Mitral valve surgery in heart failure: Insights from the Acorn Clinical Trial

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Supplemental material is available online.

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Objective: The study objective was to evaluate in a prospective, randomized, multicenter trial the safety and efficacy of mitral valve surgery with and without the CorCap cardiac support device (Acorn Cardiovascular, St Paul, Minn) in patients with New York Heart Association Class II to IV heart failure.

Background: Although mitral valve surgery has been performed successfully in patients with heart failure, the safety and long-term efficacy have not been established in a multicenter prospective trial. Cardiac support devices that reduce ventricular wall stress and promote beneficial reverse remodeling have been proposed as a new treatment option as a stand-alone procedure and as an adjunct to mitral valve surgery.

Methods: A subgroup of 193 patients were enrolled in the mitral valve repair or replacement stratum of the Acorn Clinical Trial; 102 patients were randomized to the mitral valve surgery alone group (control) and 91 patients were randomized to mitral valve surgery with implantation of the CorCap cardiac support device. Patients were followed for a median duration of 22.9 months.

Results: For the entire mitral valve surgery group, the 30-day operative mortality rate was only 1.6% at 30 days. Mitral surgery was associated with progressive reductions in left ventricle end-diastolic volume, left ventricle end-systolic volume, and left ventricular mass, and increases in left ventricle ejection fraction and sphericity index, all consistent with reverse remodeling. Recurrence of clinically significant mitral regurgitation was uncommon. Quality of life, exercise performance, and New York Heart Association functional class were all improved. Finally, the addition of the CorCap cardiac support device led to greater decreases in left ventricular end-diastolic volume and left ventricular end-systolic volume, a more elliptical shape, and a trend for a reduction in major cardiac procedures and improvement in quality of life compared with mitral surgery alone.

Conclusions: These findings suggest that there is clear benefit to the surgical elimination of mitral regurgitation and that there is additional benefit with the CorCap cardiac support device. Given the improvement in left ventricle structure and function, along with a low mortality rate, physicians should strongly consider offering mitral valve surgery in combination with the CorCap cardiac support device to patients with heart failure who are on an optimal medical regimen.

Mitral regurgitation (MR) is commonly observed in patients with heart failure (HF) and is associated with a poor prognosis.[1-4] Mitral valve repair or replacement to restore valve competency is a well-established procedure when there are symptoms of HF and primary disease of the valve leaflets (eg, degenerative valve disease).[1,3] Recent interest has focused on "functional" or secondary MR in which the valve leaflets are anatomically normal but do not fully coapt because of annular dilation and restricted leaflet motion secondary to increased left ventricular (LV) size and sphericity.[5,6] Valve surgery in this situation is controversial because MR is the consequence and not the cause of LV dysfunction, the prognosis is more related to the underlying cardiomyopathic process, and the elimination of a low-pressure run-off might worsen the overload on the left ventricle. Nonetheless, MV repair with a ring to reduce annular size has been associated with improved LV structure and patient symptoms.[7-10] However, the perioperative mortality risk, long-term survival, and actual clinical benefit are unknown.

We previously reported the results of the Acorn Clinical Trial demonstrating the safety and efficacy of the CorCap cardiac support device (CSD) (Acorn Cardiovascular, St Paul, Minn) in patients with HF.[11] This multicenter, prospective, randomized trial enrolled 300 patients with HF into 1 of 2 strata, including the mitral surgery stratum (n = 193 patients) and the no MV surgery stratum (n = 107 patients). The primary objective of the mitral surgery stratum was to determine whether the addition of the CorCap CSD added incremental value to MV surgery. However, it also provided an opportunity to assess the long-term effects of MV surgery in a large cohort of patients with HF followed in a prospective multicenter trial with the use of an echocardiographic core laboratory.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CSD = cardiac support device
HF = heart failure
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MCP = major cardiac procedure
MLHF = Minnesota Living with Heart Failure Questionnaire
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
OR = odds ratio
SF-36 = Short-Form 36
6MWT = 6-minute walk test

Methods

The Acorn Trial was a prospective, randomized, controlled evaluation of the CorCap CSD in patients with dilated cardiomyopathy, as previously described.[12] Patients were enrolled into 1 of 2 strata depending on whether they required MV surgery because of significant MR, based on the assessment by site clinicians. Patients who had clinically significant MR and an indication for MV surgery were enrolled in the MV surgery stratum (n = 193 patients) and then randomized to treatment (MV surgery plus CSD, n = 91) or control (MV surgery alone, n = 102). Patients without a clinical indication for MV surgery were enrolled in the no MV surgery stratum (n = 107 patients), but they are not discussed in this report.

Patients were eligible for the Acorn Trial if they had New York Heart Association (NYHA) Class III and IV HF of ischemic or non-ischemic cause and were between the ages of 18 and 80 years. All patients had an LV ejection fraction of 35% or less, LV dilation (defined as an LV end-diastolic dimension ≥60 mm or an LV end-diastolic dimension index ≥30 mm/m^2), a 6-minute walk test (6MWT) less than 450 m, and acceptable laboratory and pulmonary function test results. Most patients received an optimal medication regimen that included a diuretic (at least "as needed"), an angiotensin-converting enzyme (ACE) inhibitor (or angiotensin receptor blocker if ACE intolerant), and a beta-blocker (for at least 3 months). There were 2 inclusion criteria specific to the MV surgery stratum. First, the doses of background medication did not have to be stable for 1 month because of concerns regarding additional safety risks to delaying surgery for significant MR. Second, patients could also be enrolled with NYHA Class II symptoms and an ejection fraction of up to 45%. Specific exclusion criteria were summarized previously.[12]

Baseline testing included blood tests, echocardiography, quality of life evaluation with the Minnesota Living with Heart Failure Questionnaire (MLHF) and the Short-Form 36 (SF-36) Questionnaire, 6MWT, and an exercise test to measure peak oxygen consumption (peak VO_2). Randomization to treatment or control groups was stratified by site and stratum and based on random permuted blocks.

MV surgery was performed using standard operative techniques including cardiopulmonary bypass and undersized MV annuloplasty ring placement or valve replacement. CorCap CSD implant techniques were summarized previously.[13] Patients were seen at 3 months, 6 months, and then every 6 months. Blood tests, echocardiography, quality of life surveys, and 6MWT were completed at all visits. Peak VO_2 was measured at 6 and 12 months. Data on events (ie, deaths, hospitalizations, adverse events, and major cardiac procedures [MCPs]) were collected until the common closing date, which was specified to be after the last enrolled patient had been followed for 1 year. All echocardiographic data (LV size, function, shape, mass, and MR severity) were obtained from readings by the Core Laboratory at the Mayo Clinic, which had no knowledge of clinical or randomization data.

