Edge-to-edge with partial band mitral valve repair compared to replacement and undersized restrictive annuloplasty for ischemic mitral regurgitation

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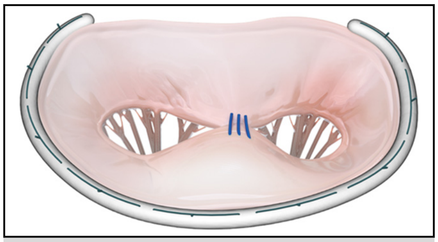
ABSTRACT

Objective: Evidence supports replacement over repair for ischemic mitral regurgitation due to improved durability; however, the latter often involves an undersized ring annuloplasty that does not include edge-to-edge approximation. The objective of this study was to evaluate the outcomes of replacement, edge-to-edge leaflet approximation with mild-undersized annuloplasty and undersized ring annuloplasty for ischemic mitral regurgitation.

Methods: This is a single-center retrospective study of patients undergoing mitral surgery for moderate-severe or greater ischemic mitral regurgitation, between 2004 and 2020, with mild-undersized annuloplasty, mitral valve replacement, or undersized restrictive annuloplasty (undersized ring annuloplasty). The primary outcome was all-cause mortality. Secondary outcomes included first recurrence of mitral regurgitation, heart failure hospitalization, and composite of valve-related events (bleeding, thromboembolism, endocarditis, and mitral valve reoperation).

Results: There were 121, 93, and 78 patients in the mitral valve replacement, mild-undersized annuloplasty, and undersized restrictive annuloplasty groups, respectively, with a median follow-up of 3.1, 5.9, and 3.8 years, respectively. Both mitral valve replacement (hazard ratio, 1.87; 95% CI, 1.029-3.415) and undersized restrictive annuloplasty (hazard ratio, 2.73; 95% CI, 1.480-5.061) were associated with worse survival compared with mild-undersized annuloplasty. At 2 years, the rate of mild-moderate mitral regurgitation was greater in the mild-undersized annuloplasty group compared with the mitral valve replacement group ($P = .001$) but less than in the undersized restrictive annuloplasty group ($P = .001$). The rate of recurrent moderate or greater mitral regurgitation at 2 years was similar between mild-undersized annuloplasty and mitral valve replacement groups but significantly higher after undersized restrictive annuloplasty ($P < .0001$). Mitral valve replacement and undersized restrictive annuloplasty were associated with a significant increase in the incidence of first heart failure hospitalization compared with mild-undersized annuloplasty ($P < .001$ and $P = .001$, respectively). Mitral valve replacement was associated with an increased incidence of valve-related events compared with mild-undersized annuloplasty ($P = .002$).

Conclusions: Surgical edge-to-edge approximation in addition to a mild-undersizing annuloplasty offers similar durability compared with replacement, with a lower rate of hospitalization for heart failure, and may confer a survival advantage. (JTCVS Techniques 2024;23:26-43)



Edge-to-edge repair with mild-undersized annuloplasty for IMR.

CENTRAL MESSAGE

Edge-to-edge repair with mild-undersizing offers similar durability to replacement, with lower HF hospitalization and improved survival after surgery for IMR.

PERSPECTIVE

Current evidence supports MVR over URA in IMR due to improved durability. Surgical edge-edge repair with mild-undersizing offers a similar rate of recurrent moderate MR as MVR. Surgical edge-edge repair with mild-undersizing was associated with lower rate of HF hospitalization and improved long-term survival compared with MVR or URA.

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Abbreviations and Acronyms

CAD = coronary artery disease
HF = heart failure
HR = hazard ratio
IMR = ischemic mitral regurgitation
MR = mitral regurgitation
MVR = mitral valve replacement
MVr = mild-undersizing annuloplasty with edge-to-edge approximation
PML = posterior mitral leaflet
SHR = subhazard ratio
TVr = tricuspid valve repair
URA = undersized restrictive annuloplasty

Coronary artery bypass grafting remains the treatment of choice for most patients with multivessel coronary artery disease (CAD) and left ventricular dysfunction.[1] This pathology may be accompanied by the presence of ischemic mitral regurgitation (IMR), which has a poor prognosis, with reported mortality up to 27% to 40% at 5 years.[2] IMR is the result of left ventricle global remodeling and papillary muscle displacement, leading to a combination of annular dilatation and tethering of the posterior mitral leaflet (PML), resulting in a coaptation defect.

Recent guidelines recommend mitral valve surgery for severe IMR when surgical myocardial revascularization is undertaken,[3] because IMR may contribute to worsening heart failure (HF) if left untreated.[4] Traditionally, many groups have advocated for the use of mitral valve repair with an undersized restrictive annuloplasty (URA).[5-8] The Cardiothoracic Surgical Trials network randomized control trial comparing URA with mitral valve replacement (MVR) for severe IMR demonstrated that the recurrence of moderate or greater mitral regurgitation (MR) was increased in the URA group at 2 years compared with MVR, and this was associated with a greater incidence of HF-related adverse events.[9] Although MVR offers a better long-term correction of IMR, it is associated with valve-related morbidity[7] and is far from the optimal treatment strategy.

Although URA reduces antero-posterior annular dilation, significant undersizing may come at the expense of further papillary muscle displacement, exacerbating tethering force at the PML.[10] We believe that mitral valve repair with undersizing and a complete ring may be compromised by increased leaflet tethering, hastening failure. Furthermore, in patients with cardiomyopathy, a ring alone also will not optimally address coaptation.

On the other hand, the principle of edge-to-edge leaflet approximation confers benefit in this population using transcatheter mitral repair. In patients with HF and severe functional MR, transcatheter edge-to-edge repair lowers hospitalization for HF and improves survival compared with medical therapy.[11] We hypothesized that routine use of a surgical edge-to-edge (Alfieri) repair, in addition to a mild-undersized annuloplasty band, as opposed to a complete ring, may improve the surgical outcome for repair of IMR. The objective of this study was to compare the early and late outcomes of patients undergoing repair using mild-undersizing annuloplasty with edge-to-edge approximation (MVr) compared with MVR, as well as URA alone, in the setting of IMR.

MATERIAL AND METHODS

Study Design

This was a retrospective cohort study of prospectively collected clinical data. We used the STROBE criteria for reporting this observational trial.[12]

Setting

Patients were identified who had undergone surgery for IMR between September 2004 and June 2020 at the University of Ottawa Heart Institute, which is a quaternary referral center and is the only cardiac center serving a population of more than 2 million patients in eastern Ontario and western Quebec. Postoperatively, patients were followed by their primary cardiologist who directed their medical therapy. All patient information was collected prospectively in a dedicated surgical database that captures detailed information on preoperative, periprocedural, and postoperative variables. Echocardiograms were obtained in a subset of patients followed in a dedicated valve clinic. The electronic medical record was reviewed to document recent visits and dates, and the family physician or cardiologist was contacted if necessary. The institutional ethics board provided approval to analyze the de-identified, prospectively collected data (Institutional Review Board Protocol #20210387-01H, June 8, 2021). Individual patient consent was waived.

Participants

All charts were screened among patients undergoing mitral valve intervention with a documented history of CAD as defined by prior myocardial infarction, prior revascularization, or presence of CAD on preoperative angiogram. Echocardiograms and operative reports were screened to identify ischemic etiology of MR as defined by the following: annular dilatation (Carpentier type I) or restricted mitral valve leaflet (particularly posterior), and apical tethering due to left ventricle dysfunction (Carpentier type IIIb) leading to abnormal leaflet coaptation or pseudo-prolapse. Angiogram reports were screened to identify obstructive coronary disease. Patients were included if they were undergoing MVR or repair with MVr or URA for IMR (Figure E1). Patients were excluded if they were undergoing aortic valve replacement or emergency acute mitral valve intervention for ruptured papillary muscles, or if the primary mechanism of the MR was structural (chordal or leaflet). Patients who had a functional nonischemic mechanism of regurgitation and those without CAD were excluded.

