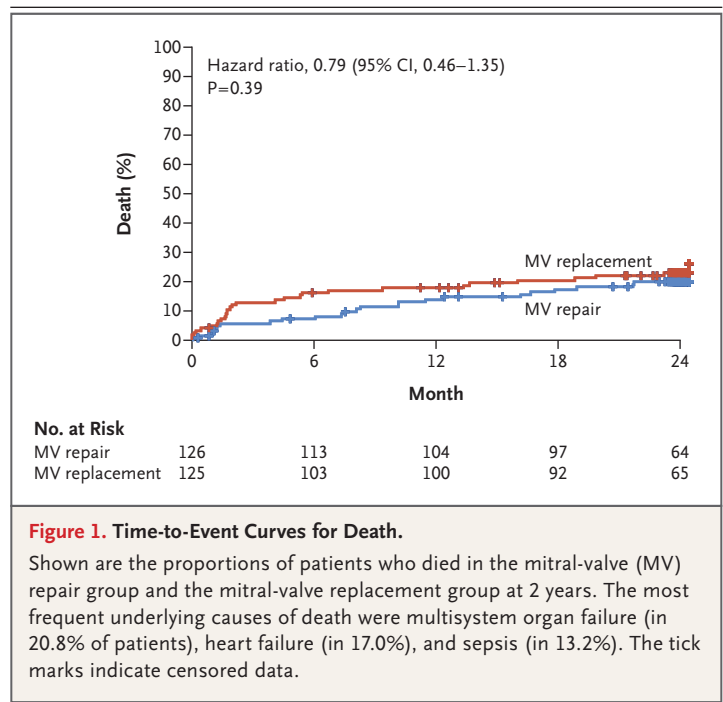
Figure 1. Time-to-Event Curves for Death.

Shown are the proportions of patients who died in the mitral-valve (MV) repair group and the mitral-valve replacement group at 2 years. The most frequent underlying causes of death were multisystem organ failure (in 20.8% of patients), heart failure (in 17.0%), and sepsis (in 13.2%). The tick marks indicate censored data.

Figure 2. Cumulative Failure of Mitral-Valve Repair or Replacement.

Failure of the intervention was defined as death, moderate or severe mitral regurgitation (MR) as seen on transthoracic echocardiography, or mitral-valve reintervention.

ing 5 patients in whom no attempt at repair was made and 6 patients who underwent replacement after full repair), and 1 patient who was assigned to the replacement group underwent repair.

LEFT VENTRICULAR DIMENSIONS AND FUNCTION

The mean 2-year LVESVI among surviving patients was 52.6±27.7 ml per square meter in the repair group and 60.6±39.0 ml per square meter in the replacement group (mean change from baseline, −9.0 ml per square meter and −6.5 ml per square meter, respectively), with the vast majority of total improvement (81.8% in the repair group and 96.3% in the replacement group) occurring during the first year.

At 2 years, the mean left ventricular ejection fraction was 42.5±11.8% in the repair group and 37.6±11.8% in the replacement group. The rank-based assessment of LVESVI at 2 years (incorporating death) showed no significant between-group difference (z score=−1.32, P=0.19).

RATES OF DEATH, REOPERATION, AND RECURRENCE

Outcomes at 30 days and 1 year have been described previously.[1] At 2 years, we observed no significant difference in cumulative mortality between treatment groups, with a rate of 19.0% in the repair group and 23.2% in the replacement group (Table 1), for a hazard ratio with mitral-valve repair of 0.79 (95% confidence interval [CI], 0.46 to 1.35; P=0.39 by the log-rank test) (Fig. 1).

Six patients who were assigned to the repair group were converted to valve replacement before leaving the operating room because the repair procedure did not sufficiently correct the mitral regurgitation, and 4 patients in the repair group underwent mitral-valve reoperation at a later date (at 10, 41, 268, and 434 days after the procedure). One recipient of a bioprosthesis in the replacement group underwent a mechanical replacement at 18 months to correct leaflet immobility and severe mitral regurgitation. Three patients in the replacement group had a paravalvular leak of mild severity but did not require intervention.

