Asymptomatic degenerative mitral regurgitation repair: Validating guidelines for early intervention

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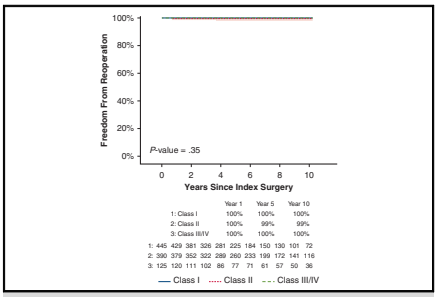
ABSTRACT

Introduction: Mitral repair for asymptomatic (New York Heart Association [NYHA] class I) degenerative mitral regurgitation (MR) is supported by the guidelines, but is not performed often. We sought to determine outcomes for asymptomatic patients when compared with those with symptoms.

Methods: Between 2004 and 2018, 1027 patients underwent mitral replacement (22) or repair with or without other cardiac surgery (1005), the latter being grouped by NYHA class: I (n = 470; 47%), II (n = 408; 40%), or III/IV (n = 127; 13%). Statistical analyses included propensity score matching and weighting, and multistate models.

Results: The proportion of patients designated as NYHA class I undergoing surgery increased steadily during this period ($P < .001$). Overall, 30-day mortality was 0.4%, and zero for patients designated NYHA class I. Unadjusted 10-year survival was significantly greater in patients designated NYHA class I compared with II and III/IV ($P < .001$). Freedom from reoperation at 10 years was 99.8% overall, and 100% for patients designated NYHA class I. In patients designated as NYHA class I, predischarge and 10-year moderate MR were 0.7% and 20.1%, whereas more than moderate was zero and 0.6%. Preoperative ejection fraction less than 60% was associated with late mortality ($P = .025$). After covariate-adjustments, freedom from MR and tricuspid regurgitation were not statistically significantly different by NYHA class. However, overall survival was significantly worse in patients with NYHA class III/IV, compared with class II.

Conclusions: Mitral repair in asymptomatic patients is safe and durable. Careful monitoring until class II symptoms is appropriate. However, repair before ejection fraction decreases below 60% is important for late overall survival. (J Thorac Cardiovasc Surg 2021;161:981-94)



In asymptomatic DMR repair patients, 10-year reoperation was 0%, and late 3-4+ MR was low.

CENTRAL MESSAGE

Repair of degenerative mitral regurgitation in 470 asymptomatic patients was low risk (30-day survival 100%) and durable, with 10-year 100% freedom from reoperation and low rates of recurrent MR.

PERSPECTIVE

Repair of asymptomatic degenerative mitral regurgitation (DMR) is a Class IIa recommendation but not widely practiced. The repair rate was 99%, with 100% 30-day survival in 470 patients. Ten-year freedom from reoperation was 100% and from recurrent greater than moderate MR was 99.4%. This approach is safe and effective.

See Commentary on page 995.

In North America and Europe, guidelines are similar for the treatment of degenerative mitral regurgitation (DMR) and are based upon 2 classes of triggers.[1-4] Class I triggers, which prompt early surgery, include

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ADULT

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
DMR = degenerative mitral regurgitation
HL = Hosmer–Lemeshow
HR = hazard ratio
LV = left ventricle
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
PS = propensity score
TR = tricuspid regurgitation

valve-related symptoms, ejection fraction <60%, and left ventricular end-systolic diameter >40 mm. Class IIa criteria for asymptomatic patients include a repair rate that exceeds 95%, an expected 30-day mortality less than 1%, and the surgery is performed in a "center of excellence." Debate still exists about this strategy, however. "Watchful waiting" is advocated by some,[5] but others note an "outcome penalty" when waiting until class I criteria have been met.[6] Recent data indicate that only 4.4% of DMR repairs are performed in patients designated New York Heart Association (NYHA) class I.[2,6-8]

We sought to determine: (1) early and late clinical and echocardiographic outcomes for patients designated NYHA functional class I with DMR surgery compared with NYHA II and III/IV, (2) freedom from atrial fibrillation (AF) for those treated with concomitant surgical ablation by NYHA class, (3) the impact of ventricular dysfunction on late outcomes by NYHA class, and (4) the impact of recurrent moderate mitral regurgitation (MR) on late survival by NYHA class.

METHODS

Study Population

Eligible patients were those who underwent mitral valve (MV) surgery for asymptomatic DMR between April 2004 and July 2018 by a single surgeon (P.M.M.). Preoperative, intraoperative, and postoperative data were obtained from the Cardiovascular Research Database in the Clinical Trial Unit of the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital (institutional review board at Northwestern University STU00012288 which includes a waiver for informed written consent for publication) and medical record review. Those with previous MV intervention, "mixed" etiology of valve dysfunction, emergent cases, or concomitant AV surgery, and patients who refused to participate in, or withdrew from the database, were excluded. The CONSORT (Consolidated Standards of Reporting Trials) diagram in Figure 1 depicts the process of identifying the study cohort.

Patients underwent routine intraoperative and predischarge echocardiograms, and received surveys at 3, 6, and 12 months after surgery and annually thereafter to report quality of life surveys, medical visits, and tests. Medical records were obtained to verify operations, echocardiogram reports, and hospitalizations. Echocardiographic assessments of MR were graded as: none or trivial (0); mild (1+); moderate (2+); moderate to severe (3+); and severe (4+).[9] The Society of Thoracic Surgeons definitions were used to determine complications. Mortality data were aggregated continuously consulting sources that included: (1) Cardiovascular Research Database registry; (2) reviews of medical records and correspondence with the treating physician; (3) online death searches and genealogy resources (ancestry.com); and (4) newspaper death notices.

Statistical Analyses

Data elements were summarized using means/standard deviations, medians/interquartile ranges, or counts/percentages. Group comparisons were based on the 1-way analysis of variance, the Kruskal–Wallis test, the Wilcoxon rank sum test, and the χ^2 or Fisher exact test. Pairwise comparisons among NYHA classes I, II, and III/IV used 1:1 propensity score (PS) matching to reduce confounding. Explanatory variables in each PS model