Operative Procedures

This was a concurrent series, and the valve procedure was based on the surgeon's preference. Whereas there was directed referral of MR cases involving degenerative disease, cases of IMR were randomly distributed to all surgeons throughout the study period. Valves were implanted with horizontal mattress sutures of 2-0 pledgeted polyester sutures. The choice of prosthetic valve was according to the discretion of the surgeon. The subvalvular apparatus of the posterior leaflet was preferentially preserved,

TABLE 1. Demographics and operative variables in MVr, MVR, and URA groups

Variable	MVr (n = 93)	MVR (n = 121)	URA (n = 78)	*P*
Age (y)	69 (62-75)	69 (61-76)	70 (62-76)	.904
Atrial fibrillation	27 (29.0)	39 (32.2)	20 (25.6)	.606
BSA	1.92 ± 0.23	1.90 ± 0.21	1.90 ± 0.22	.795
CABG	76 (81.7)	101 (84.2)	81 (95.3)	.018
CCS				.100
0	42 (45.2)	47 (38.8)	28 (35.9)	
I	7 (7.5)	12 (9.9)	4 (5.1)	
II	17 (18.3)	25 (20.8)	12 (14.1)	
III	17 (18.3)	12 (10.0)	11 (12.9)	
IV	10 (10.8)	24 (20.0)	25 (29.4)	
Creatinine clearance <60 mL/min	47 (50.5)	56 (46.3)	38 (48.7)	.823
CVA	4 (4.3)	10 (8.3)	7 (9.0)	.418
Current smoking	30 (32.3)	32 (26.4)	14 (18.0)	.104
Diabetes	31 (33.3)	42 (34.7)	37 (47.4)	.113
Dialysis	3 (3.2)	1 (0.8)	2 (2.6)	.440
euroSCORE > 10	27 (29.0)	43 (35.5)	25 (32.1)	.599
Female	26 (28.0)	42 (34.7)	23 (29.5)	.533
Hypertension	69 (74.2)	86 (71.2)	62 (79.5)	.415
Insulin	10 (10.8)	22 (18.2)	12 (15.4)	.320
NYHA				.138
1	10 (10.8)	10 (8.3)	16 (20.5)	
2	27 (29.0)	28 (23.1)	16 (20.5)	
3	45 (48.3)	60 (49.6)	36 (46.1)	
4	11 (11.8)	23 (19.0)	10 (12.8)	
Peripheral vascular disease	11 (11.8)	10 (8.3)	7 (9.0)	.665
Left main	17 (18.3)	29 (24.0)	22 (28.2)	.302
Vessels diseased	3 (2,3)	3 (2,3)	3 (2,3)	.375
Preoperative MI	71 (76.3)	92 (76.0)	61 (78.2)	.844
Prior PCI	18 (19.4)	30 (24.7)	15 (19.2)	.531
Prior CABG	8 (8.6)	12 (9.9)	1 (1.3)	.058
Recent MI (<6 wk)	33 (35.5)	45 (37.5)	34 (40.0)	.824
Preoperative IABP	3 (3.2)	6 (5.0)	5 (6.4)	.620
Operative priority				.532
Elective	52 (55.9)	55 (45.5)	36 (46.2)	
Urgent	32 (34.4)	55 (45.5)	35 (44.9)	
Emergency	9 (9.7)	11 (9.1)	7 (9.0)	
Degree MR				<.001
Moderate	8 (8.7)	5 (4.5)	15 (20.0)	
Moderate-severe	38 (41.3)	37 (33.3)	37 (49.3)	
Severe	46 (50.0)	69 (62.2)	23 (30.7)	
Left atrial size (cm)	4.7 (4.2-5.1)	4.5 (4-5)	4.4 (4.2-4.9)	.278
LVESD (cm)	4.8 (4.2-5.3)	4.6 ± 1.1	4.6 ± 1.0	.587
LVEDD (cm)	5.9 (5.3-6.4)	5.6 (5.1-6.4)	5.7 (5.3-6.3)	.327
LVEF (%)	39 (30-52)	39 (30-52)	36 (30-45)	.493
RVSP (mm Hg)	45 (35-50)	45 (35-58)	44 (36-52)	.708

(Continued)

TABLE 1. Continued

Variable	MVr (n = 93)	MVR (n = 121)	URA (n = 78)	*P*
Mechanism MR				
Annular dilation (type I)	55 (59.1)	58 (48.7)	44 (56.4)	.287
Restriction (type IIIb)	72 (77.4)	101 (84.2)	62 (79.5)	.439
Severe MR	46 (49.5)	69 (57.0)	23 (29.5)	.001
CPB time (min)	137 (113-157)	141 (120-174)	133 (115-155)	.092
XC time (min)	95 (80-112)	99 (84-120)	93 (79-108)	.215
No. distals	2 (1-3)	2 (2-3)	3 (2-3)	<.001
Redo sternotomy	9 (9.7)	14 (11.6)	2 (2.6)	.077
Mechanical valve	-	11 (9.3)	-	-
TVr	11 (11.8)	18 (14.9)	6 (7.7)	.313
Aortic surgery	1 (1.1)	0	0	.342
Arrhythmia surgery	16 (17.2)	16 (13.2)	10 (12.8)	.641

Continuous results presented mean ± standard deviation or median (IQR). Categorical variables presented as number (%). *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *BSA*, body surface area; *CABG*, coronary artery bypass grafting; *CCS*, Canadian Cardiovascular Society (Class 0–asymptomatic; I–normal activity; II–slightly limited; III–markedly limited; IV–symptoms at rest); *CVA*, cerebrovascular accident; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *NYHA*, New York Heart Association class (Class, 1 – asymptomatic; 2 – slightly limited; 3 – markedly limited; 4 – symptoms at rest); *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *IABP*, Intra-aortic baloon pump; *MR*, mitral regurgitation; *LVESD*, left ventricular end-systolic dimension; *LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction; *RVSP*, estimated right ventricular systolic pressure; *CPB*, cardiopulmonary bypass; *XC*, crossclamp time; *TVr*, tricuspid valve repair.

whereas the anterior leaflet was resected. MVr was completed with an incomplete annuloplasty band (CG Future Annuloplasty Band or Duran Band) sized according to the surface of the anterior mitral leaflet. Annuloplasty sutures were placed in horizontal mattress fashion using 2-0 polyester, with successive suture overlap in the P2-P3 region of the annulus. An Alfieri stitch was placed between the medial aspect of A2 and P2 using 2 4-0 polytetrafluoroethylene interrupted sutures (Gore-Tex, WL Gore & Associates). To ensure an adequate mitral orifice area, the medial and lateral orifices were sized with Hegar dilators, for a minimum a total cutoff diameter of 28 mm (sum of both dilator sizes). For URA, an annuloplasty band (Future or Duran) was chosen by sizing the anterior leaflet and then choosing a prosthesis 1 to 2 sizes smaller. Myocardial protection was provided using antegrade cold (4 °C) blood cardioplegia.