End points included all-cause mortality and change in NYHA functional class, quality of life, 6MWT and peak VO_2, LV ejection fraction, LV volumes, MR, and LV sphericity index. Patients were also followed for the need for additional MCPs (transplant, left ventricular assist device, biventricular pacemakers, repeat MV

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TABLE 1. Mitral regurgitation severity mitral valve replacement stratum (core laboratory)

	Baseline (189 patients)		6 mo (154 patients)		12 mo (145 patients)		18 mo (95 patients)	
MR severity	No.	%	No.	%	No.	%	No.	%
0	14	7.4	94	61.0	81	55.9	56	58.9
1+	20	10.6	34	22.1	40	27.6	28	29.5
2+	44	23.3	13	8.4	16	11.0	7	7.4
3+	49	25.9	10	6.5	6	4.1	2	2.1
4+	62	32.8	3	1.9	2	1.4	2	2.1
Mean score	2.66		0.67		0.67		0.59	
P vs baseline	—		<.0001		<.0001		<.0001	

MR, Mitral regurgitation.

surgery, tricuspid valve surgery, and coronary artery bypass grafting), which would indicate worsening of HF. Biventricular pacemakers and repeat MV surgery were adjudicated by an independent Clinical Events Review Committee, and only those events considered to be associated with worsening HF were counted toward the end point. Safety end points included the rate of deaths and serious adverse events overall. All efficacy and safety end points were analyzed according to the intention-to-treat principle. Cumulative survival curves for all events were constructed according to the Kaplan-Meier method, and differences were tested by the Cox-risk statistic. Comparisons of changes from baseline to follow-up were evaluated with *t* tests, chi-square statistics, or longitudinal regression analysis as appropriate.

Results

A total of 193 patients were enrolled in this study (Table E1). The mean age was 53.4 ± 12.6 years. The mean LV volume was 270.1 ± 100.3 mL, LV end-diastolic dimension was 69.7 ± 8.8 mm (site assessment), and LV ejection fraction was 23.9% ± 8.9% (site assessment). Patients had limited functional capacity with a mean 6MWT of 344.3 ± 90.4 m, a peak VO_2 of 14.1 ± 4.3 mL/kg/min, an MLHF score of 58.8 ± 23.9 units, and a physical functioning score (SF-36) of 37.1 ± 22.9 units. This trial was different from other HF trials because a majority of the patients in this trial were female (54.4%), with a large percentage of non-white minorities (39.9%). Most patients were in NYHA Class III (71.5%), with 23.3% in Class II and 5.2% in Class IV. The cause of HF was idiopathic in most patients; only 12 patients (6.2%) had ischemic heart disease. Background medical therapy included 97.4% receiving ACE inhibitors or angiotensin receptor blockers and 80.3% receiving beta-blockers.

Table 1 summarizes the echo core laboratory determinations of MR severity. There were 44 patients (23.3%) with 2+ MR, 49 patients (25.9%) with 3+ MR, and 62 patients (32.8%) with 4+ MR. Fourteen patients (7.4%) had a core laboratory determination of 0 MR (none or trivial), and 20 patients (10.6%) had a core laboratory determination of 1+ MR. It should be noted that the echo core laboratory readings were used solely for tracking end points in the trial and were not considered in the clinical decisions to perform mitral surgery. Most patients had multiple studies assessing MR severity, including contrast ventriculograms and transesophageal echocardiography, all of which were factored in the indication of MV surgery.

Nine of the 193 patients did not undergo MV surgery (5 patients refused, 1 patient died before surgery, and it was surgically decided for 3 patients). Most patients (n = 155 patients; 84.2%) received a mitral annuloplasty ring, but 29 patients (15.8%) underwent MV replacement. The baseline characteristics of the patients who underwent repair and replacement were similar. The only statistical difference was that the MV replacement group included more patients who had a history of cardiac surgery (3 vs 1, $P = .002$). In general, surgeons chose replacement if there were anatomic abnormalities (eg, rheumatic disease) or when it was believed that repair would not yield a satisfactory result. The replacement group included 4 patients who were converted from repair to replacement at the time of the original surgery because transesophageal echocardiography monitoring indicated that the initial mitral ring did not provide a satisfactory result (eg, eccentric MR and persistent billowing of leaflets). During MV replacement surgery, most patients had preservation of both anterior and posterior chordal structures. For MV repair, a variety of different ring types were used (Table E2). Information on the ring size used in the MV repair group was available in 86% of cases. A ring size of 26 or smaller was used in 59% of cases. The remaining ring sizes used were 27 (6%), 28 (24.6%), 29 (3.7%), 30 (3.0%), 31 (0.8%), and 32 (3.0%). Most of the rings were complete (65%) compared with partial (35%).

Figure 1 summarizes the Kaplan-Meier survival curve for the overall group. At 30 days, there were 3 deaths for an overall operative mortality of 1.6%. At 12 months, the cumulative survival was 86.5%. At 24 months, the cumulative survival was 85.2%.

Figure 2 summarizes the longitudinal regression analyses for the change in left ventricular end-diastolic volume

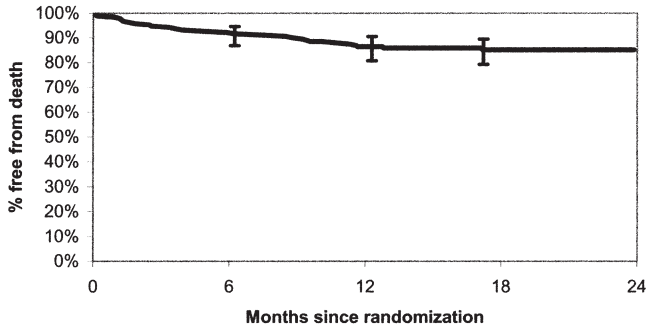

Figure 1. Kaplan-Meier survival curve for the entire group of 193 patients in the MV surgery stratum. See text for discussion.

(LVEDV) (Figure 2, *A*) and left ventricular end-systolic volume (LVESV) (Figure 2, *B*) from baseline to 24 months. There was a progressive decrease in both LVEDV and LVESV that was highly significant at all time points. Figure 3 summarizes the changes in left ventricular ejection fraction (LVEF). There were small and nonsignificant changes in ejection fraction at 3, 6, and 12 months. At 18 and 24 months, ejection fraction increased by 4.6 ($P = .003$) and 4.1 ($P = .03$), respectively.