The proportion of patients with recurrent moderate or severe mitral regurgitation at some point during the 2-year period was significantly higher in the repair group than in the replacement group (58.8% vs. 3.8%, P<0.001). Severe mitral regurgitation was present in 14% of the

Table 1. Clinical End Points, Serious Adverse Events, and Hospitalizations at 2 Years.

| Variable	Repair (N = 126)	Replacement (N = 125)	P Value*
	no./total no. of patients (%)		
Clinical end point			
Death	24/126 (19.0)	29/125 (23.2)	0.42
Stroke	10/126 (7.9)	7/125 (5.6)	0.46
Worsening New York Heart Association class†	5/85 (5.9)	5/84 (6.0)	1.0
Rehospitalization for heart failure	27/126 (21.4)	22/125 (17.6)	0.44
Failed index mitral-valve procedure	6/126 (4.8)	0	0.03
Mitral-valve reoperation	4/126 (3.2)	1/125 (0.8)	0.37
Moderate or severe recurrent mitral regurgitation	57/97 (58.8)	3/79 (3.8)	<0.001
MACCE‡	53/126 (42.1)	53/125 (42.4)	0.96
Canadian Cardiovascular Society class III or IV	4/82 (4.9)	0/80	0.19
	no. of events (rate/100 patient-yr)		
Serious adverse event			
Any event	291 (145.6)	247 (129.8)	0.18
Heart failure	48 (24.0)	29 (15.2)	0.05
Neurologic dysfunction	19 (9.5)	10 (5.3)	0.12
Stroke	12 (6.0)	6 (3.2)	0.19
Other condition	7 (3.5)	4 (2.1)	0.41
Myocardial infarction			
Nonperioperative	5 (2.5)	1 (0.5)	0.11
Perioperative	0	2 (1.1)	0.16
Renal failure	6 (3.0)	11 (5.8)	0.19
Bleeding	7 (3.5)	10 (5.3)	0.41
Arrhythmia			
Supraventricular	26 (13.0)	19 (10.0)	0.38
Ventricular	12 (6.0)	17 (8.9)	0.29
Localized infection	25 (12.5)	29 (15.2)	0.47
Endocarditis	0	2 (1.1)	0.16
Sepsis	12 (6.0)	6 (3.2)	0.19
Respiratory failure	14 (7.0)	19 (10.0)	0.31
Hospitalization			
Rehospitalization	152 (78.9)	121 (66.0)	0.14
Readmission for cardiovascular event	93 (48.3)	59 (32.2)	0.01

* P values were calculated by means of the chi-square test or Fisher's exact test for the clinical end points and Poisson regression for serious adverse events and hospitalizations.
† Worsening of New York Heart Association class was defined as an increase of one grade or more.
‡ A major adverse cardiac or cerebrovascular event (MACCE) was defined as death, stroke, hospitalization for heart failure, worsening heart failure, or mitral-valve reintervention.

patients with recurrence in the repair group and in none of the patients in the replacement group. In the repair group, patients without recurrent moderate or severe mitral regurgitation within 2 years had a greater degree of reverse remodeling than did patients who had such regurgitation (LVESVI, 62.6±26.9 and 42.7±26.4, respectively; P<0.001).
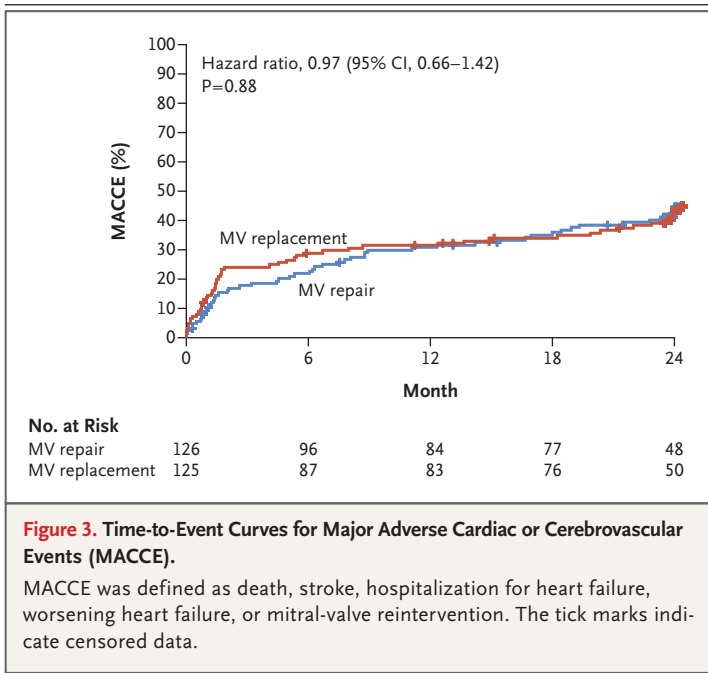
Figure 3. Time-to-Event Curves for Major Adverse Cardiac or Cerebrovascular Events (MACCE).