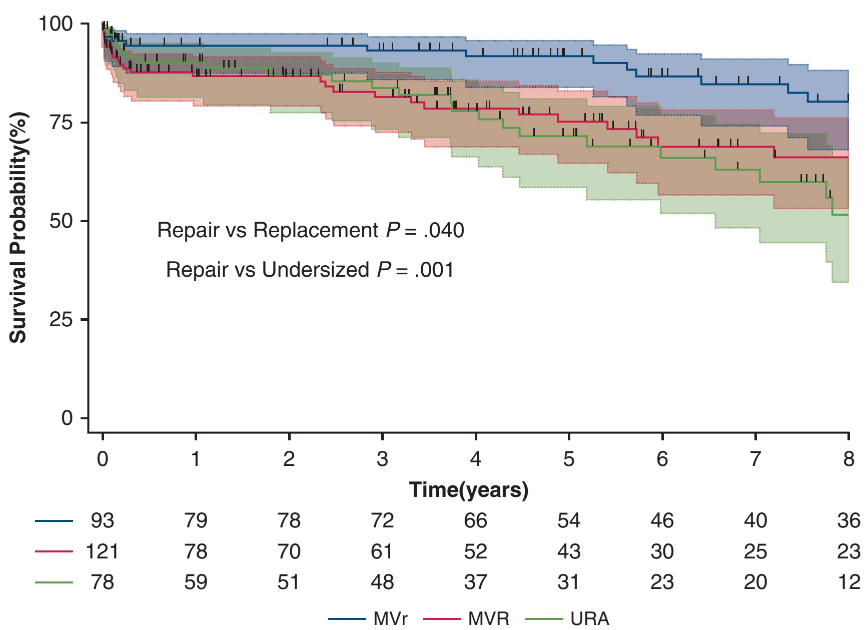

FIGURE 1. Freedom from all-cause mortality in patients undergoing surgery for IMR. *Shaded lines* represent 95% CI. *Hash marks* represent each censoring time. Groups analyzed using multivariable Cox proportional hazards model. *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

TABLE 2. Covariates associated with long-term survival after surgery for ischemic mitral regurgitation

Mitral valve intervention	Hazard ratio (95% CI)	*P*
MVr	Reference	
MVR	1.874 (1.029-3.415)	.040
URA	2.736 (1.480-5.061)	.004
Left main	1.815 (1.090-3.023)	.022
Prior PCI	2.069 (1.205-3.552)	.008
Dialysis	4.007 (1.378-11.649)	.011
Creatinine clearance <60 mL/min	2.074 (1.275-3.372)	.003

Multivariable Cox proportional hazards model with 10-fold imputation for missing variables. *CI*, Confidence interval; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *PCI*, percutaneous coronary intervention.

Echocardiography

MR severity was assessed by a level 3 echocardiographer as mild, moderate, and severe based on integrative criteria using transthoracic echocardiography. The assessment of the severity of MR was guided by the ratio of the jet area to the left atrial area, the width of the vena contracta, the density of the continuous-wave Doppler profile, the pulsed-Doppler mitral inflow pattern, the pulmonary-vein systolic flow pattern, the proximal isovelocity surface area radius, and the quantitative measures of effective regurgitant orifice area and regurgitant volume, where available.[13] Patients not fulfilling criteria for mild or severe regurgitation were subsequently subclassified where possible as mild-moderate or moderate or moderate-severe, based on the effective regurgitant orifice area and regurgitant volume where available or based on whether the majority of the specific criteria were suggestive of mild or severe regurgitation, respectively.[13]

Outcomes

The primary outcome was the rate of long-term all-cause mortality. Secondary outcomes included the rates of recurrence of mild-moderate or greater and moderate or greater MR, and hospitalization for HF and the composite of valve-related events (bleeding, thromboembolism, endocarditis, mitral valve reoperation) as defined by Mitral Valve Academic Research Consortium.[14]

Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median (interquartile range). Categorical variables were reported as counts and percentages. One-way analysis of variance with Bonferroni correction for multiple comparisons and Kruskal–Wallis tests were used to compare continuous variables. For categorical variables, chi-square was used. The Shapiro–Wilk test was used to test normalcy of data. Event time was defined as the date of the index surgery until the date of the event or, if censored at the back end, the date of the last follow-up.

Multiple imputation was applied to continuous variables with less than 10% missing (Table E1). The imputation model included all covariates and outcomes as well as the derived cumulative hazard.[15,16] A total of 10 datasets were imputed, of which regression coefficients and standard errors were pooled using Rubin's rules.[17] Multivariable Cox proportional hazards regression models were used for time-to-event outcomes using stepwise regression. The proportionality assumption was tested using Schoenfeld residuals.

We estimated the cumulative incidence of each of the secondary outcomes by using cumulative incidence functions, assessing for significance of differences between groups using the Fine and Gray subdistribution hazard model with death as a competing risk. The measures of association were the hazard ratio (HR) with 95% CIs and subhazard ratios (SHRs). Serial echocardiographic measures of mitral valve gradients, left ventricular end-diastolic diameter, and ejection fraction were analyzed as panel data with random effects models. All statistical analyses including multiple imputation and plots were performed with Stata version 17.0 (StataCorp LLC).

Sensitivity Analysis

The primary outcome was further tested to assess the effect of the operating surgeon by pairwise treatment-effects analysis in the following groups: MVr versus MVR, MVr versus URA, and MVR versus URA. In each pair, propensity scores were derived using the following covariates: surgeon, age, sex, number of distals, diabetes, hypertension, creatinine, preoperative New York Heart Association class, preoperative Canadian Cardiovascular Society class, preoperative myocardial infarction, recent myocardial infarction, prior percutaneous coronary intervention, current smoking, cerebrovascular accident, dialysis, peripheral vascular disease, atrial fibrillation, priority class, and reoperation. The analysis was completed using Cox proportional hazards with inverse proportional treatment weighting to derive the average treatment effect.

RESULTS

Patient flow is illustrated in Figure E1. There were 93 patients in the MVr group, 121 patients in the MVR group, and 78 patients in the URA group. Baseline demographics and operative differences between the 2 valve groups are presented in Table 1. There were no major differences between the groups, but more patients in the URA group underwent concomitant coronary artery bypass grafting ($P = .005$) with more grafts ($P < .001$). The median European System for Cardiac Operative Risk Evaluation was similar between all the groups (MVr 5.9 [3.4-10.6], MVR 6.4 [3.5-13.1], URA 7.6 [4.2-11.9] $P =$ NS). In those patients in whom the mitral jet was reported, it was central in 29.2% in the MVr group, 21.5% in the MVR group, and 30.8% in the URA group ($P =$ NS). Median band size was smaller in the URA group (28 mm [28-30]) compared with the MVr group (30 mm [28-30]); however, this was not significant ($P = .324$). Median valve size in the MVR group was 29 mm (27-31).

Follow-up was significantly longer in the MVr group (5.9 years [3.5-10.7]) compared with the MVR (3.1 years [0.3-6.0]) and URA (3.8 years [1.0-7.0]) groups ($P < .001$).

Perioperative outcomes in the 2 groups are listed in Table E2. The incidences of prolonged ventilation and the need for renal replacement therapy were increased in the MVR group, but these were not statistically significant. There was no difference in 30-day mortality between groups ($P = .465$). Intensive care unit length of stay was prolonged in the MVR group ($P = .004$), as was the hospital length of stay ($P = .003$).