Sphericity index increased by 0.037 at 3 months ($P = .02$), 0.092 at 6 months ($P < .0001$), 0.088 at 12 months ($P < .0001$), 0.116 at 18 months ($P < .0001$), and 0.197 at 24 months ($P < .0001$), all consistent with a more ellipsoidal shape. LV mass index also decreased, consistent with a beneficial effect on remodeling. From a baseline of 306.7 g/m^2, LV mass index decreased by 38.0 at 3 months ($P < .0001$), 48.1 at 6 months ($P < .0001$), 47.4 at 12 months ($P < .0001$), 47.4 at 18 months ($P = .0004$), and 72.81 at 24 months ($P < .0001$).

Overall, there was a dramatic reduction in the severity of MR (Table 1). The mean MR severity at baseline of 2.66 was reduced to 0.67 at 6 months ($P < .0001$), 0.67 at 12 months ($P < .0001$), and 0.59 at 18 months ($P < .0001$). Repeat MV surgery was performed in only 4 patients during follow-up.

Figure E1 summarizes the changes in MLHF. Overall scores decreased significantly at 3, 6, 12, 18, and 24 months (all $P < .0001$), consistent with an improvement in quality of life. Similarly, improvements were observed with the

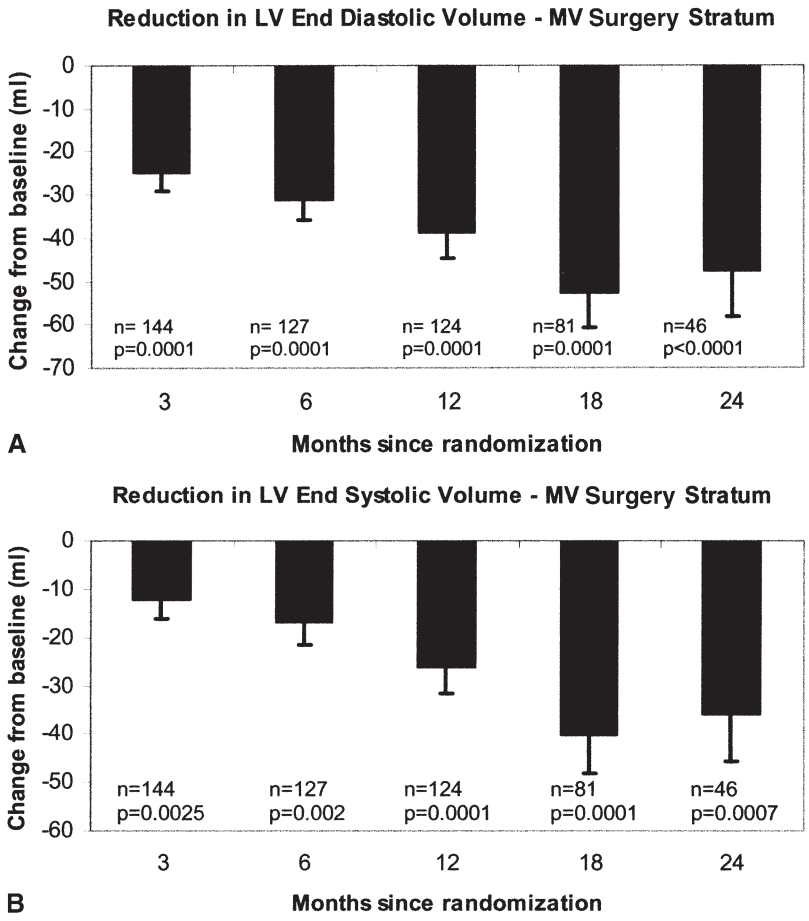

Figure 2. A, Reduction in LVEDV for the entire group of 193 patients in the MV surgery stratum. There was a progressive and significant reduction in LVEDV at 3, 6, 12, and 18 months, consistent with reverse remodeling. The number of patients studied at each time point is indicated. B, Reduction in LVESV for the entire group of 193 patients in the MV surgery stratum. Similar to the changes in LVEDV, there was a progressive and significant decrease in LVESV at 3, 6, 12, and 18 months. *LV,* Left ventricular.

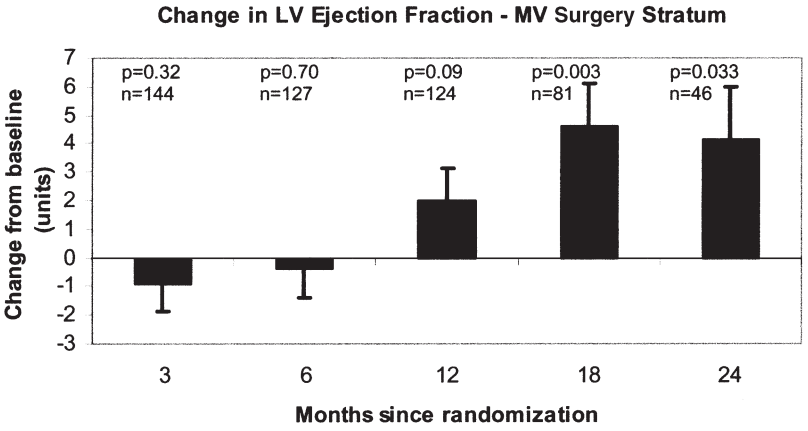

Figure 3. Change in LV ejection fraction for the entire group of 193 patients in the MV surgery stratum. There were insignificant changes in LVEF at 3, 6, and 12 months. The increase in ejection fraction at 18 months was significant at $P = .003$. *LV,* Left ventricular.

SF-36, a general quality of life instrument, with significant improvements in the general health domain at 3, 6, and 12 months. NYHA functional class also improved. The baseline NYHA class of 2.82 was reduced to 2.36 at 3 months ($P < .0001$), 2.34 at 6 months ($P < .0001$), 2.31 at 12 months ($P < .0001$), 2.20 at 18 months ($P < .0001$), and 2.25 at 24 months ($P < .0001$). Exercise performance as measured by the 6MWT also increased significantly for the overall group. There were significant increases of 21.8 ± 7.1 m at 3 months ($P < .003$), 26.4 ± 7.3 m at 6 months ($P = .0004$), 32.2 ± 7.4 m at 12 months ($P < .0001$), and 40.4 ± 9.9 m at 18 months ($P < .0001$). There were no significant changes in peak VO_2 for the entire group at 6 months (mean change −0.11 mL/kg/min; $P = .76$) or 12 months (mean change −0.07 mL/kg/min; $P = .85$).

The 84% of patients undergoing MV repair were compared with the 16% of patients undergoing MV replacement. There were no differences in survival between the repair and replacement groups. At 30 days, there were 3 deaths in the repair group (155 patients) and no deaths in the replacement group (29 patients).