MACCE was defined as death, stroke, hospitalization for heart failure, worsening heart failure, or mitral-valve reintervention. The tick marks indicate censored data.

At 2 years, 75 of 111 patients (67.6%) who underwent mitral annuloplasty died, had moderate or severe mitral regurgitation, or underwent mitral-valve reoperation, as compared with 31 of 107 patients (29.0%) in the replacement group (relative risk, 2.3; 95% CI, 1.69 to 3.22; P<0.001). Rates of the composite end point over time are provided in Figure 2.

COMPOSITE CARDIAC END POINT, ADVERSE EVENTS, AND HOSPITALIZATION

At 2 years, the rates of major adverse cardiac or cerebrovascular events did not differ significantly between the treatment groups (42.1% in the repair group and 42.4% in the replacement group) (Table 1), for a hazard ratio of 0.97 (95% CI, 0.66 to 1.42; P=0.88 by the log-rank test) (Fig. 3). There also was no significant difference in the rate of the individual components of the primary end point (Table 1). The repair group had significantly more serious heart-failure events at 2 years (24.0 per 100 patient-years vs. 15.2 per 100 patient-years, P=0.05), although the rates of other serious adverse events were not significantly different between groups. Overall readmission rates did not differ between groups, but patients in the repair group had a significantly higher rate of readmission for cardiovascular causes (48.3 vs. 32.2 per 100 patient-years, P=0.01). This difference was largely driven by rehospitalization for

heart failure and the need for an implantable cardioverter–defibrillator or permanent pacemaker (59 readmissions in the repair group and 38 in the replacement group, for rates of 30.6 vs. 20.7 per 100 patient-years; P=0.06).

QUALITY OF LIFE

The pattern of change in quality-of-life measures over the duration of follow-up was similar in the two groups, with most improvement occurring in the first 6 months after surgery. There were no significant between-group differences in scores on the SF-12 physical and mental subscales or in the EQ-5D scores. On the Minnesota Living with Heart Failure questionnaire (with scores ranging from 0 to 105, with higher scores indicating a worse quality of life), there was a trend toward greater overall improvement in scores among patients in the replacement group as compared with those in the repair group (Fig. 4). At 2 years, the mean change in heart-failure symptoms from baseline was 20.0 in the repair group versus 27.9 in the replacement group (P=0.07). Among all patients regardless of treatment assignment, the improvement from baseline was 26.6 among patients who did not have recurrent mitral regurgitation versus 16.2 among those with recurrence (P=0.04).