Primary Outcome

The numbers of primary and secondary outcome events in the 3 groups are listed in Table E3. The Kaplan–Meier curve illustrating long-term survival in the 3 groups is

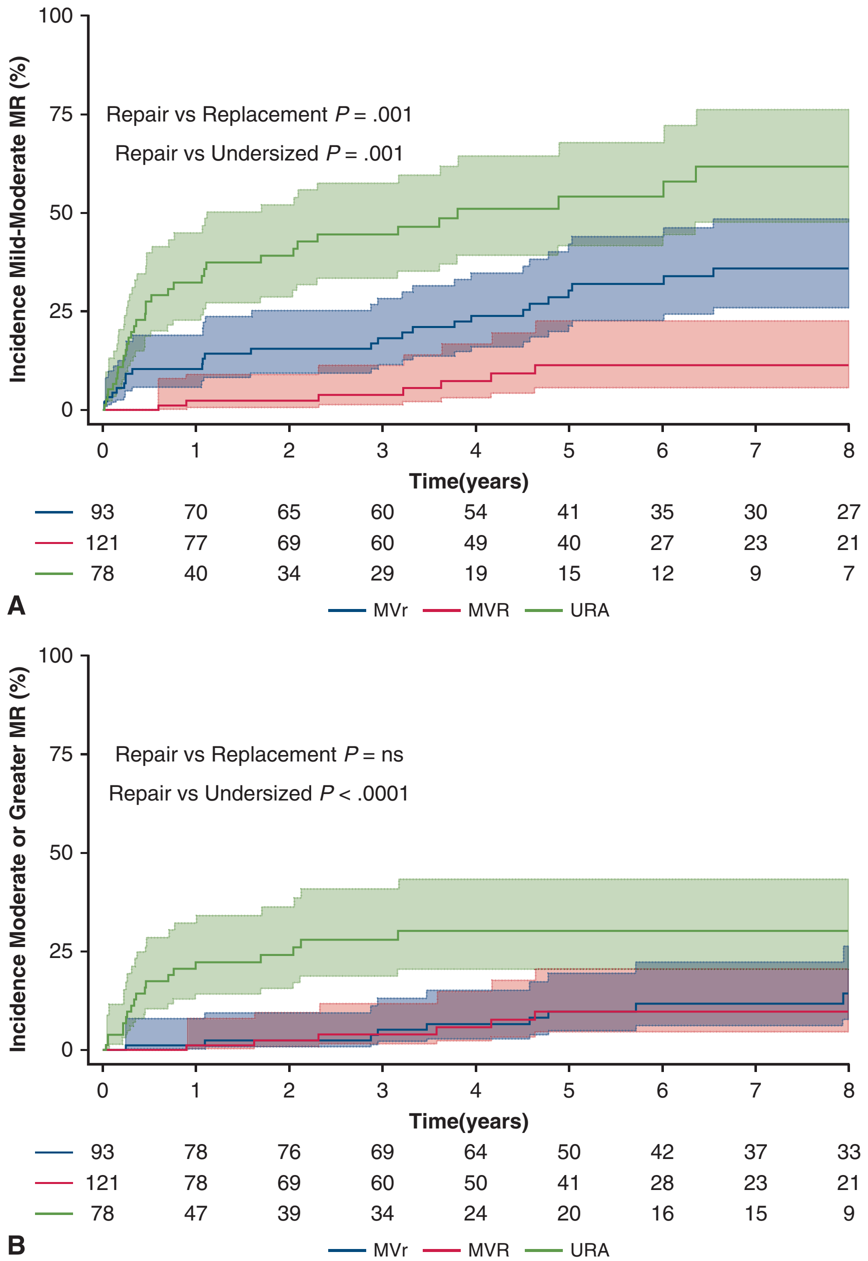

FIGURE 2. A, Incidence of mild-moderate or greater MR in patients with IMR with all-cause death as a competing event. B, Incidence of moderate or greater MR in patients with IMR with all-cause death as a competing event. *Shaded lines* represent 95% CI. *MR*, Mitral regurgitation; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

shown in Figure 1. Factors associated with long-term mortality in the multivariable Cox analysis are presented in Table 2. These included MVR (P = .040), URA (P = .001), left main (P = .022), prior percutaneous coronary intervention (percutaneous coronary intervention, P = .008), preoperative dialysis (P = .011), and low creatinine clearance (P = .003).

The effect of preoperative severe MR is shown in Figure E2 and Table E4. There was no significant difference in the survival among patients stratified by preoperative MR severity (P = .539). The 2- and 5-year survivals in the 3 groups are shown in Table E5.

Secondary Outcomes

The rate of recurrence of mild-moderate MR or greater in the 3 groups is shown in Figure 2, *A*. Mild-moderate MR in the MVr group was greater than in the MVR group (SHR, 0.294 [0.141-0.615], P = .001) but less than in the URA group (SHR, 2.395 [1.448-3.963], P = .001). The incidence of mild-moderate or greater MR at 2 years in the MVr group

TABLE 3. Secondary outcomes after surgery for ischemic mitral regurgitation

Outcome	MVr	MVR		URA	
		SHR (95% CI)	*P*	SHR (95% CI)	*P*
First HF hospitalization	Ref	5.522 (2.190-13.922)	<.001	5.441 (2.061-14.365)	.001
Reoperation	Ref	1.903 (0.596-6.078)	.277	0.824 (0.158-4.306)	.818
Valve-related events	Ref	2.725 (1.424-5.215)	.002	1.000 (0.403-2.485)	.999

Analyzed using Cox proportional hazards model with all-cause death as competing risk and MVr as reference (Ref). *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *SHR*, subhazard ratio; *CI*, confidence interval; *HF*, heart failure.

was 15.6% (95% CI, 9.3-25.4), 2.4% in the MVR group (95% CI, 0.1-9.2), and 38.6% in the URA group (95% CI, 28.1-51.6). The rate of recurrence of moderate MR or greater in the 2 groups is shown in Figure 2, *B*. This was similar between the MVr and MVR groups (SHR, 0.842 [0.344-2.060], $P = .706$) but significantly higher after URA (SHR, 4.540 [2.208-9.335], $P < .001$). The incidence of moderate MR or greater at 2 years was 2.5% (95% CI, 0.6-9.5) and 1.8% (95% CI, 0.6-9.7) in the MVr and MVR groups, respectively, whereas it was 26.9% (95% CI, 17.8-39.4) in the URA group.

The SHRs for the other secondary outcomes are presented in Table 3. The cumulative incidences of first hospitalization for HF and valve-related events are presented in Figure 3, *A* and *B*. HF hospitalization was significantly increased in both the MVR ($P < .001$) and URA groups ($P = .001$) compared with the MVr group. There was no difference in the incidence of valve-related events between the MVr group and the URA group ($P =$ NS). Valve-related events were significantly increased in the MVR group (MVR vs MVr, $P = .003$). The total number of valve-related events occurring in each of the groups is presented in Table E6. The rate of reoperative mitral valve intervention is shown in Figure E3. There was no significant difference between the groups ($P =$ NS). In the MVr group, 4 patients underwent reoperation for recurrent MR and 1 patient for symptomatic moderate mitral stenosis. In the URA group, 2 patients required reoperation for recurrent severe MR. Five patients underwent mitral reoperation in the MVR group: 1 patient for thrombectomy, 2 patients for structural valve deterioration, and 2 patients for paravalvular leak (1 treated percutaneously, 1 treated surgically). Three additional patients in the MVR group underwent cardiac transplantation.

At least 1 postoperative echocardiography was performed in 73 patients in the MVr group, 91 patients in the MVR group, and 64 patients in the URA group (Table E7). There was no difference in the number of postoperative echocardiograms among the 3 groups (MVr 2 [1-4], MVR 1 [1-3], URA 2 [1-4], $P = .161$). There was a decrease in ejection fraction over time in the MVr group ($P = .010$) equivalent to a relative decrease of 2.6% over 5 years. There were no significant changes in ejection fraction for the MVR or URA groups. Gradients were significantly higher in the MVR group compared with the MVr group ($P = .004$); however, they were not significantly different from the URA group ($P = .083$). There were no statistically significant changes in gradients over time in any group (Figure E4).