The MV surgery/CSD (treatment) group and the MV surgery alone (control) group were compared to assess the additive effect of the CorCap CSD to MR surgery. There was no significant difference in survival between the treatment and control groups. At 30 days, there were 2 deaths in the treatment group (2.2%) and 1 death in the control group (1.0%). At 12 and 24 months, the cumulative mortality rate was 12.1% and 13.5%, respectively, in the treatment group compared with 14.8% and 15.9%, respectively, in the control group.

The Kaplan-Meier freedom from MCP curve (Figure E2) shows that the treatment group tended to have fewer MCPs than the control group ($P = .11$). Compared with the control group, the treatment group had fewer cardiac transplants (6 vs 12), fewer left ventricular assist devices (3 vs 7), fewer repeat MV operations (1 vs 3), fewer biventricular pacemakers (6 vs 8), and fewer tricuspid valve surgeries (0 vs 2), but none of these differences were statistically significant. Figure E3shows the freedom from the combined end point of death or MCP, with a trend for a reduction in the treatment group ($P = .09$).

The control group demonstrated a progressive decrease in LVEDV (Figure 4, *A*), which likely reflects the beneficial effects of MV surgery. The treatment group demonstrated a significantly greater decrease in LVEDV (average difference = 15.5 mL; $P = .043$) indicating that the CorCap CSD had an additive effect to the MV surgery. Similar changes were observed with LVESV (Figure 4, *B*). The average reduction in LVESV in the treatment group was significantly greater than in the control group by 14.6 mL ($P = .044$). The treatment group had a greater increase of 1.87 ejection fraction units compared with the control group, but this difference was not significant ($P = .23$).

Sphericity index increased more in the treatment group (0.071 units, $P = .003$). LV mass index tended to decrease more in the treatment group by an average reduction of 6.4 g/m^2, but this difference was not significant ($P = .23$). MR severity was similar between the 2 groups. In the treatment group at 6 months, 60.3% had no MR, 28.2% had 1+ MR, and 2.6% and 2+ MR. In the control group, 61.8% had no MR, 15.8% had 1+ MR, and 14.5% had 2+ MR. There was no significant difference in MR severity between the groups at 6, 12, or 18 months.

MLHF scores decreased in both groups consistent with an improvement in quality of life specific to HF. The treatment group demonstrated a greater decrease in MLHF (−4.22 units) when compared with the control group ($P = .13$). Similar patterns were observed in the SF-36. Compared with the control group, the treatment group demonstrated a greater improvement in the general health domain (10.39 units, $P < .0001$) and the physical function domain (5.16 units, $P = .078$).

Comparison of 6MWT and peak VO_2 responses between the treatment and control groups was difficult because data were missing for cause. Many patients could not perform the

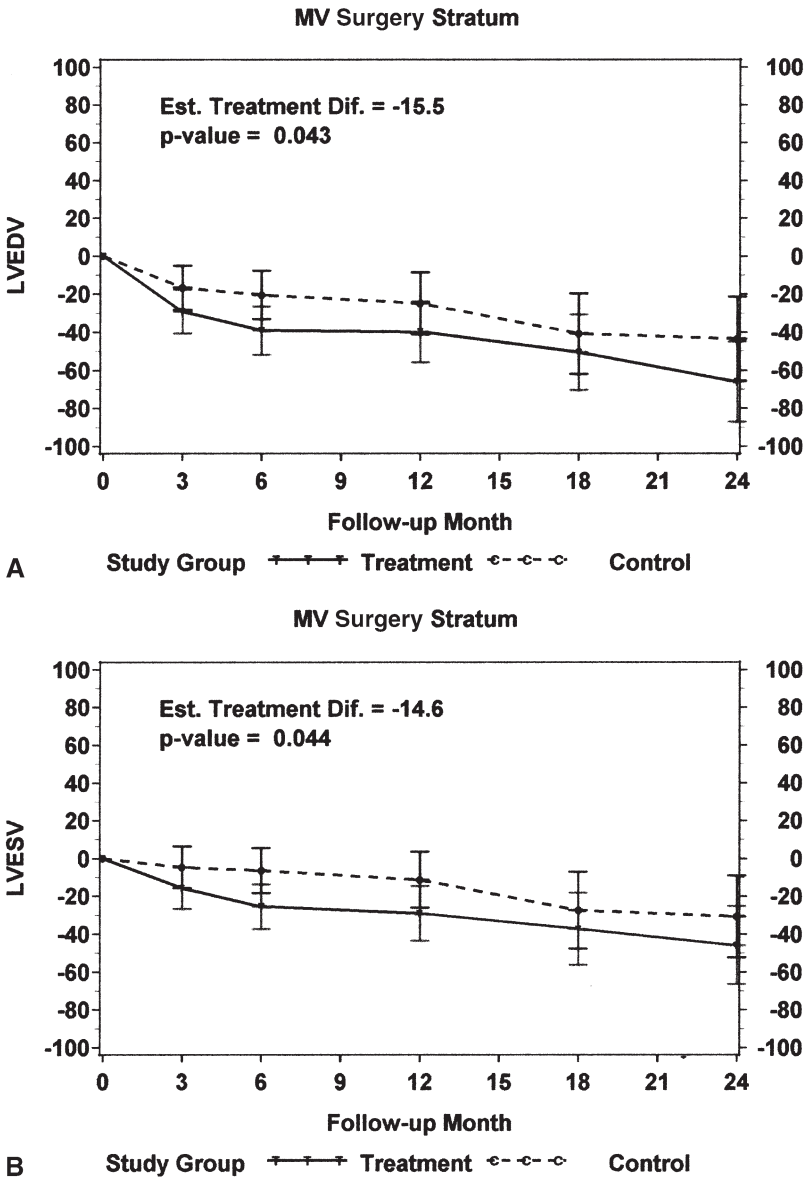

Figure 4. A, Reduction in LVEDV (longitudinal regression analysis) for the control group (no CSD) and treatment group (with CSD). The control group demonstrated a reduction in LVEDV consistent with a reverse remodeling effect from the mitral surgery alone. The treatment group had a statistically significantly greater reduction in LVEDV ($P = .043$), indicating that the CorCap CSD had an additive effect to MV surgery. B, Reduction in LVESV (longitudinal regression analysis) for the control group (no CSD) and treatment group (with CSD). Findings are similar to the changes in LVEDV. See text for discussion. *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume.

follow-up exercise test typically because of clinical deteriorations. Moreover, patients who missed tests had significantly more advanced HF than patients who completed the laboratory tests. Furthermore, patients in the control group were missing tests. Therefore, to avoid the bias produced by missing tests, we performed rank-order analysis. For the 6MWT, patients in the treatment group tended to have a better category than the control group at 6 months (odds ratio [OR] = 1.40; $P = .19$) and 12 months (OR = 1.37; $P = .22$), but neither change was significant. Similarly, for peak VO_2, patients in the treatment group tended to have a better category at 6 months (OR = 1.36 ; $P = .27$) and 12 months (OR = 1.47; $P = .16$), but neither change was significant.