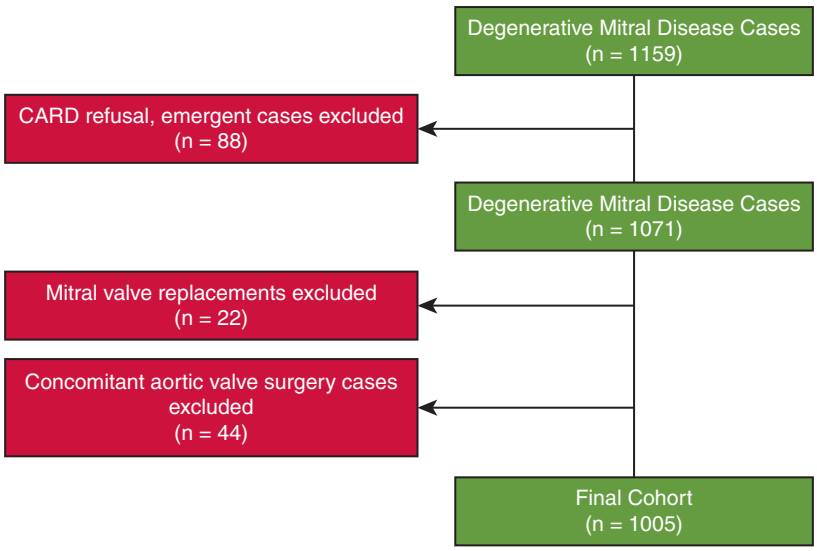


FIGURE 1. Consolidated Standards of Reporting Trials diagram of patients eligible for analysis. Patients were excluded for refusal to participate in follow-up database, emergent cases, mitral valve replacement, and concomitant aortic valve replacement. *CARD*, Cardiovascular Research Database.

were age, body surface area, body mass index, creatinine level, ejection fraction, CHADS2 (congestive heart failure, hypertension, age, diabetes, sex) score, sex, diabetes, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular disease, cerebrovascular accidents, coronary artery disease, AF history, previous myocardial infarction, previous congestive heart failure, previous pacemaker, repeat sternotomy, previous coronary artery bypass graft, previous valve surgery, concomitant procedures (aortic/tricuspid valve surgery, coronary artery bypass graft), MV repair technique (Alfieri stitch, commissuroplasty, chordal transfer), and surgical status (elective vs not). PS matching used a greedy algorithm with a caliper of size 0.2 logit PS (for class I vs II, class I vs III/IV, and II vs III/IV) standard deviation units. Standardized mean differences were used to assess covariate balance after PS matching, with absolute values less than 0.2 reflecting adequate balance (Figure E1).[10,11] The Hosmer–Lemeshow (HL) statistic for calibration and the C-index indicate the PS model adequacy. Freedom-from-reoperation estimation used cumulative incidence functions for competing risks models, and group comparisons involved Gray's test. In addition, analyses based on the entire trajectory of MR assessments per patient were performed to estimate the probabilities of late moderate (2+) MR or of late moderate-severe or greater MR (3-4+) (as a yes/no outcomes) were created using generalized linear modeling. Estimation was based on generalized estimating equations under a working independence within-patient correlation structure.

We performed an additional robustness 3-way PS-based analysis of overall survival. Matching weights were obtained based on a generalized (3-level outcome) logistic regression PS model in which the outcome was NYHA class (I vs II vs III/IV) and explanatory variables those used in PS modeling (Table E1). Unweighted and M-weighted log-rank tests were then used to compare overall survival among NYHA classes. Unadjusted and covariate-adjusted Cox regression models were also used to model relative risk: adjustment covariates were those used in creating the PS models.

The association between developing late moderate MR and overall survival was evaluated using joint modeling of the 2 processes that included normally distributed random slopes and random intercepts, as implemented in the SAS macro %JM.[12] An unstructured covariance matrix was assumed for the longitudinal moderate MR values.

Statistical significance was declared at 2-sided 5% alpha level, with no adjustments for multiplicity. Analyses were performed using SAS, version 9.4 software (SAS Institute, Inc, Cary, NC) and R, version 3.6.1 (www.R-project.org), including the package TriMatch.

RESULTS

Perioperative Characteristics in the Original (Unmatched) Groups

After we excluded concomitant AV surgery cases, DMR surgery was performed in 1027 patients, of whom 474 (46.2%) were NYHA class I, 416 (40.5%) class II, and 134 (13.1%) class III, and 3 (0.3%) class IV. MV repair was performed in 1005 of 1027 (97.9%) patients; by NYHA class: 99.2% (470/474) in class I; 98.1% (408/416) in class II; and 93.4% (127/136) in class III/IV ($P < .0001$). Replacement was performed in 22 patients (mean age 77.3 ± 5.8 years), primarily for extensive leaflet disease and calcification, and 30-day mortality was 4.5% (1/22). Of the 4 replacements in the asymptomatic group, 3 had a class I indication for surgery. Only 1 asymptomatic patient, with recent endocarditis, had a class IIa indication for surgery. Late echocardiograms were obtained in 871 of 1027 (84.8%) of patients at a mean follow-up of 4.2 ± 3.4 (median 3.2) years.

Our focus is the MV repair group (1005 patients) and we report in detail their clinical and echocardiographic results. Pre- and intra- and postoperative characteristics, by NYHA class, are shown in Table 1. On average, patients designated NYHA class I were younger than classes II and III/IV, fewer were female, or had comorbidities such as congestive heart failure or history of AF. Significantly fewer patients in NYHA class I and II had moderate or greater tricuspid regurgitation (TR), compared with class III/IV (9.8% vs 14.0% vs 27.6%, $P < .001$). Among patients designated NYHA I, 154 (32.8%) had an American Heart Association/American College of Cardiology class I indication for surgery as judged by left ventricle (LV) size and function. Of these, 60 had left ventricular ejection fraction (LVEF) <60% only, 51 had left ventricular end-systolic diameter ≥40 mm only, and 39 patients met both criteria.

The proportion of patients who were NYHA class I in our cohort was much greater than the recent US national average (4.4%) from the beginning and increased steadily over time (Figure 2, *A*, $P < .001$). The percent of patients with preoperative AF ($P = .19$) or those with moderate or more TR ($P = .25$) did not change significantly over time.

Thirty-day mortality was 0.4% overall, and zero for patients who were NYHA class I. Freedom from AF off antiarrhythmics at last follow-up for patients with AF ablation (Figure 2, *B*) was 80.5% for patients designated NYHA I compared with 74.2% for patients designated NYHA II and 59.5% for patients designated NYHA III/IV ($P = .063$). Similarly, freedom from anticoagulation at last follow-up was 74.7% for NYHA I compared with 62.5% for patients designated as NYHA II and 51.3% for patients designated as NYHA III/IV ($P = .033$). Furthermore, freedom from stroke at any time was 98.8% for NYHA I compared with 97.1% for NYHA III and 92.7% for NYHA III/IV ($P = .22$).

Freedom from reoperation at 10 years was 99.8% in the entire cohort, and 100% for patients who were NYHA I (Figure 3, *A*). Predischarge moderate MR in patients designated NYHA I was 0.7% and none had more than moderate MR, whereas their 10-year freedom from 2+ and 3-4+ MR estimates were 79.9% and 99.4%, respectively (Figure 3, *B* and *C*). There were no statistically significant differences in freedom from MR or reoperation between groups ($P = .35$). Overall survival was significantly greater in patients designated NYHA I compared with NYHA II and III/IV ($P < .001$) (Figure 4, *A*).