DISCUSSION

The results of this 2-year study advance our understanding of the relative benefits of mitral-valve repair and mitral-valve replacement for the management of severe ischemic mitral regurgitation. As in the 1-year study, we observed no significant between-group difference in the rank-based assessment of left ventricular reverse remodeling at 2 years. Although the LVESVI significantly improved over baseline in the two groups during the first year after surgery, there was little further improvement during the second year. Similarly, in the second year after surgery, there were few additional deaths, which were equivalently distributed between the two groups. As such, we observed nonsignificant differences in 2-year mortality (19.0% in the repair group and 23.2% in the replacement group), although the study had insufficient power to draw any definitive conclusions about the relative effects of the two surgical procedures on survival. The rates of death that we observed in our trial were
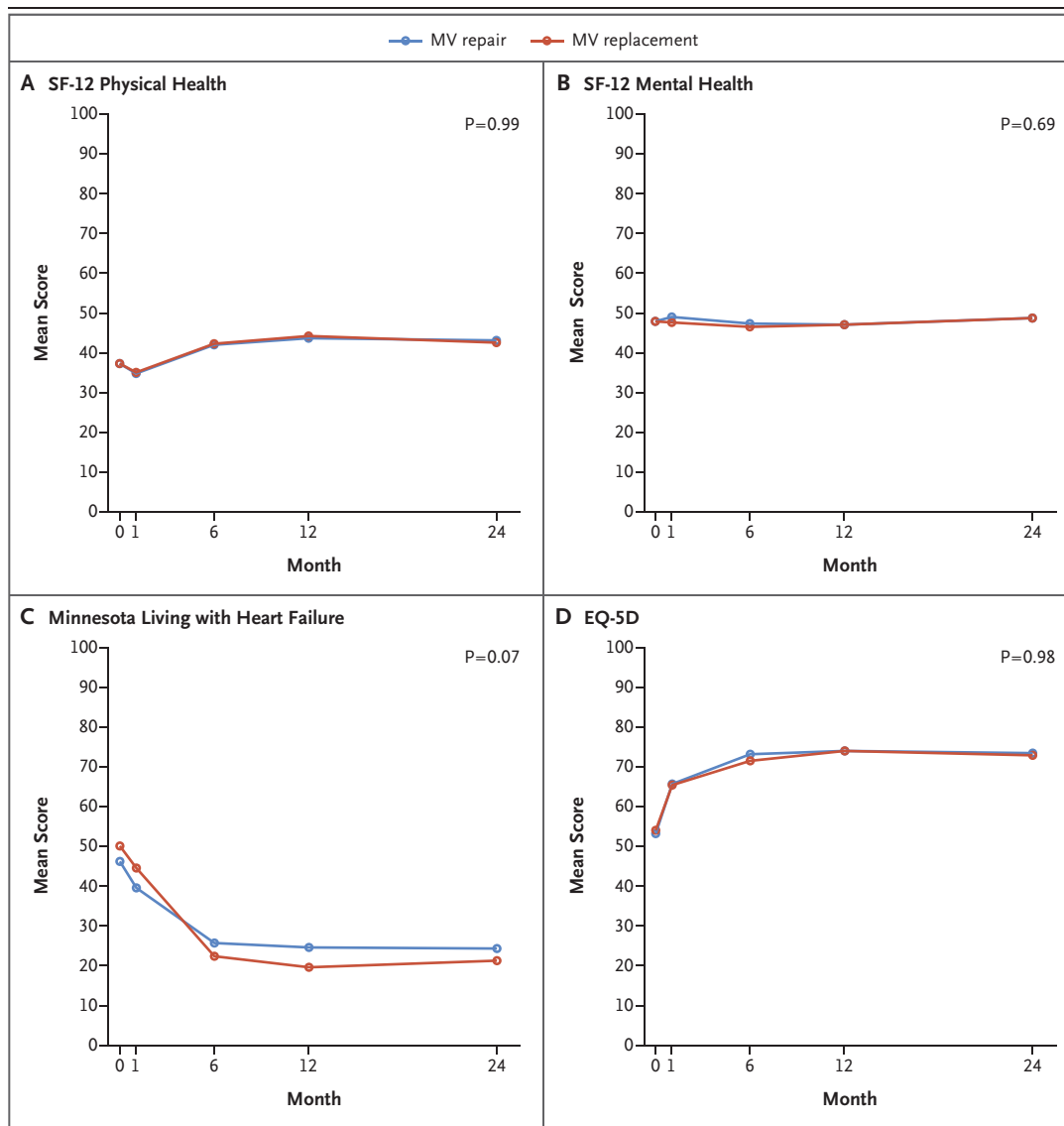
Figure 4. Quality-of-Life Scores.

Shown are the mean scores on the Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12) for physical health (Panel A) and mental health (Panel B). The SF-12 scale ranges from 0 to 100, with higher scores indicating better health. Panel C shows mean scores on the Minnesota Living with Heart Failure questionnaire, which ranges from 0 to 105, with higher scores indicating a lower quality of life. Panel D shows mean scores on the European Quality of Life–5 Dimensions (EQ-5D) survey, with scores ranging from 0 to 100, with higher scores indicating a better quality of life.

consistent with results that have been published previously.[24,25]

However, we observed that the recurrence of mitral regurgitation, which was mostly moderate in degree, remained a progressive and excess hazard for patients undergoing mitral-valve repair. During the 2-year follow-up period, 58.8% of patients in the repair group had moderate or severe regurgitation, as compared with 3.8% in the replacement group. This deficiency in the durability of correction of mitral regurgitation is disconcerting, given that recurrence confers a predisposition to heart failure, atrial fibrillation, and repeat interventions and hospitalizations.[26-28] We found that patients in the repair group had more serious adverse events of heart failure and

hospital readmission for cardiovascular causes. The findings of the Minnesota Living with Heart Failure questionnaire, although not conclusive, were consistent with these clinical events. The 7.9-point difference in average improvement over baseline in favor of the replacement group was not significant (P=0.07), but the magnitude of change exceeded the 5-point threshold for clinically meaningful improvement used in other studies.[29]