Table 2 summarizes the number of patients experiencing a serious adverse event at any time during follow-up. Overall, 82.4% of the treatment group and 79.4% of the control group had a serious adverse event. The number of patients and types of adverse events were not statistically different between the groups. There were no clinical cases of constriction in any patient.

Discussion

The Acorn Clinical Trial represented a unique opportunity to prospectively assess the safety and efficacy of MV surgery in patients with HF. Twenty-nine centers participated, a single echocardiography core laboratory made all of the cardiac structural measurements, and all patients were

TABLE 2. Patients experiencing serious adverse events by treatment group: Mitral valve surgery stratum

	Treatment (n = 91)		Control (n = 102)		
	No. of patients	Percentage of 91	No. of patients	Percentage of 102	*P* value*
Allergic response	3	3.3	1	1.0	.22
Arrhythmia	33	36.3	44	43.1	.35
Bleeding	6	6.6	13	12.7	.14
Hemodynamic compromise	52	57.1	47	46.1	.13
Hepatic compromise	2	2.2	0	0.0	.14
Infection/pneumonia	33	36.3	28	27.5	.19
Myocardial infarction	0	0.0	1	1.0	.35
Neurologic deficit/stroke	14	15.4	7	6.9	.06
Peripheral thrombus/embolism	2	2.2	2	2.0	.92
Pulmonary compromise	22	24.2	19	18.6	.35
Pulmonary embolism	0	0.0	1	1.0	.35
Renal compromise	8	8.8	6	5.9	.42
Other	36	39.6	43	42.2	.68
Any of the above SAE	75	82.4	81	79.4	.61

SAE, Serious adverse event. *Obtained from Cochran-Mantel-Haenszel test.

treated with intensive background medical therapy. In patients with primarily non-ischemic HF and severe LV dysfunction, the present trial demonstrated that MV surgery was safe, had a low operative mortality rate, and was associated with a remarkable reversal of LV remodeling, as manifested by a decrease in LVEDV and LVESV, an improvement in LVEF and sphericity index, and a reduction in LV mass. MR was effectively reduced and maintained for at least 18 months of follow-up. Patient quality of life was improved, as demonstrated by significant improvements in 2 different quality of life measures and submaximal exercise. Finally, the concomitant implant of the CorCap CSD had an additive effect, with a significantly greater reduction in LV size, a more elliptical shape, and a trend for a reduction in MCPs and improvement in quality of life.

LV remodeling is characterized by progressive LV dilatation and a change to a more spherical shape. In response to infarction or volume overload, the ventricle dilates, resulting in an increased radius of curvature and increased LV wall stress, both of which propagate progressive LV remodeling.[14,15] However, there are no therapies specific for the treatment of progressive LV dilation, which is one of the strongest predictors of mortality.[16,17]

Progressive LV remodeling can also result in functional MR because of annular dilatation, papillary muscle displacement, and chordal tethering. This functional MR leads to increased preload, increased wall tension, and increased LV work load, all of which contribute in a positive feedback loop to progressive HF. The presence of MR is an independent risk factor of poor outcome.[2-4]

Although traditional teaching is that surgical correction of MR may have a prohibitive operative mortality,[18,19] this view has been challenged by Bolling and others.[7-10,14,20-22] The alternate hypothesis is that reconstruction of the MV annulus with an undersized ring, by restoring valvular competency, would alleviate excessive ventricular workload. Tibayan and colleagues[14] reported in an ischemic sheep model of MR that reduction of the annulus by a small ring reduces the radius of curvature of the LV at the base, equatorial, and apical levels. This decrease in the radius of curvature supports the concept that a small ring can restore a more elliptical shape.

In a recent retrospective analysis, Wu and colleagues[23] examined 126 patients treated with MV repair and a control group of 293 patients treated medically and matched by propensity methods. In this nonrandomized series, the outcomes indicated that there was no mortality benefit of MV repair. This study did not report changes in LV size or function or patient symptoms.

In the present trial, the overall 30-day mortality was 1.6%. This is one of the lowest mortality rates of any series[9,20-22] and is especially noteworthy because it represents the outcomes of multiple centers. Repair of functional MR with a small annuloplasty ring remained stable over time with more than 80% of patients with 0/1+ MR at 6 to 18 months. The reversal of LV remodeling, manifested by a decrease in LVEDV and LVESV, an improvement in LVEF and sphericity index, a reduction in LV mass, and an improvement in quality of life and exercise, all suggest that MV surgery in patients with non-ischemic HF is a safe and effective procedure. Because only 6% of patients had ischemic heart disease in this trial, we cannot make statements regarding patients with ischemic MR. Further, a trial in which patients are randomized to MV surgery or medical therapy will be necessary to provide definitive data on the "MR hypothesis."[24]

Passive containment by the CorCap CSD was first reported in an animal model of chronic dilated cardiomyopathy.[25-27] These studies demonstrated that CSD-treated

hearts actually demonstrated significant decreases in volume and improvement in function, all consistent with reverse remodeling. A reversal of remodeling on a cellular and molecular level was further demonstrated.[25-27] More recently, the CSD has also been shown in an acute infarct model to limit infarct expansion, improve myocardial energetics, and attenuate the expression of certain cellular determinants of the remodeling process.[28,29] The results of the multicenter, randomized, prospective trial of the CorCap CSD in patients with advanced HF have been reported.[11] More patients "improved" and fewer patients "worsened" in the CSD group (OR of 1.73) (1.07-2.79; $P = .02$) compared with the control group. The CSD group had fewer MCPs compared with the control group (19 vs 33; $P = .01$), a greater reduction in LV end-diastolic ($P = .008$) and systolic volumes ($P = .017$), a greater improvement in sphericity index ($P = .031$), and improved quality of life. There were no reports of constrictive physiology in these patients.

Although not powered to be considered separately, the MVR stratum demonstrated that the addition of the CorCap CSD to standard MV surgery resulted in significant additive benefit. There was a significantly greater reduction in LV volumes and greater improvements in the sphericity when a CSD was added to MV surgery. In addition, there was a trend toward fewer MCPs. The need for an additive ventricular procedure such as the CSD was suggested by Hung and colleagues,[30] who studied 30 patients with ischemic cardiomyopathy. They demonstrated that recurrent MR after initial repair with ring annuloplasty paralleled increases in LV volumes and sphericity index, suggesting that the effects of the annuloplasty ring can be overwhelmed by ongoing ventricular remodeling.