PS-Matched Groups: Characteristics and Late Outcomes

There were 297 pairs of PS-matched patients with NYHA I and II (PS model HL test = 5.3, $P = .73$, C-index = 0.73), 80 pairs of I versus III/IV (PS model HL = 4.4, $P = .82$,

TABLE 1. Pre-, intra,- and postoperative characteristics and outcomes by New York Heart Association class

Variable	N available entire cohort (per group)	Entire cohort (N = 1005)	Class I (N = 470)	Class II (N = 408)	Class III IV (N = 127)	*P* value
Preoperative characteristics						
Age, y	1005 (470, 408, 127)	60.1 ± 12.11	58.6 ± 11.63	60.6 ± 12.20	63.7 ± 12.77	<.001
Sex (female)	1005 (470, 408, 127)	323 (32.1%)	131 (27.9%)	137 (33.6%)	55 (43.3%)	.003
Previous myocardial infarction	1001 (468, 406, 127)	24 (2.4%)	8 (1.7%)	9 (2.2%)	7 (5.5%)	.044
Coronary artery disease	956 (449, 384, 123)	183 (19.1%)	71 (15.8%)	78 (20.3%)	34 (27.6%)	.010
Repeat sternotomy	1005 (470, 408, 127)	20 (2.0%)	5 (1.1%)	6 (1.5%)	9 (7.1%)	<.001
Atrial fibrillation history	1005 (470, 408, 127)	232 (23.1%)	88 (18.7%)	104 (25.5%)	40 (31.5%)	.003
Atrial fibrillation type	234 (87, 106, 41)					.341
Not documented		8 (3.4%)	3 (3.4%)	3 (2.8%)	2 (4.9%)	
Paroxysmal		144 (61.5%)	56 (64.4%)	69 (65.1%)	19 (46.3%)	
Permanent		48 (20.5%)	19 (21.8%)	17 (16.0%)	12 (29.3%)	
Persistent		34 (14.5%)	9 (10.3%)	17 (16.0%)	8 (19.5%)	
Mitral insufficiency	1002 (468, 407, 127)					.774
1 = Mild		1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	
2 = Moderate		64 (6.4%)	31 (6.6%)	26 (6.4%)	7 (5.5%)	
3 = Moderate/severe		77 (7.7%)	31 (6.6%)	37 (9.1%)	9 (7.1%)	
4 = Severe		860 (85.8%)	405 (86.5%)	344 (84.5%)	111 (87.4%)	
Tricuspid insufficiency	1004 (469, 408, 127)					<.001
0 = None/trivial		547 (54.5%)	254 (54.2%)	240 (58.8%)	53 (41.7%)	
1 = Mild		319 (31.8%)	169 (36.0%)	111 (27.2%)	39 (30.7%)	
2 = Moderate		118 (11.8%)	39 (8.3%)	50 (12.3%)	29 (22.8%)	
3 = Moderate/severe		10 (1.0%)	3 (0.6%)	4 (1.0%)	3 (2.4%)	
4 = Severe		10 (1.0%)	4 (0.9%)	3 (0.7%)	3 (2.4%)	
Intraoperative outcomes						
Cardiopulmonary median bypass time, min	1005 (470, 408, 127)	85 (73, 104)	83 (71, 98)	89 (76, 109)	93 (72, 113)	<.001
Aortic crossclamp time	1005 (470, 408, 127)	73 (62, 87)	71 (60, 83)	76 (65, 91)	73 (61, 90)	<.001
CABG	1005 (470, 408, 127)	136 (13.5%)	53 (11.3%)	56 (13.7%)	27 (21.3%)	.014
Aortic valve surgery	1005 (470, 408, 127)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Tricuspid valve surgery	1005 (470, 408, 127)	89 (8.9%)	37 (7.9%)	31 (7.6%)	21 (16.5%)	.005
Atrial fibrillation ablation	1005 (470, 408, 127)	234 (23.3%)	87 (18.5%)	106 (26.0%)	41 (32.3%)	.001
Urgent surgery	1005 (470, 408, 127)	20 (2.0%)	5 (1.1%)	6 (1.5%)	9 (7.1%)	<.001
Postoperative outcomes						
Postoperative length of stay, d	1005 (470, 408, 127)	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	6.00 (5.00, 8.00)	<.001
30-d mortality	1005 (470, 408, 127)	4 (0.4%)	0 (0.0%)	3 (0.7%)	1 (0.8%)	.171
Predischarge mitral regurgitation	929 (434, 379, 116)					.441
None/trivial		857 (92.2%)	404 (93.1%)	348 (91.8%)	105 (90.5%)	
Mild		67 (7.2%)	27 (6.2%)	29 (7.7%)	11 (9.5%)	
Moderate		3 (0.3%)	3 (0.7%)	0 (0.0%)	0 (0.0%)	
Moderate/severe		1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	
Severe		1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	

Values are mean ± SD, n (%), or median (interquartile range). *CABG*, Coronary artery bypass graft.

C-index = 0.82), and 119 pairs of II versus III/IV (PS model HL = 20.2, $P = .01$, C-index = 0.69). Adequate baseline covariate balance has been achieved in the first and third comparisons, as indicated by the standardized mean differences (less than 0.2 in absolute value) in Figure E1, *A* and *C*. Residual imbalances in current smoking status, peripheral vascular disease, and repeat sternotomy were observed in the NYHA II versus III/IV comparison (Figure E1, *C*). Compared with patients were designated as NYHA II and to NYHA III/IV, patients designated as NYHA I had shorter extreme (90th percentile) postoperative length of stay: 7 versus 8 days ($P = .014$); and 7 versus 9 days ($P = .004$), respectively.