Our results reflect the expertise of experienced surgeons, as reflected in the low 30-day mortality (1.6% for repair and 4.0% for replacement), as compared with the national rates of 5.3% and 8.5%, respectively, reported by the Society of Thoracic Surgeons.[30] With the exclusion of the 6 patients who required conversion to mitral-valve replacement, patients in the repair group left the operating room with only trace or no mitral regurgitation. Ninety-three percent of patients received a mitral-valve ring measuring 30 mm or less; the average valve annulus size was 31.0 mm, and the average ring size was 27.9 mm. Among the patients who underwent mitral-valve replacement, only 3 were found to have paravalvular leaks, all of which were mild in severity and did not require subsequent intervention.

Patients in the repair group who did not have recurrent mitral regurgitation had significant reverse remodeling. Moreover, among all the patients who underwent randomization, the absence of recurrent moderate or severe mitral regurgitation was associated with a better quality of life, as measured on the Minnesota Living with Heart Failure questionnaire. These findings raise the question of whether the selection of patients for repair could be improved by identifying baseline clinical or echocardiographic predictors of recurrence of mitral regurgitation. Echocardiography-based studies have identified several valvular measures (e.g., tenting area and coaptation distance) and ventricular measures (e.g., LVESVI and sphericity index) as possible predictors of recurrent mitral regurgitation.[7,14,31-36] Our previous analysis did not corroborate these observations and identified only the presence of a basal aneurysm or dyskinesis as an independent predictor of recurrent mitral regurgitation.[37] The need to identify the best candidates for restrictive annuloplasty is an important area for further research.

Such studies need to be paired with investigations that further elucidate the mechanism underlying recurrence of mitral regurgitation in recipients of restrictive annuloplasty. It has been suggested that the persistence or recurrence of mitral regurgitation after restrictive annuloplasty is due to augmented leaflet tethering caused by the anterior displacement of the posterior leaflet,[31] as well as progressive adverse global and localized left ventricular remodeling.[38] Therefore, there is potential for restrictive annuloplasty alone to potentiate a tendency to regurgitation. Adjunctive subvalvular procedures that address pathologic leaflet tenting in combination with restrictive annuloplasty are undergoing investigation.[39]

Mitral-valve replacement provides considerably more durable correction of mitral regurgitation, which may have an important effect on long-term outcomes but must be weighed against the adverse consequences related to the use of a prosthetic valve. In the first 2 years of this trial, we observed mild paravalvular leaks in 3 patients, prosthetic-valve endocarditis in 2 patients, and the need for mitral-valve reoperation for leaflet immobility in 1 patient. There was no increased incidence of serious thromboembolic or bleeding events among patients in the replacement group, as compared with the repair group. Longer-term follow-up is needed to more fully assess the frequency of these events in recipients of prosthetic valves.

This trial has several limitations. First, the primary end point was an echocardiographic measure of left ventricular remodeling, not a clinical outcome such as survival. A randomized trial with a 1-year or 2-year end point of death would have required the inclusion of thousands of patients. On the other hand, there is strong evidence correlating the LVESVI with clinical outcomes, including NYHA class, hospitalization, and survival.[40-43] Second, transthoracic echocardiography may have underestimated the presence and severity of mitral regurgitation in patients after replacement. However, among the patients in the replacement group, the mitral-valve inflow velocities and estimated diastolic gradients were within the normal ranges for the sizes of the prostheses that were implanted, which suggests the absence of substantial mitral regurgitation. Finally, the observations were made during a relatively short period. Additional events

would be captured with longer follow-up in these patient cohorts.

In conclusion, at 2 years after either mitral-valve repair or mitral-valve replacement for severe ischemic mitral regurgitation, there were no significant between-group differences with respect to left ventricular reverse remodeling or survival. However, the rate of recurrence of moderate or severe mitral regurgitation was significantly high-

er with mitral-valve repair, resulting in more heart-failure–related adverse events and cardiovascular admissions.

APPENDIX

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