Conclusion

The low operative mortality, impressive 2-year survival, and evidence of improvement in LV function and NYHA Class after MV surgery show a clear benefit to the surgical elimination of MR and a significant additional benefit with the CorCap CSD. This combined surgical approach results in additional reverse remodeling, minimizing ventricular volumes and optimizing ventricular geometry. Given the improvement in left ventricle structure and function, along with a low mortality rate, physicians should strongly consider offering mitral valve surgery in combination with the CorCap CSD to patients with HF who have been medically optimized yet remain symptomatic with significant MR.

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Discussion

Dr D. Miller (*Stanford, Calif*): I want to be the first to congratulate Dr. Acker and his colleagues for conducting this randomized prospective controlled trial. Few of you realize how much work and effort is involved in bring one of these studies to fruition. This success is a testimonial to the investigators and a credit to the AATS; it represents what we need more of at this meeting and in our journals. This is real science.

I have a question about your patient selection, Mike. They are solid NYHA III, had an LV end-diastolic dimension of 7 cm, an EF of 24%, and a peak VO2 of 14. But, just how sick really were these individuals? Could that perhaps explain why you didn't see differences in survival? The overall survival rate in the Acorn CSD group at two years was 82%. Further, the BNP levels were normal in over half of these patients, which our heart failure cardiologists find hard to believe. You and the Acorn investigators tell me the BNP levels were normal due to the maximal medical therapy these patients were receiving preoperatively, but I am just not sure it was a sick enough subset of patients to demonstrate the differences you wanted to show in terms of survival and clinical benefit.

You told us that the vast majority of your patients had idiopathic or valvular-related cardiomyopathy, not ischemic cardiomyopathy. I would like you to address that fact because I don't want the audience trying this at home in a coronary disease population of patients with CHF. The ischemic MR patients are a totally different kettle of fish.

For those of you who are interested in this field, there was a paper in JACC from Michigan by Aubrey Wu outlining Steve Bolling's entire 10-year experience in February that showed no difference in event-free survival at five years. This has thrown cold water on the whole concept of undersized mitral ring annuloplasty for CHF. Our heart failure cardiologists wondered at the time why was this well-done paper was accepted for publication, since they all thought they already knew a Bolling does not work? Well, the data you have presented today is going to open their eyes. To be fair, however, the Michigan CHF patients were probably sicker than the Acorn patients.

What you have shown convincingly is that there is favorable reverse LV remodeling going on, not just in terms of EDV, but also for LV ESV. The external constraint must be inducing some uncharacterized biological signal that over time is promoting progressive reduction in end-systolic LV volume and a more elliptical LV shape. You also have shown, in contrast to the AHA presentation of the overall Acorn trial last November, that the effects on LV size persist over time. The effectiveness of the Acorn CSD in your patients, which notably was additive to mitral annuloplasty or replacement, was still present out at 18 months. The skeptics at the AHA were saying that the Acorn trial picked an optimal 12-month interval to report their results, but you have now shown there is ongoing salutary reverse remodeling. There was no difference in survival, but it would be very difficult to demonstrate an improvement in survival given the very low mortality rate or even in major adverse clinical events. Can you comment on the postoperative exercise maximum VO2 data? This would reflect more directly whether any functional cardiac benefits were achieved, which would explain why these patients felt better.

Dr Acker. As far as patient selection is concerned, I do believe these were sick patients. These are not generally Class IV patients. These are Class III patients of long duration of heart failure treated remarkably well. I want to point out that the 80% of patients who were on both a beta blocker and ACE inhibitor is the highest rate of use of beta blockers in any randomized trial to date, and I think this really has a tremendous effect on BNP. It is our feeling, especially at Penn, that BNP is not useful in a very, very well managed, medically optimized group of patients to judge their prognosis. In fact, we do not use it at all when we discuss whether someone is a heart transplant candidate or not.

And finally, the recent Cleveland Clinic report of a very sick group of patients shows that 21% of that group of patients had an absolutely normal BNP. So I think though BNP is wonderful for the patient with new heart failure, it is unclear what its value is prognostically in a very well optimally managed medically treated group.

As far as ischemic cardiomyopathy and ischemic MR are concerned, you are right, this study does not address that subgroup of patients. It would be wonderful to do a specific study for ischemic patients. My conjecture is that it still probably is a good idea to eliminate MR if only for symptoms alone, but again, we cannot draw any conclusions on that.

The Michigan paper I think added significantly to the field. I want to remind everyone, it was not a randomized paper. It was a retrospectively case-controlled paper that looked only at survival, and they found that mitral valve annular repair did not impact, was not an independent predictor of outcome survival transplant VAD.

However, they did not look at symptoms, they did not look at LV morphology or ejection fraction as we did in a multi-institutional approach, and I think this does add significantly to the field. Also, what is neat about this multi-institutional approach is that we all know Steve Bolling is an excellent surgeon and he can get these patients through, but what we showed in this study is that 30 different surgeons or more can do this type of operation with a very low mortality of 1.6%.

LV remodeling, which you talked about, we showed is progressive. It is not just the jacket being put on, being tightened down, and of course, the LVs are smaller. In fact, what we saw, as Dr. Miller pointed out, was that the LV remodeling is progressive, indicating that a signal is being changed, perhaps the relief of diastolic wall stress, and this results in a progressive change in the ventricle.

And finally, regarding exercise, the analysis for the entire mitral valve group for exercise is not completed yet, but I suspect it will show a small but significant increase in 6-minute walk and also in peak VO2, though I do have to look at the final statistics to know if that will be significant or not.

Dr Miller: May I ask one more question? It is important to the Wall Street analysts in the audience, if there are any, the cardiologists, Betsy Nabel, who is here with us from NIH, and some surgeons. You and I both know that the mitral regurgitation probably is not the fundamental problem in these CHF patients. As Steve Bolling has told us over and over, "this is a ventricular disease, dummy, not a valvular disease." In 1994, when I discussed Bolling's first report at the Western Thoracic Surgical Association meeting, I said I was flabbergasted that most patients did not die immediately postoperatively. Your results in the mitral ring-only group now prove that Steve's concept has merit, and can be done safely in many centers. The venture capitalists, the big companies, and a dozen or more start-ups, however, mistakenly believe that the MR is the primary problem, not the ventricle. They are working on minimizing functional MR (FMR) and IMR with an indirect coronary sinus "Cerclage" approach or doing something akin to an Alfieri suture between the leaflets. Do you think this thrust is missing the boat? Do you think they have any plausible hope of affecting subvalvular left ventricular geometry, which might then induce the favorable LV reverse remodeling changes that you have presented today after a small mitral ring or mitral valve replacement?