Cox regression models adjusting for variables used in constructing the PS models suggest that there might be significant overall survival differences by NYHA class, although not all comparisons reach statistical significance (NYHA I vs III/IV; hazard ratio [HR], 0.57; 95%

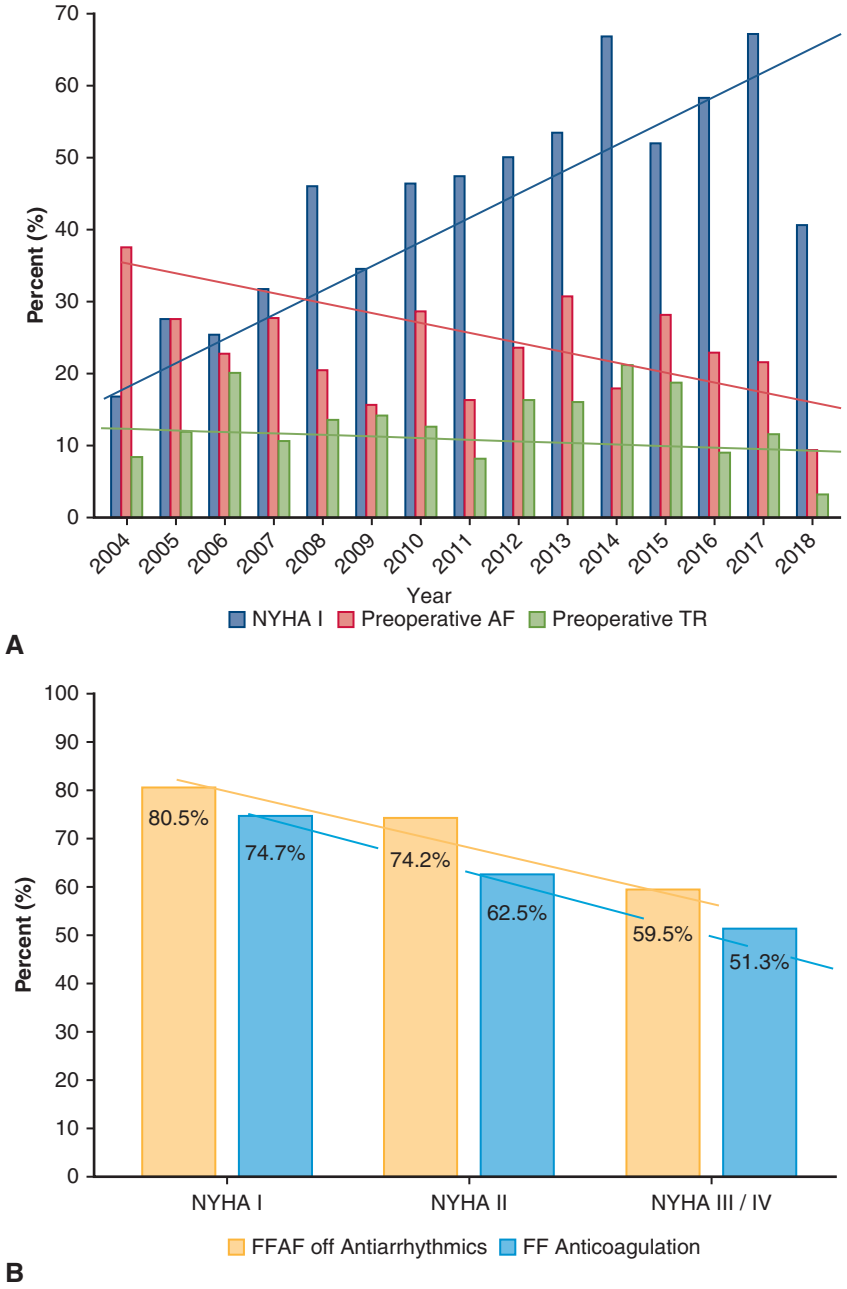
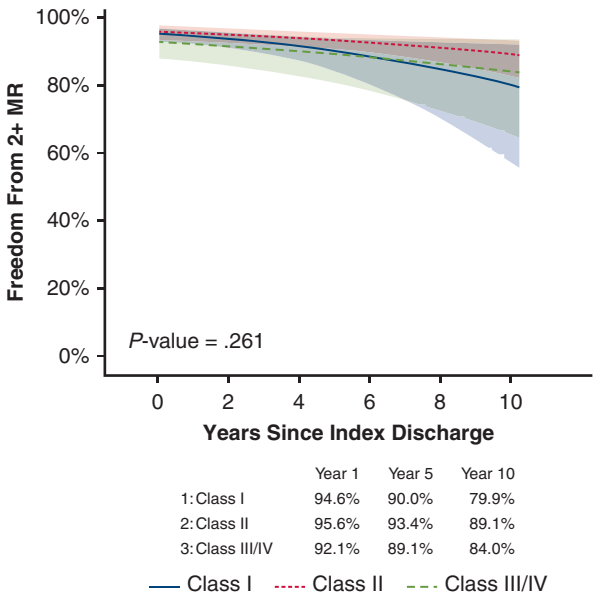


FIGURE 2. A, Annual trend of degenerative mitral regurgitation patient surgery characteristics. The proportion of patients in class I was much greater than the recent US national average (4.4%) from the beginning and steadily increased over time. The incidence of preoperative AF did not change significantly over time ($P = .19$), or the frequency of moderate or more TR. B, FFAF off antiarrhythmics and freedom from anticoagulation at last follow-up in patients with AF ablation. FFAF off antiarrhythmics at last follow-up for patients with AF ablation was 80.5% for patients designated NYHA I compared with 74.2% for patients designated NYHA II and 59.5% for patients designated NYHA III/IV ($P = .063$). Freedom from anticoagulation at last follow-up ($P = .033$) also steadily declined from NYHA I to NYHA II/IV groups. *NYHA*, New York Heart Association; *AF*, atrial fibrillation; *TR*, tricuspid regurgitation; *FFAF*, freedom from atrial fibrillation; *FF*, freedom from.

confidence interval [95% CI], 0.29-1.14, $P = .11$; NYHA II vs III/IV; HR, 0.49; 95% CI, 0.28-0.85, $P = .011$, Table E2). Upon applying matching weights, unadjusted analyses continue to suggest the possibility of overall survival differences among NYHA classes, despite a lack of statistical significance (NYHA I vs III/IV; HR, 0.72; 95% CI, 0.27-1.96, $P = .52$; NYHA II vs III/IV HR, 0.65; 95% CI, 0.24-1.79, $P = .41$, Table E2). Upon further covariate adjustments, M-weighted models continue to support these conclusions (Table E2).