Sensitivity Analysis

In the pairing of MVR and MVr, if all patients underwent MVr, there would a prolongation of survival of 6.63 years (95% CI, 4.13-9.13; $P < .0001$). In the pairing of URA and MVr, if all patients underwent MVr, there would be a prolongation of survival of 3.16 years (95% CI, 0.79-5.53; $P = .009$). Finally, in the pairing of URA and MVR, if all patients underwent replacement, there would be a prolongation of survival of 2.71 years (95% CI, 0.89-4.53; $P = .004$).

DISCUSSION

We have presented a retrospective cohort study examining the early and long-term outcomes of mitral valve repair with edge-to-edge leaflet approximation and mild-undersizing annuloplasty versus MVR or URA alone for IMR. MVr was associated with improved survival compared with MVR or URA alone. Although late mild-moderate MR was common in both forms of repair, clinically significant moderate MR rates were low with MVr and the incidence of reoperation was low in all 3 groups. MVr was associated with a reduction in hospitalization for HF compared with URA or MVR, whereas MVR had a higher incidence of valve-related events (Figure 4).

IMR remains a significant surgical challenge. Bolling and colleagues[8] introduced the concept of URA to address IMR by targeting annular dilation to improve leaflet coaptation. The Cardiothoracic Surgery Network trial demonstrated inferior long-term durability of URA compared with replacement, with a 59% recurrence of moderate or greater MR at 2 years. These findings contributed to a preferential replacement strategy for IMR.[18] The rate of recurrent moderate or greater MR after URA in the current study was significantly higher than after replacement, reaffirming the conclusion by Goldstein and colleagues[9] that undersizing annuloplasty alone is not a

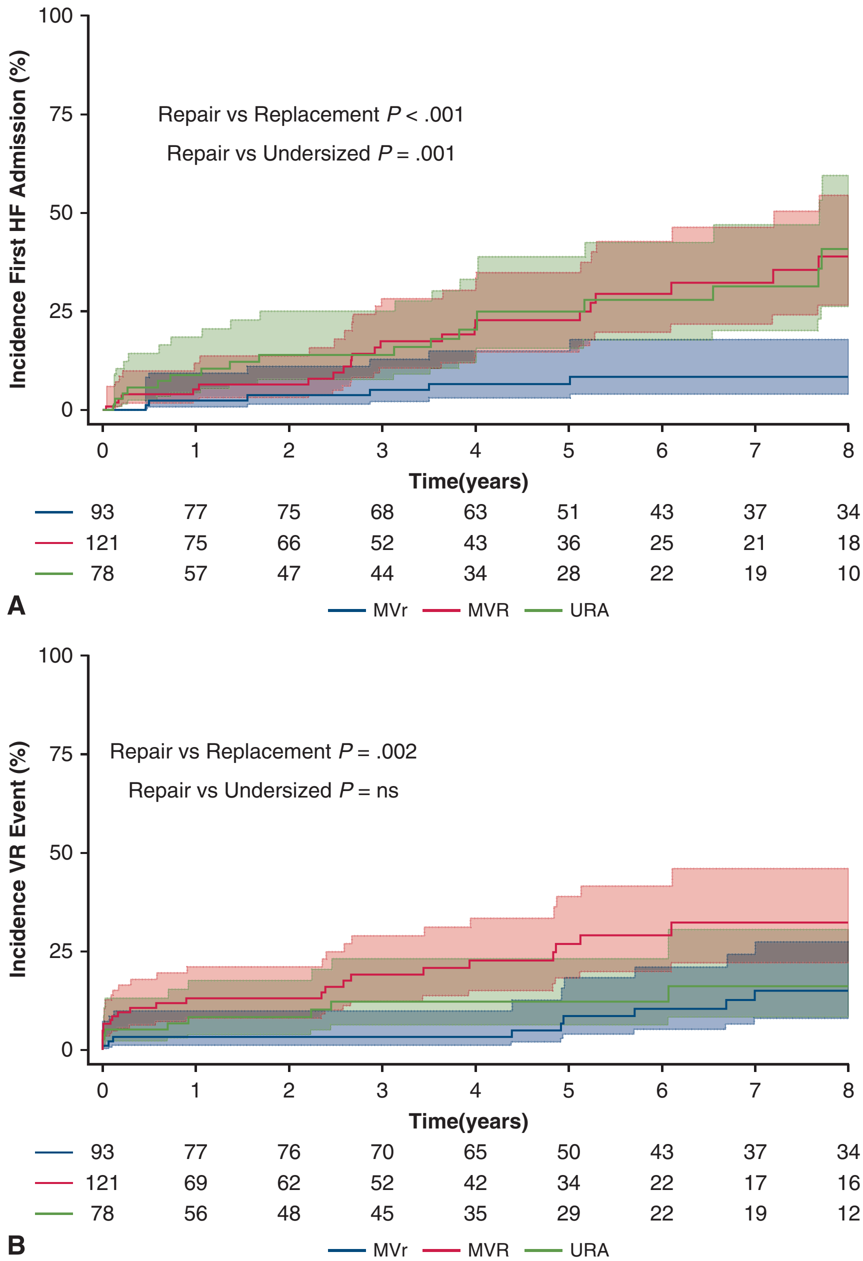

FIGURE 3. A, Incidence of first hospitalization for HF. B, Incidence of valve-related events including bleeding, thromboembolism, endocarditis, and mitral valve reoperation. *Shaded lines* represent 95% CI. Groups analyzed using multivariable Cox proportional hazards model. *HF*, Heart failure; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *VR*, valve related.

durable therapy in severe IMR. It has been suggested that recurrent MR after URA occurs due to persistent PML tethering.[10] Undersizing hoists the posterior annulus anteriorly, further distancing it from the papillary muscles, thereby paradoxically augmenting PML tethering and hastening failure.[10] In contrast, MVr had superior durability to URA, with a rate of recurrent moderate MR that did not differ from replacement over time.

We observed a survival advantage after MVr compared with replacement or URA alone. Although our study is nonrandomized, there was no difference in baseline demographics or predicted operative risk to account for this outcome. The survival difference may be explained by either worsening HF clinical status, as suggested by increased incidence of hospitalization for HF after MVR and URA, or risk of valve-related events including bleeding