Dr Acker. You and I have similar views on this, as you know. There are all different types of percutaneous approaches. The majority that deal just with the coronary sinus with the attempts of effecting the annulus substantially, and more importantly, the ventricle, I believe will fail. There are other noninvasive approaches that are ventricular approaches that may have benefit. But I think what it does speak to is that when one does this operation, one probably does need, at least in my belief, to add a ventricular solution to a ventricular problem, such as the Acorn CorCap, which can be easily combined with mitral valve surgery to really affect the ventricular problem.

Dr G. Bolotin (*Tel-Aviv, Israel*). Do you have any data regarding the severity of the adhesions from the Acorn device if the patient in the future needs a heart transplant?

Dr Acker. Yes. There have been several heart transplants done worldwide with people who have had Acorn jackets. Sometimes the adhesions are severe, but no more severe than any difficult redo. The adhesions are less severe than a redo LVAD/BVAD out six months or more. You must give yourself enough time to dissect through the adhesions, and we had no deaths in the entire group and all the heart transplants were successful.

Appendix E1: Clinical Centers

Advocate Christ Medical Center, Oaklawn, Ill: M. Slaughter, M. Silver, T. George, H. Lonergan-Thomas; Albert Einstein College of Medicine, Bronx, NY: T. LeJemtel, M. Camacho, N. Cesare, P. Sicilia; Baylor College of Medicine/VAMC Houston, Tex: E. Soltero, D. Mann, T. Lynch; Boston Medical Center, Boston, Mass: R. Shemin, G. Philippides, M. Cheney; Bryan LGH Heart Institute, Lincoln, Neb: E. Raines, S. Krueger, V. Norton; Cedars-Sinai Medical Center, Los Angeles, Calif: K. Magliato, S. Khan, L. Defensor, M. De Robertis, D. Gallegos; Cleveland Clinic Foundation, Cleveland, Ohio: N. Smedira, R. Starling, R. Schott, B. Gus; Columbia-Presbyterian Medical Center, New York, NY: N. Edwards, D. Mancini, K. Idrissi, J. Dimitui Vallarta; Duke University Medical Center, Durham, NC: C. Milano, S. Russell, S. Welsh, A. Skye, R. Larsen; Henry Ford Hospital, Detroit, Mich: R. Brewer, B. Czerska, K. Leszczynski, N. Wulbrecht; Hospital of the University of Pennsylvania, Philadelphia, Pa: M. Acker, M. Jessup, S. Baker, M. O'Hara; Jewish Hospital at University of Louisville, Louisville, Ky: R. Dowling, G. Bhat, L. Muncy, K. Daley; Nebraska Heart Institute, Lincoln, Neb: D. Gangahar, K. Ayala, L. Taylor; New England Medical Center at Tufts University, Boston, Mass: K. Khabbaz, D. DeNofrio, C. Grodman; Newark Beth Israel, Newark, NJ: D. Goldstein, M. Zucker, J. Casida; Oschner Heart and Vascular Institute, New Orleans, La: C. Van Meter, M. Mehra, B. Harris; Penn State/Milton Hershey Medical Center, Hershey, Pa: W. Pae, J. Boehmer, P. Ulsh, K. McFadden; Royal Victoria Hospital/McGill University, Montreal, PQ, Canada: R. Cecere, N. Giannetti, C. Barber; St Louis University, St Louis, Mo: A. Aharon, P. Hauptman, M. Jacob; Stanford University Medical Center/Kaiser Permanente, Stanford, Calif: R. Robbins, M. Fowler, D. Weisshaar, A. Mullin, K. Town; University of Alabama at Birmingham, Birmingham, Ala: J. Kirklin, B. Rayburn, K. Harper; University of Florida/Shands Hospital, Gainesville, Fla: E. Staples, J. Aranda, D. Leach; University of Maryland Medical Center, Baltimore, Md: J. Gammie, S. Gottlieb, J. Marshall; University of Michigan Hospital, Ann Arbor, Mich: S. Bolling, K. Aaronson, M. Jessup, P. Obriot; University of Minnesota Medical Center, Minneapolis, Minn: S. Park, L. Miller, J. Graziano; University of Pittsburgh Medical Center, Pittsburgh, Pa: K. McCurry, S. Murali, T. Ryan, D. Zaldonis; VA Medical Center San Diego Health Care System, San Diego, Calif: M. Madani, R. Shabetai, C. Jaynes, R. Cremo, N. Gardetto; VA Medical Center Minneapolis, Minneapolis, Minn: H. Ward, I. Anand, J. Whitlock; Washington Hospital Center, Washington, DC: M. Dullum, B. Carlos, J. Richmond, C. Bither, W. Varmer; Steering Committee: D. Mann (Principal Investigator), M. Acker, M. Jessup, H. N. Sabbah, R. Starling; Data and Safety Monitoring Committee: G. Francis (Chair), J. Neaton, D. Homans, C. O'Connor, W. Curtis. Clinical Events Review Committee: S. Goldstein (Chair), F. Spinale, J. Lindenfeld.

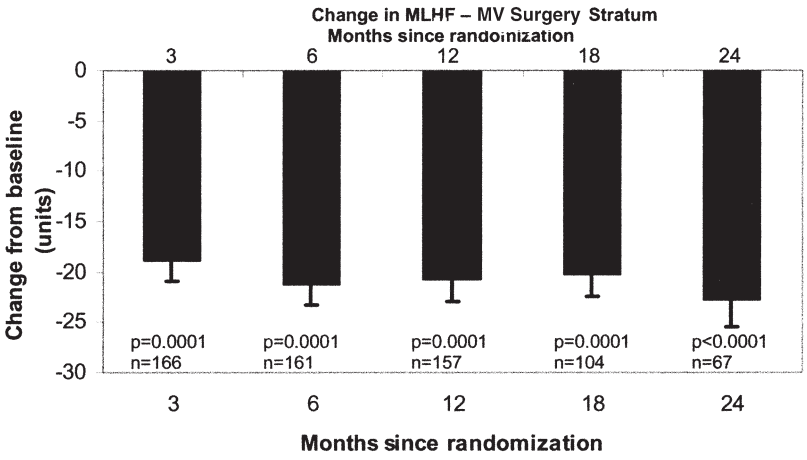

Figure E1. Changes in quality of life as measured by the MLHF for the entire group of 193 patients in the MV surgery stratum. A reduction in MLHF indicated an improvement in quality of life. There were significant improvements in quality of life at 3, 6, 12, and 18 months. *MLHF,* Minnesota Living with Heart Failure Questionnaire.