A



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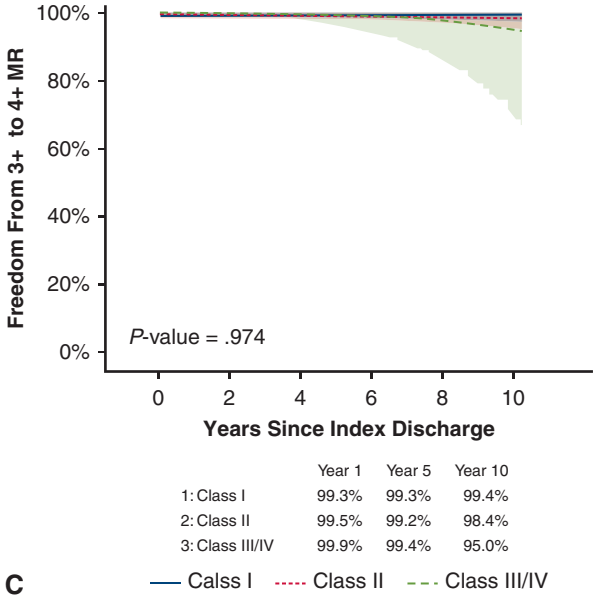
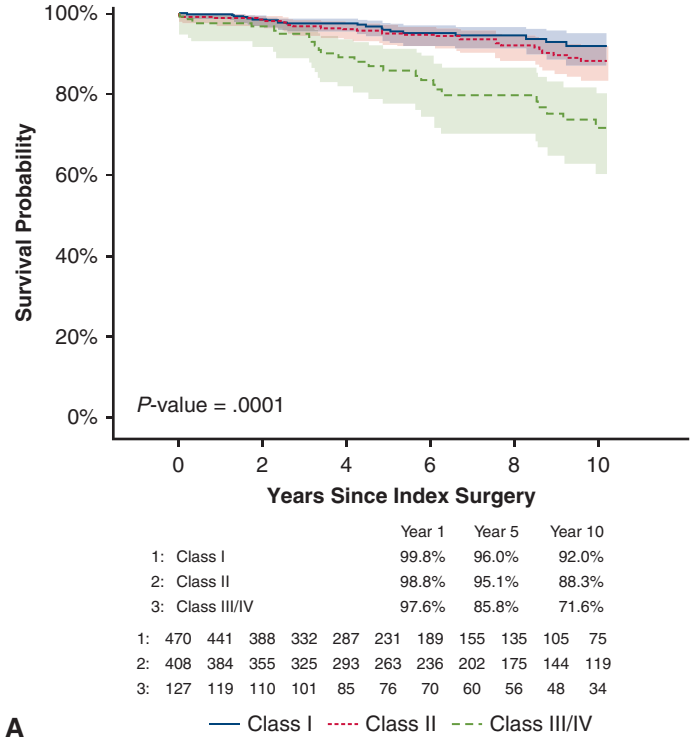


C

FIGURE 3. Freedom from reoperation and recurrent MR among various New York Heart Association class patients. A, At 10 years postsurgery, freedom from mitral valve reoperation was 99.8% overall, and 100% for class I. B, by generalized estimating equations for patients with class I, freedom from moderate MR was 79.9%; and C, freedom from moderate-severe or greater MR was 99.4%. *MR*, Mitral regurgitation.

Table E3 shows unadjusted and covariate-adjusted overall survival analyses of the PS-matched groups. Patients who are NYHA class I versus II appear to have comparable overall survival, as further confirmed in Figure E2, *A* ($P = .97$). When we compared NYHA I and III/IV, covariate-adjusted analyses aimed at addressing residual imbalances continue to suggest the possibility of superior overall survival among patients designated NYHA I, as indicated by HRs substantially less than 1 (HR, 0.72; 95% CI, 0.31-1.64, $P = .43$ based on the original groups; HR, 0.51; 95% CI, 01.16-1.63, $P = .25$, for the PS-matched groups). The same pattern is observed in Figure E2, *B* ($P = .13$). Comparisons of NYHA II and III/IV groups reveal significantly lower overall survival among



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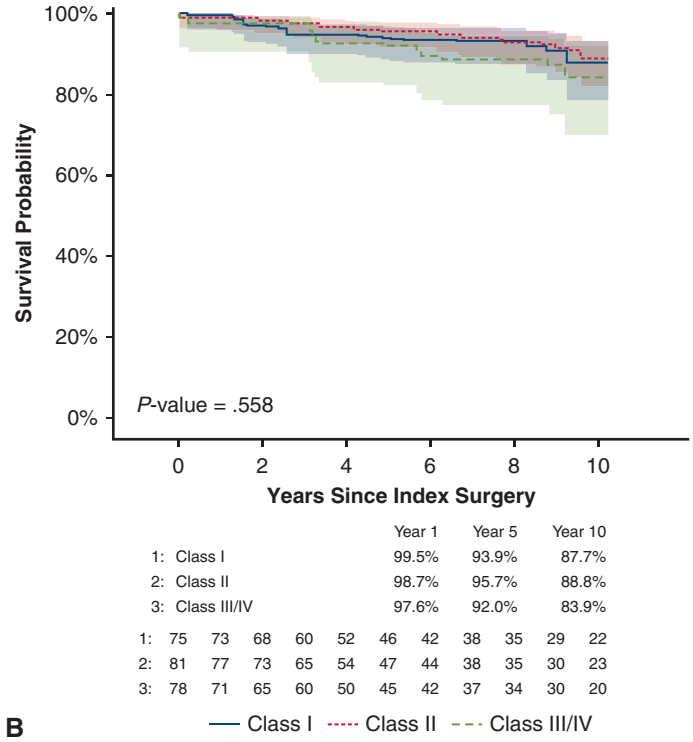
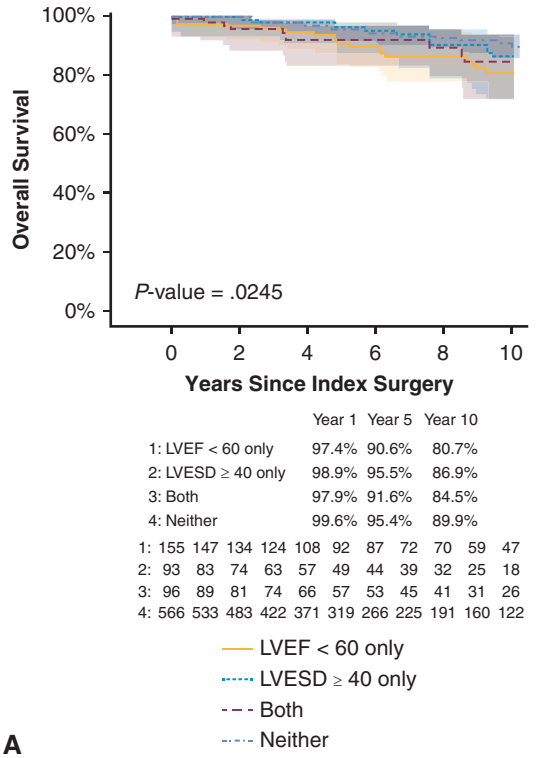


B

FIGURE 4. Kaplan–Meier curves for overall survival of various New York Heart Association class with corresponding numbers at-risk. A, Patients in the unweighted groups. B, Patients in the M-weighted groups. In the unweighted groups, class I had significantly greater overall survival ($P < .001$), but after M-weighting overall survivorship was similar across New York Heart Association classes ($P = .558$).