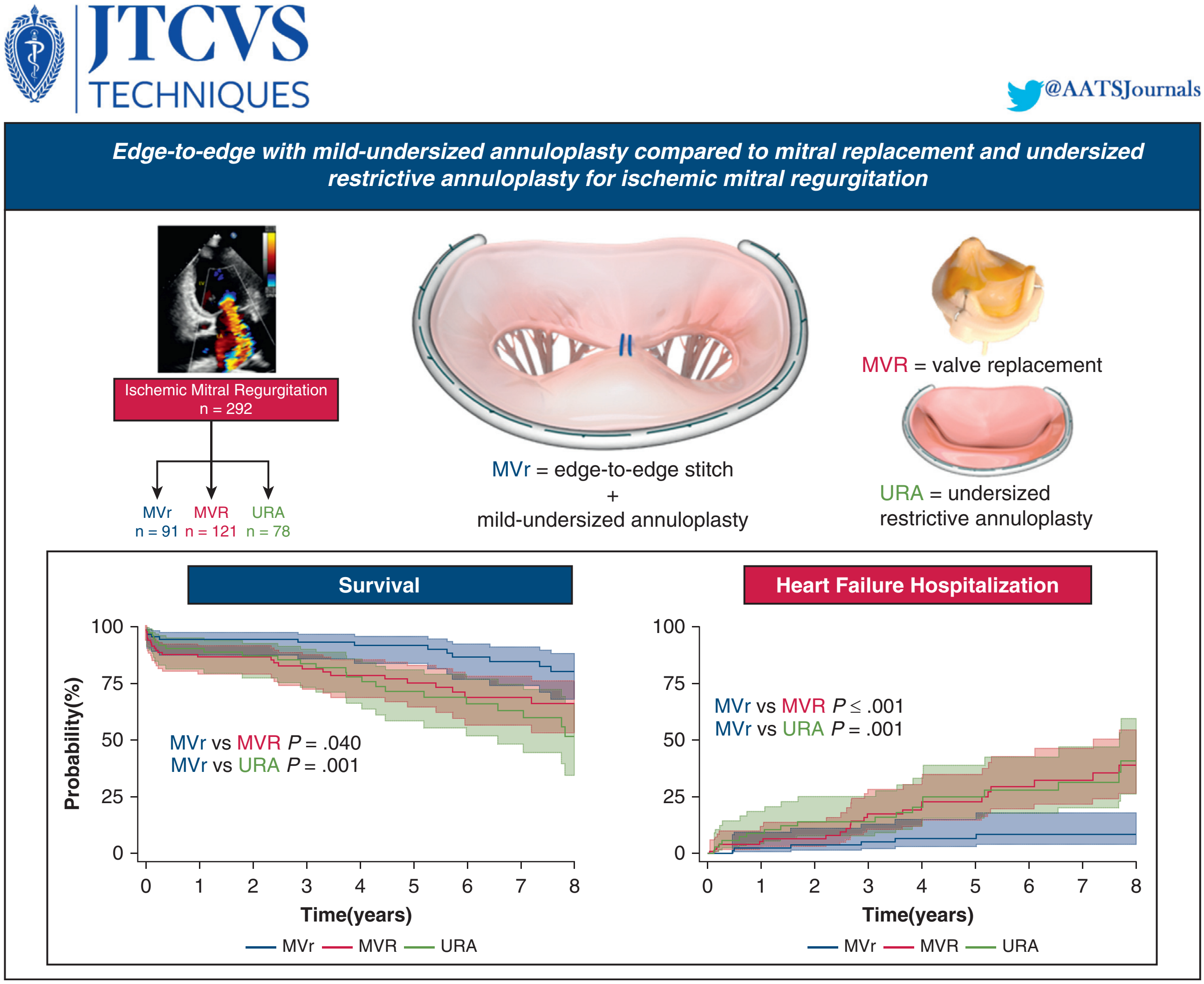

FIGURE 4. Surgical edge-to-edge repair with mild-undersized annuloplasty lowers HF hospitalization and improves survival in IMR compared with MVR and URA. *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

and stroke after replacement. The improvement in survival with MVr in this study is clinically impactful because the number needed to treat with MVr as opposed to MVR to prevent 1 death at 5 years is 6 patients.[19] Despite having a lesser degree of MR ($P < .001$), patients who underwent URA still had more frequent recurrence of MR, hospitalizations, and poorer survival.

The principle of the Alfieri stitch has been applied to transcatheter edge-to-edge repair among patients with HF and secondary MR who have persistent symptoms despite guideline-directed medical therapy, resulting in a lower rate of hospitalization for HF and all-cause mortality compared with medical therapy.[11] The results of the MVr technique are congruent to those seen with transcatheter edge-to-edge repair, which is successful in reducing severe MR, despite accepting a moderate incidence of mild-moderate MR.[11,20] Surgical leaflet approximation was similarly associated with improved outcomes including a reduction in hospitalization for HF when compared with URA or MVR. This would suggest that the physiologic effect of edge-to-edge approximation, whether achieved surgically or percutaneously, may be beneficial in patients with HF and secondary MR.

The success of MVr appears to depend on 3 principles. First, the annuloplasty should be sized to the anterior mitral leaflet surface, with only a mild degree of undersizing to avoid major reductions in antero-posterior diameter and resultant PML tethering. Because some degree of posterior restriction occurs after annuloplasty, coaptation becomes dependent on the anterior mitral leaflet,[21] whose mobility is respected by the posterior band sized in this fashion. Finally, asymmetric tethering forces at P2/P3 present in IMR[22] are offset by an Alfieri stitch placed slightly medially, as well as the use of overlapping annular sutures from P2-P3, preferentially shrinking the posteromedial annulus. Verification of adequate mitral double-orifice area ensures that hemodynamically significant mitral stenosis should not occur. Maisano and colleagues[23] reviewed the hemodynamic outcomes after the Alfieri repair and confirmed that restrictive gradients do not develop in follow-up. Although mean gradients after edge-to-edge repair increase in response to exercise, they generally remain below 5 mm Hg[24] and are not significantly different compared with non-Alfieri repair techniques.

Study Limitations

There are several limitations to this analysis. First, this is a retrospective study and thus open to indication biases that may have influenced treatment allocation. However, in our institution, whereas complex nonischemic MR may be specifically referred to surgeons with repair expertise, cases with ischemic MR are randomly referred to all surgeons. Further, we addressed this by including surgeon as a covariate in the sensitivity analysis, and there was still a significant benefit seen with MVr. Second, there have been many advances in guideline-directed medical therapy for HF that may have influenced outcomes. However, the MVr group has more patients with a longer follow-up who may not have benefited from these advances, and yet their heart failure–related outcomes were still improved. Third, although almost all patients underwent early postoperative echocardiography, later echocardiograms were obtained at the discretion of the treating clinician. There is a potential that there may have been more patients with mild-moderate MR who did not undergo echocardiographic evaluation; however, because our institution is the sole provider for cardiac surgical care in a large jurisdiction, it is unlikely that clinically relevant MR that would require further intervention would not be detected. Fourth, we recognize that the small sample sizes of the 3 groups may present some concerns regarding the power of the study. Finally, because the URA group included patients with incomplete annuloplasty bands, this study did not test the effect of complete versus incomplete band.

CONCLUSIONS

The data presented in this article support the use of MVr as a viable treatment option for IMR at the time of revascularization. Compared with MVR, this repair technique offers similar long-term durability and lower hospitalization for HF, and may confer a survival benefit. Further prospective studies are required to validate these findings.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: edge-to-edge repair, heart failure, ischemic mitral regurgitation, mitral valve repair, mitral valve replacement