ACD

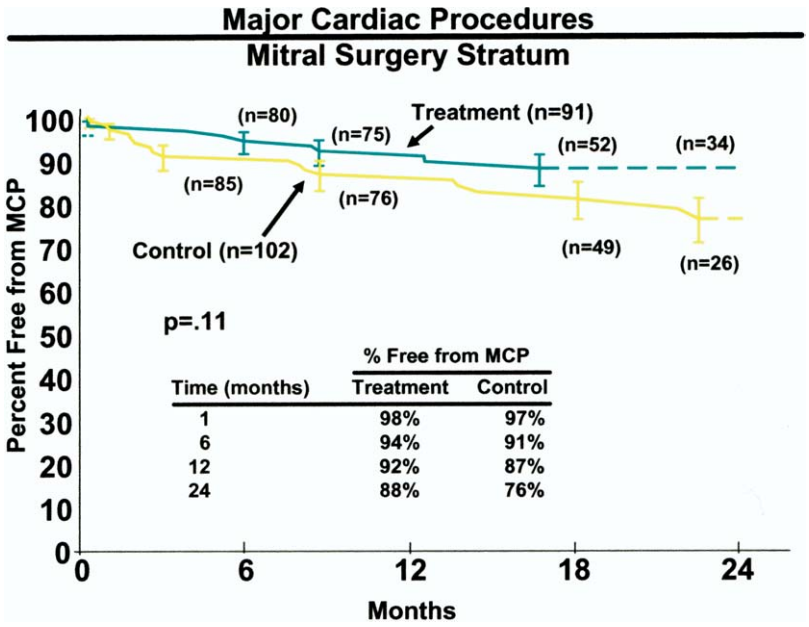

Figure E2. Kaplan-Meier freedom from MCPs for the entire group of 193 patients in the MVR stratum. The control group (*bold line*; n = 102 patients) had a greater number of MCPs than the treatment group (*regular line*; n = 91 patients). *MCP,* Major cardiac procedure.

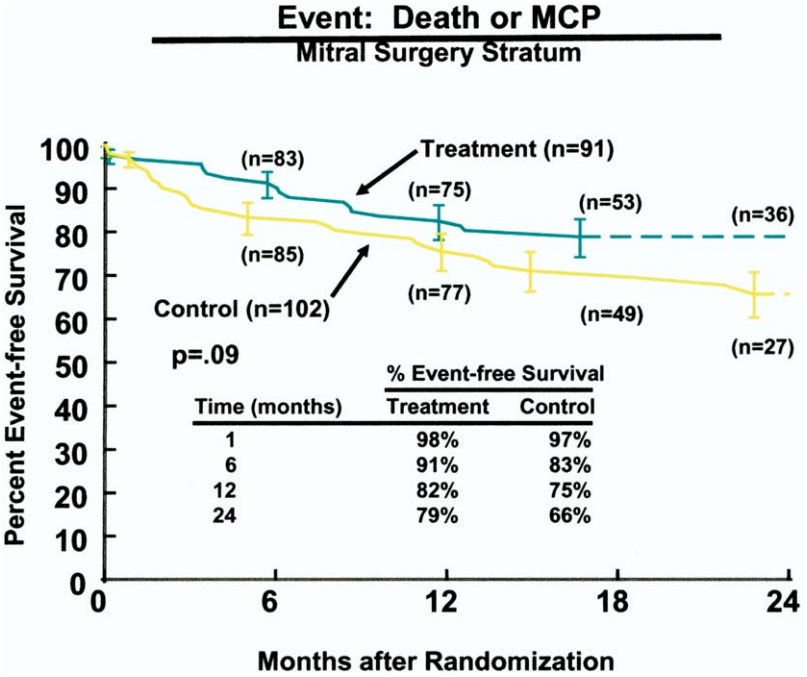

Figure E3. Kaplan-Meier freedom from the combined end point of death or MCP for the 193 patients in the MV surgery stratum. Control patients tended to have more deaths and MCPs when compared with the treatment group (*P* = .09). *MCP,* Major cardiac procedure.

ACD

TABLE E1. Baseline characteristics: Mitral valve replacement stratum

Baseline characteristic	No. with data	Mean or percentage
Age (y)	193	53.4
No. of previous hospitalizations	193	1.0
Years since heart failure diagnosis	193	4.7
LVEDD (mm) (site)	193	69.7
LV volume (mL) core	174	270.1
LVEF (%) (site)	193	23.9
6-minute walk distance (m)	191	344.3
MLHF score	193	58.8
Physical Function Domain, SF-36	192	37.1
General Health Domain, SF-36	193	36.8
Peak $V0_2$ (mL/kg/min) site	172	14.4
BUN (mg/dL)	193	23.4
Creatinine (mg/dL)	193	1.2
Sodium (meq)	193	138.5
Heart rate	193	77.3
DBP (mm Hg)	193	70.0
SBP (mm Hg)	193	111.1
Gender: male	88	45.6
Gender: female	105	54.4
Race: white	116	60.1
Race: black	59	30.6
Race: other	18	9.3
NYHA Class II (site assessed)	45	23.3
NYHA Class III (site assessed)	138	71.5
NYHA Class IV (site assessed)	10	5.2
Percentage on beta-blocker	155	80.3
Percentage on ACE or ARB	188	97.4
Percentage on spironolactone	84	43.5
Cause†		
Ischemic heart disease	12	6.2
Idiopathic	117	60.6
Valvular	33	17.1
Other	52	27.0

LVEDD, Left ventricular end-diastolic diameter; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *MLHF*, Minnesota Living with Heart Failure Questionnaire; *SF-36*, Short-Form 36; *BUN*, blood urea nitrogen; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *NYHA*, New York Heart Association; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker. **P* value is based on comparing log-transformed mean values. †Patients can have more than 1 cause.

TABLE E2. Mitral valve ring type

Ring type	No. of patients	Percentage of 155
Baxter/Cosgrove/Edwards (Edwards Lifesciences, Irvine, Calif)*	67	43.2
Physio-ring (Edwards Lifesciences)	31	20.0
Duran (Medtronic, Minneapolis, Minn)	22	14.2
Carbomedics (Austin, Tex)	16	10.3
Carpentier-Edwards (Edwards Lifesciences)	12	7.7
Seguin (St Jude Medical, St Paul, Minn)	6	3.9
St Jude Tailor (St Jude Medical)	1	0.6

*These include Baxter Physio rings, Cosgrove Edwards Annuloplasty rings, and Edwards Lifesciences rings.