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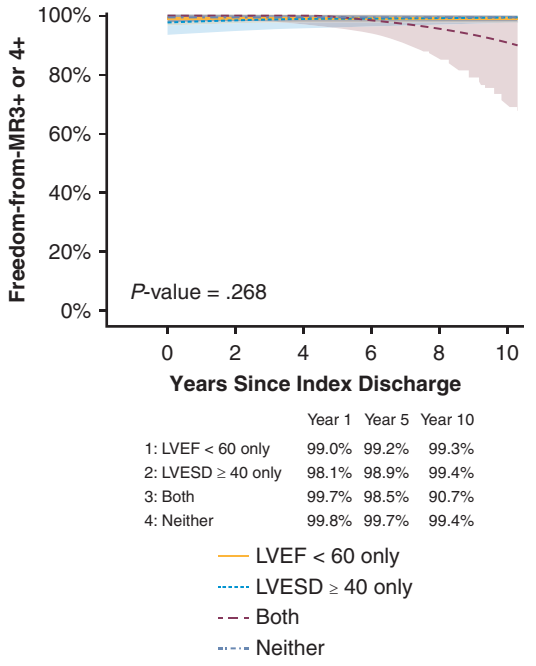

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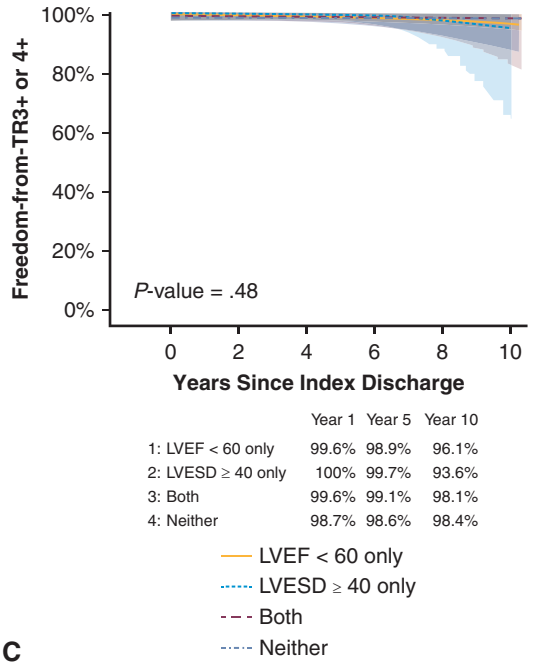


C

FIGURE 5. Comparison of overall survival and freedom from MR/TR by LV function. A, Overall survival was worse in patients with reduced LVEF ($P = .025$) but not increased LVESD. B, No significant difference was found for those with recurrent 3-4+ MR ($P = .268$). C, No significant difference was found in those with recurrent 3-4+TR ($P = .480$). *LV*, Left ventricle; *LVEF*, left ventricular ejection fraction; *LVESD*, left ventricular end-systolic diameter; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation.

patients in class III/IV, in both unadjusted and adjusted analyses, as well as in Figure E2, *C*.

Pre-existing LV Dysfunction: Impact on Outcomes

To determine the impact of pre-existing LV dysfunction on late outcomes, MV repair patients were classified (whenever adequate echocardiographic information was available) into 4 groups: (1) normal LV function (N = 566; 56.3%); (2) LVEF <60% only (155; 15.4%); (3) left ventricular end-systolic diameter ≥40 mm only (93; 9.3%); or (4) both abnormalities (96; 9.6%). For the entire cohort survival was worse (Figure 5, *A*; $P = .025$) for those with reduced LVEF, but was not different for increased left ventricular end-systolic diameter, and there was no significant difference in recurrent 3-4+ MR or 3-4+ TR ($P = .268$ and .480, Figure 5, *B* and *C*, respectively). There was no statistically significant association with overall survival for NYHA class I, II, or III/IV (Figure E3, *A,* for Class I; *B* for Class II; *C* for Class III/IV). However, despite the lack of statistical significance, for patients in class III/IV the data suggest that worst survival was for those with LVEF <60% (Figure E3, *C*, $P = .077$).

Association of Recurrent Moderate MR With Late Survival

None of the patients had moderate residual MR in the operating room, but some developed moderate recurrent MR at least one point in time during follow-up. We retrospectively depict survivorship in these 2 categories of patients in Figure 6. State-of-the-art joint modeling of overall survival and moderate recurrent MR as a longitudinal process revealed no statistically significant late survival worsening among patients who develop moderate MR in follow-up: HR, 1.16; 95% CI, 0.93-1.44, $P = .19$.

FIGURE 6. Survival by recurrent moderate MR in follow-up. No survival difference was detected among patients who developed recurrent moderate MR compared with those who did not. *MR*, Mitral regurgitation.

DISCUSSION

Our study shows that in a center of excellence, the results of surgery for patients with NYHA I DMR are excellent, with a high repair rate (99%), zero 30-day mortality, very little residual MR on the predischarge echocardiogram (0.7% moderate, none more than that), 100% freedom from reoperation at 10 years, and 99.4% free from more than moderate MR and 79.9% free from moderate MR (Figure 7). The survival for our patients with NYHA class I at 10 years was high (92.2%). We did not detect decreased survival for the small group with recurrent moderate MR. These results are all consistent with the class IIa guideline recommendations for asymptomatic patients with severe MR.

Despite having conducted several types of analyses, we were not able to identify an "outcome penalty" when we compared the survival of patients designated as NYHA I versus II. We found repair rates, freedom from recurrent MR, and reoperation to be similar, whereas early and late survival were nearly identical. Also, within the NYHA I patient group was a significant subset (33%) with guideline Class I indications for surgery based on LV dysfunction and/or LV end systolic dimension. We were not able to demonstrate an impact on late survival for those patients either. For patients with NYHA I and II compared with patients with NYHA III/IV symptoms, the repair rates were greater and there was a trend toward better survival with earlier surgery. The sample size after matching these very different groups only showed a trend, however.

Early surgery has been associated with lower long-term cardiac mortality when compared with conservative management in previous studies.[13] Our current practice is to offer surgery to patients who are NYHA I with severe DMR who are otherwise healthy and have a high likelihood of successful repair. Many patients want to proceed before the onset of AF, symptoms, or potentially LV dysfunction. Others undergo stress testing and may meet criteria due to the development of pulmonary hypertension. Interestingly, while patients report that they have no symptoms, follow-up exercise testing after repair has documented improved peak oxygen performance and maximal workload.[14] For patients who choose to defer surgery, we recommend every 6 months echocardiograms and careful follow-up with a cardiologist experienced in the care of heart valve patients. Surgery then is planned at the onset of even mild symptoms, progressive LV dilation or drop in LVEF, the onset of AF, or