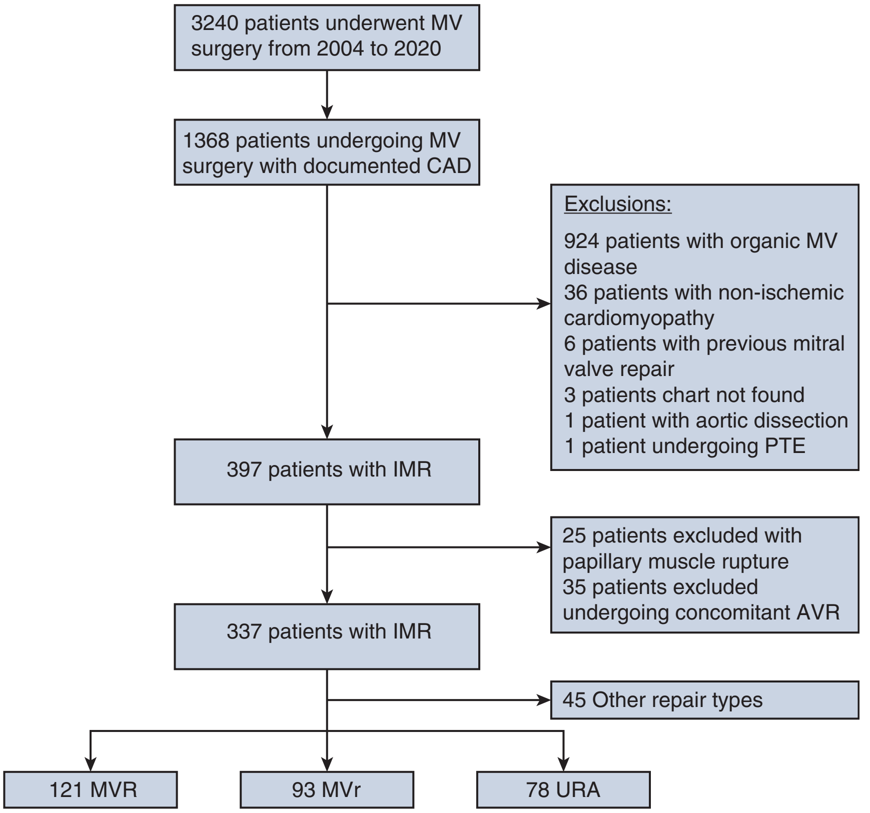

FIGURE E1. Patient flow. *MV*, Mitral valve; *CAD*, coronary artery disease; *IMR*, ischemic mitral regurgitation; *PTE*, pulmonary thromboendarterectomy; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *URA*, undersized restrictive annuloplasty.

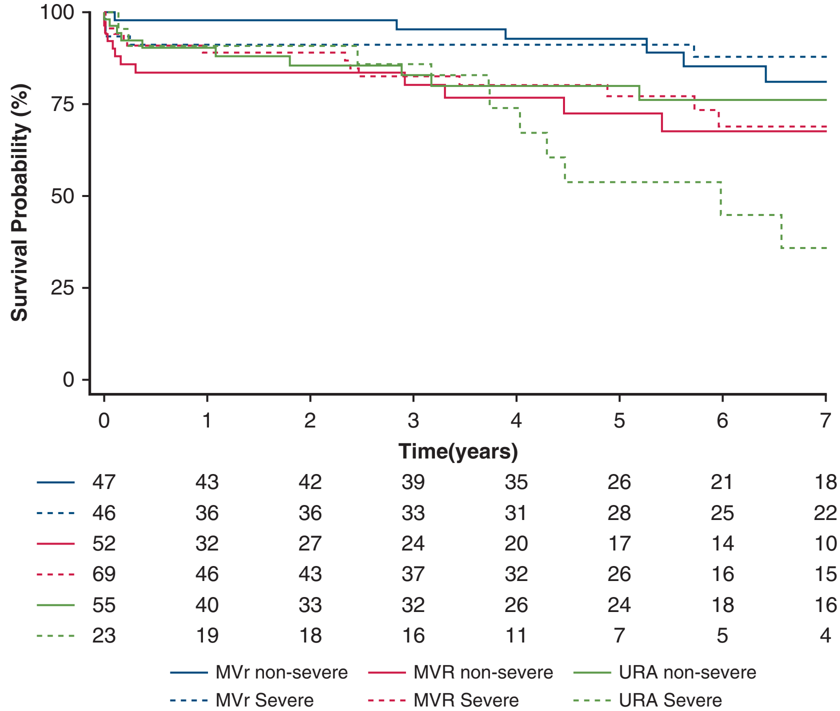

FIGURE E2. Freedom from all-cause mortality in patients undergoing surgery for IMR stratified by preoperative severe MR. Groups analyzed using multivariable Cox proportional hazards model; 95% CIs are presented in Table E7. *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

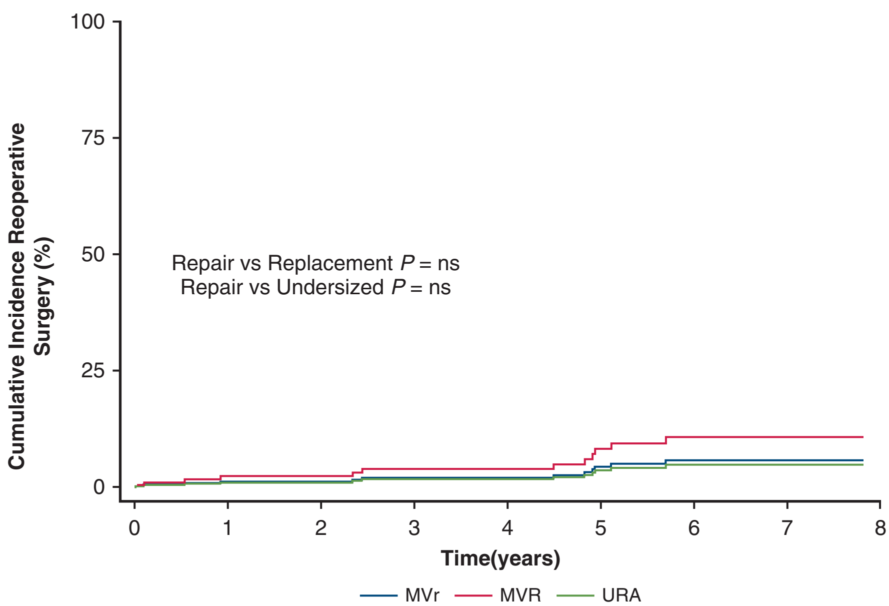

FIGURE E3. Incidence of mitral valve–related reoperation in patients with IMR. *Shaded lines* represent 95% CI. Groups analyzed using multivariable Cox proportional hazards model. *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

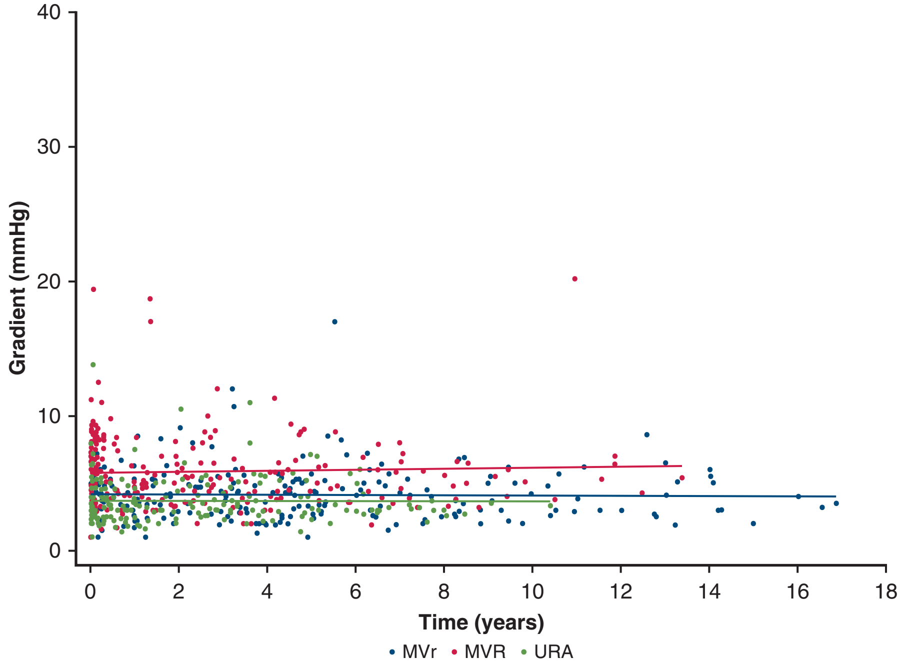

FIGURE E4. Follow-up echocardiographic evaluation of mean mitral gradient in patients with IMR. *MVr*, Mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

TABLE E1. Imputed preoperative demographic variables

Variable	Imputed
BSA	15/292 (5.1%)
LVEDD	18/292 (6.2%)
LVESD	27/292 (9.2%)
Ejection fraction	14/292 (4.8%)

BSA, Body surface area; *LVEDD*, left ventricular end-diastolic diameter; *LVESD*, left ventricular end-systolic diameter.