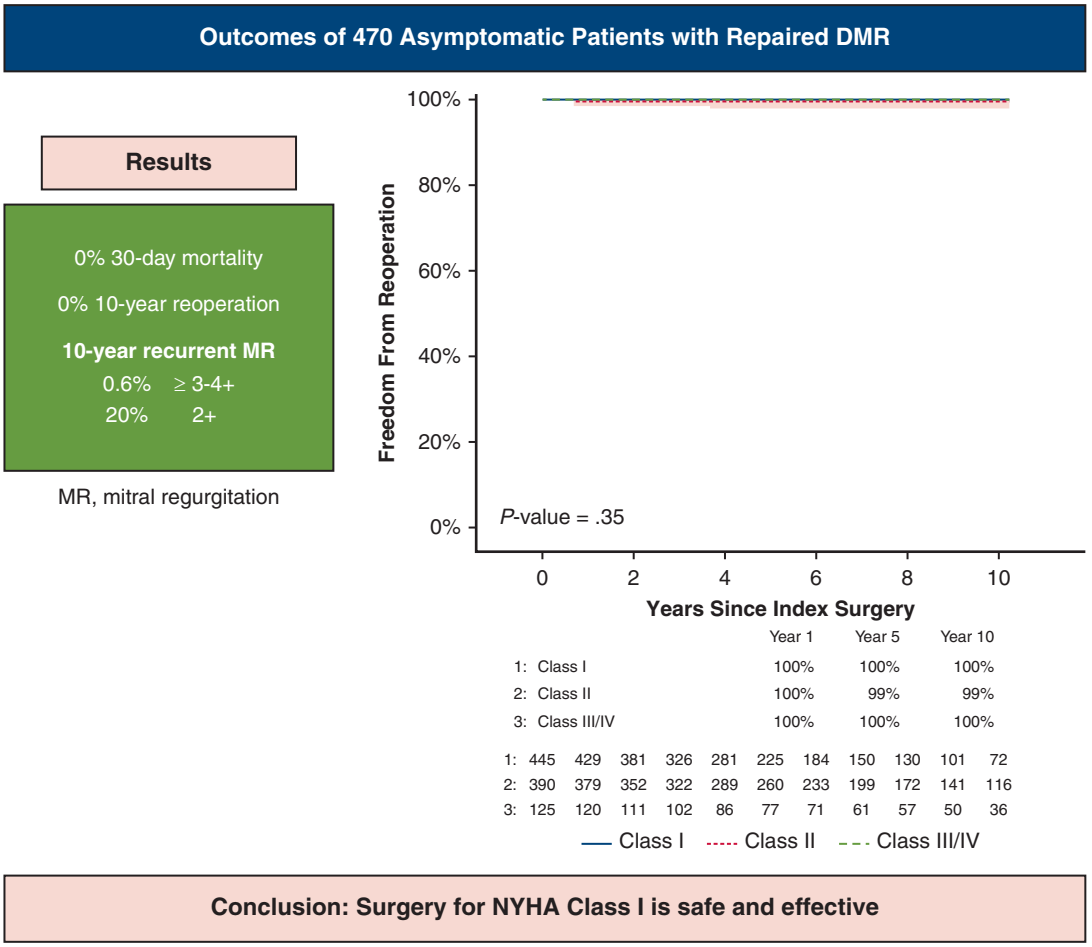


FIGURE 7. Outcomes of mitral valve repair in asymptomatic patients with DMR. The results of mitral valve repair surgery for patients with NYHA class I DMR are excellent, with zero 30-day mortality, 100% freedom from reoperation at 10 years, and 99.4% free from more than moderate MR and 79.9% free from moderate MR. *DMR*, Degenerative mitral regurgitation; *MR*, mitral regurgitation; *NYHA*, New York Heart Association.

decreased exercise capacity documented on sequential exercise echocardiograms (Video 1). This report confirms that waiting until the LVEF drops below 60% impacts late survival so follow-up needs to be timely and routine.

VIDEO 1. Dr Patrick McCarthy and Dr James Thomas discuss the manuscript. Video available at: https://www.jtcvs.org/article/S0022-5223(20)33153-6/fulltext.

We investigated the relationship of preoperative AF and TR in DMR patients previously.[15] We noted that as we saw more patients who were NYHA I over time, we also saw fewer with preoperative AF ($P = .19$). We also looked at the relationship of moderate or more TR, assuming early referrals would also have less significant TR, but did not demonstrate a change over time. Annual moderate or more TR varied considerably from a high of 20% down to a low of 3% of patients. In the unmatched groups, the success of AF ablation was better in patients designated NYHA I, perhaps related to less atrial dilation and shorter duration of AF before surgery.

Study Limitations

This study is retrospective and a single-surgeon experience with the usual limitations of such investigations and may not be widely generalizable.[16] These results only reflect a surgical repair strategy and cannot be compared with asymptomatic patients who were not treated

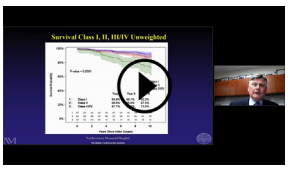
("watchful waiting"). Allocation bias also exists in that surgeon discretion was used in those patients who underwent tricuspid valve annuloplasty. In addition, our follow-up echocardiographic data were incomplete (85%), and so it is possible that over- or underestimation of the incidence for recurrent MR occurred. Due to the length of the study, changes in practice patterns as well as the ability to quantify MR or TR by echocardiography may have occurred and impacted our results. Notably, our study showed better overall survival for patients undergoing MV surgery than other similar reports at similar institutions, and this likely led to fewer mortality differences noted between asymptomatic patients compared to symptomatic patients with more advanced disease. As with many observational studies, the possibility of residual bias cannot be completely dismissed. As in comparisons involving overall survival end points statistical power is driven by the number of events, we have paid special attention to making sure that our conclusions did not rely primarily on statistical significance. Instead, we have made an effort to focus on the clinical significance of the findings.

CONCLUSIONS

The treatment of asymptomatic patients with severe DMR has been controversial. Our study suggest that an early operation is safe, effective, durable, and associated with improved AF ablation outcomes. While there was a trend toward better survival compared with patients with NYHA III/IV, no significant differences were identified between patients who were NYHA I and II. Mitral repair for patients designated class I, as suggested by the American Heart Association/American College of Cardiology Guidelines, is a good approach, but intervention with the earliest onset of symptoms also yields excellent results. Careful follow-up of patients designated class I is important, as waiting until LVEF is less than 60% was associated with reduced survival.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/20AM/Presentations/Asymptomatic%20Degenerative%20Mitral%20Reg.mp4.



Conflict of Interest Statement

Dr McCarthy reported Edwards Lifesciences: speaking fees and royalties; Medtronic and AtriCure: speaking fees; Abbott: surgical primary investigator REPAIR-MR Trial. Dr Cox reported Adagio Medical: co-founder, board of directors, consultant; AtriCure: consultant; SentreHEART: consultant; PAVmed: board of directors; Lucid Diagnostics: board of directors; PotentiaMetrics: board of directors. Dr Thomas reported Abbott, Edwards, General Electric, and Caption Health: consultant; spouse employment by Caption Health. All other 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.