TABLE E2. Perioperative outcomes in MVr, MVR, and URA groups

Variable	MVr (n = 93)	MVR (n = 121)	URA (n = 78)	*P*
Reopening	2 (2.2)	10 (8.3)	4 (5.1)	.148
Tamponade	2 (2.2)	2 (1.7)	2 (2.6)	.904
LCOS	15 (16.3)	26 (21.5)	22 (28.2)	.171
Prolonged ventilation	5 (5.4)	12 (9.9)	12 (15.4)	.093
Renal replacement therapy	6 (6.5)	12 (9.9)	13 (16.7)	.096
CVA	3 (3.2)	4 (3.3)	2 (2.6)	.953
SWI	5 (5.4)	13 (10.7)	8 (10.3)	.349
Postoperative AF	38 (40.9)	52 (43.3)	40 (51.3)	.366
Perioperative MI	2 (2.2)	1 (0.8)	0 (0.0)	.366
PPM insertion	2 (2.2)	4 (3.3)	3 (3.9)	.801
ICU LOS (d)	2.9 (1.1-6.4)	4.7 (2.0-11.0)	3.0 (1.8-9.0)	.004
Hospital LOS (d)	13.0 (8.0-26.0)	20.0 (12.0-38.0)	18.0 (10.0-27.0)	.003
Mortality (30 d)	3 (3.2)	8 (6.6)	3 (3.9)	.465

Continuous results presented as median (IQR). Categorical variables presented as number (%). Differences between groups tested as chi-square. *MVr*, Mild-undersizing annuloplasty band with Alfieri; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *LCOS*, low cardiac output syndrome; *CVA*, cerebrovascular accident; *SWI*, sternal wound infection; *AF*, atrial fibrillation; *MI*, myocardial infarction; *PPM*, permanent pacemaker; *ICU*, intensive care unit; *LOS*, length of stay.

TABLE E3. Number of primary and secondary outcome events in the 3 groups

Outcome	Total events	MVr (n = 93)	MVR (n = 121)	URA (n = 78)
All-cause mortality	75	21	28	26
Recurrence mild-moderate MR	74	30	8	36
Recurrence moderate MR	40	11	7	22
MV reoperation	14	5	7	2
First HF admission	51	8	25	18
First valve-related event	46	13	26	9

MVr, Mild-undersizing annuloplasty with Alfieri; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *MR*, mitral regurgitation; *HF*, heart failure; *MV*, mitral valve.

TABLE E4. Freedom from all-cause mortality with 95% CI in patients undergoing surgery for ischemic mitral regurgitation stratified by preoperative severe mitral regurgitation

Group	Severe MR	Time (y)	Survival	Lower boundary	Upper boundary
MVr	No	1	0.978	0.856	0.997
		2	0.978	0.856	0.997
		3	0.954	0.829	0.988
		4	0.928	0.792	0.976
		5	0.928	0.792	0.976
		6	0.854	0.676	0.938
		7	0.811	0.617	0.913
	Yes	1	0.911	0.781	0.966
		2	0.911	0.781	0.966
		3	0.911	0.781	0.966
		4	0.911	0.781	0.966
		5	0.911	0.781	0.966
		6	0.879	0.729	0.949
		7	0.879	0.729	0.949
MVR	No	1	0.836	0.698	0.915
		2	0.836	0.698	0.915
		3	0.802	0.649	0.894
		4	0.768	0.602	0.871
		5	0.725	0.544	0.844
		6	0.677	0.480	0.812
		7	0.677	0.480	0.812
	Yes	1	0.890	0.783	0.947
		2	0.890	0.783	0.947
		3	0.825	0.696	0.903
		4	0.802	0.666	0.887
		5	0.772	0.626	0.867
		6	0.690	0.512	0.814
		7	0.690	0.512	0.814
URA	No	1	0.903	0.783	0.959
		2	0.855	0.718	0.929
		3	0.829	0.685	0.912
		4	0.800	0.646	0.892
		5	0.800	0.646	0.892
		6	0.762	0.593	0.868
		7	0.762	0.593	0.868
	Yes	1	0.909	0.683	0.976
		2	0.909	0.683	0.976
		3	0.859	0.622	0.952
		4	0.740	0.478	0.884
		5	0.538	0.277	0.741
		6	0.448	0.193	0.676
		7	0.359	0.125	0.603

Groups analyzed using multivariable Cox proportional hazards model. *MR*, Mitral regurgitation; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *MVR*, mitral valve replacement; *URA*, undersized ring annuloplasty.

TABLE E5. The 2- and 5-year survivals in the MVr, MVR, and URA groups as well as survival in groups stratified by presence of severe preoperative mitral regurgitation

Group	2-y survival (95% CI)	5-y survival (95% CI)
MVr	94.6 (87.4-96.7)	91.9 (83.7-96.1)
MVr less than severe MR	97.8 (85.6-99.7)	92.8 (79.2-97.6)
MVr severe MR	91.1 (78.1-96.6)	91.1 (78.1-96.6)
MVR	86.7 (78.9-91.8)	75.3 (64.6-83.2)
MVR less than severe MR	83.6 (69.8-91.5)	72.5 (54.4-84.4)
MVR severe MR	89.1 (78.3-94.7)	77.2 (62.6-86.7)
URA	87.2 (76.8-93.2)	71.5 (57.8-81.5)
URA less than severe MR	85.5 (71.8-92.9)	80.0 (64.6-89.2)
URA severe MR	90.9 (68.3-97.7)	53.8 (27.7-74.1)

CI, Confidence interval; *MVr*, mild-undersizing annuloplasty with edge-to-edge approximation; *MR*, mitral regurgitation; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty.

TABLE E6. Valve-related events in MVr, MVR, and URA groups

Outcome	MVr	MVR	URA
Valve dysfunction requiring reoperation	5	5	2
Bleeding	2	21	4
Stroke/TIA	6	11	3
Valve thrombosis	0	3*	0
Peripheral embolism	1	1	0
Endocarditis	1	4	1
Total	15	45	10

MVr, Mild-undersizing annuloplasty band with Alfieri; *MVR*, mitral valve replacement; *URA*, undersized restrictive annuloplasty; *TIA*, transient ischemic attack. *One patient required thrombectomy, 1 patient presented in cardiogenic shock leading to death, and 1 patient had thrombus resolution with medical management.

TABLE E7. Number (%) of patients undergoing postoperative echocardiograms

Echocardiogram No.	MVr (n = 73)	MVR (n = 93)	URA (n = 66)
1	16 (21.9)	37 (39.8)	19 (28.8)
2	12 (20.5)	15 (16.1)	16 (24.2)
3	14 (19.2)	11 (11.8)	8 (12.1)
4	12 (16.4)	12 (12.9)	8 (12.1)
5	5 (6.9)	7 (7.5)	2 (3.0)
6	5 (6.9)	5 (5.4)	5 (7.6)
7	1 (1.4)	3 (3.2)	3 (4.6)
8	2 (2.7)	2 (2.2)	4 (6.1)
9	3 (4.1)	0	0
10	0	0	0
11	0	0	1 (1.5)
12	0	1 (1.1)	0

MVr, Mild-undersizing annuloplasty band with Alfieri; *MVR*, mitral valve replacement; *URA*, undersized ring annuloplasty.