ADULT

References

1. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med*. 1999;341:1-7.
2. Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2015;4:220-9.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63:2438-88.
5. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238-44.
6. Enriquez-Sarano M, Suri RM, Clavel MA, Mantovani F, Michelena HI, Pislaru S, et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. *J Thorac Cardiovasc Surg*. 2015;150:50-8.
7. Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA*. 2013;310:609-16.
8. Vemulapalli S, Grau-Sepulveda M, Habib R, Thourani V, Bavaria J, Badhwar V. Patient and hospital characteristics of mitral valve surgery in the United States. *JAMA Cardiol*. 2019;3:1149-55.
9. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303-71.
10. Andrei AC, McCarthy PM. An omnibus approach to assess covariate balance in observational studies using the distance covariance. *Stat Methods Med Res*. 2020;29:1846-66.
11. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41-55.
12. Garcia-Hernandez A, Rizopoulos D. % JM: a SAS macro to fit jointly generalized mixed models for longitudinal data and time-to-event Responses. *J Stat Softw*. 2018;84:1-29.
13. Kang DH, Park SJ, Sun BJ, Cho EJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. *J Am Coll Cardiol*. 2014;63:2398-407.
14. Madaric J, Watripont P, Bartunek J, Casselman F, Vanderheyden M, Van Praet F, et al. Effect of mitral valve repair on exercise tolerance in asymptomatic patients with organic mitral regurgitation. *Am Heart J*. 2007;154:180-5.
15. McCarthy PM, Szlapka M, Kruse J, Kislitsina ON, Thomas JD, Liu M, et al. The relationship of atrial fibrillation and tricuspid annular dilation to late tricuspid regurgitation in patients with degenerative mitral repair. *J Thorac Cardiovasc Surg*. December 12, 2019 [Epub ahead of print].

16. Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. *JACC Cardiovasc Interv*. 2008;1:211-7.

Key Words: mitral valve, mitral regurgitation, guidelines, atrial fibrillation, tricuspid regurgitation, New York Heart Association

ADULT

Discussion

Presenter: Dr Patrick M. McCarthy

Dr David H. Adams *(New York, NY)*. Thank you very much, Pat. I am delighted that I have the opportunity to discuss your paper.

I want to start the discussion by congratulating you and your team on these extraordinary results of mitral valve repair in patients with degenerative disease. These results are among the best reported and will influence future guidelines and help define what is possible in the contemporary era of surgical valve reconstruction.

Given the outcomes you now report, which asymptomatic patients with severe mitral regurgitation (MR) and preserved left ventricular function would you be willing to follow at this point? From 20,000 feet, it seems to me like the guidelines have it right. The presence of severe, degenerative MR should trigger treatment in the modern era if results approaching yours are achievable.

Dr Patrick M. McCarthy *(Chicago, Ill)*. Thanks, David. The decision is up to the patient. We're recommending surgery for typical patients. Sometimes they've just been diagnosed and it takes them a little while to become comfortable with the idea of heart surgery. They may want to follow with an exercise echo in 6 months. We may be more conservative if the patient has prolapse but no ruptured cords or flail leaflet. If they have only late systolic MR on echo, we also may suggest 6-month follow-up.

We use exercise echo often to help guide the decision. If their exercise capacity is good, and if the pulmonary artery pressures don't rise, then we're comfortable in watching them. But we counsel them to be carefully followed. We also educate them about the symptoms that they can develop and to return sooner. There have been sequential exercise studies published in allegedly asymptomatic patients. Repeat studies after surgery find exercise capacity is actually significantly better. So, many of these patients may have mild symptoms from MR and attribute some fatigue to getting older, but these sequential exercise tests indicate that the fatigue was from the MR.

Dr Adams. I wonder, Pat, if you could comment on the reasons why the replacement rate was greater in patients that were in functional class III–IV. Was this related to pathology, surgical risk, or both?

Dr McCarthy. It's a little of both. It was a group of patients that were, in general, older. On review, the 27 patients with mitral replacement had calcification of the leaflets, many were in their late 70s or 80s. Some had had subacute bacterial endocarditis with extensive leaflet damage. Some needed complex multiple valve or coronary artery bypass operations. Also, the group that were New York Heart Association (NYHA) class 3 to 4 were much more likely to be reoperations. Still, the repair rate even in older patients was very high.

Dr Adams. In a recent editorial written by myself and Ani Anyanwu in the *Journal of the American College of Cardiology*, we discussed Tirone David's publication of his very long-term outcomes in degenerative patients. We pointed out the need to address other processes associated with severe MR, and not just eliminate the MR at the time of surgery. Can you comment on your 100% use of the maze procedure in patients with atrial fibrillation in your series, which is very different than what we see in the Society of Thoracic Surgeons database? Tell us about the keys to achieve the successful results you reported as well—a 90% cure rate of atrial fibrillation in class I patients.

Dr McCarthy. A focus of our approach is to do this procedure very efficiently. Years ago, I switched to cryo-ablation instead of bipolar radiofrequency ablation. It's faster and easier. I have a technique that we're submitting for publication using 3 cryo-ablation lesions to create a box lesion that incorporates the left atrial appendage lesion, a lesion to the mitral valve annulus, and epicardial ablation of the coronary sinus. So, with 3 applications of the cryoprobe you can do the classic left-sided Cox-maze III lesions except for the septum.

Many of the patients had a left atrial only maze. We published our results with that group compared with biatrial lesions. With early referral of asymptomatic patients, there isn't as much tricuspid regurgitation, PA pressures are usually normal, they don't have a dilated right atrium, and those with atrial fibrillation usually had paroxysmal atrial fibrillation. So, for that group of patients a left atrial maze will be successful, because there's no right-sided pathology. Whether the absence of late atrial fibrillation protected them from recurrent MR—I don't know. But atrial fibrillation has been associated with recurrent tricuspid regurgitation in a study from Northwestern last year at the American Association for Thoracic Surgery.

Dr Adams. I must say when I read your paper, I speculated that your success in treating atrial fibrillation did

help the overall results, and the excellent survival you are reporting. Having said that, I'm less convinced about your conclusions regarding the impact of functional class on outcomes. One of the advantages of helping with the American Association for Thoracic Surgery Quality Gateway is that I am on the phone all the time with Gene Blackstone, and I was speaking to him earlier about something else, and ran your results by him, because they puzzled me, as this is the first time symptoms were not implicated in terms of MR outcomes. After looking at your data together, we believe your propensity matching is flawed if you look at the numbers. What I mean by that is you are taking the worst patients from the class I group and you are comparing them to better patients in the class II group, and the best patients in the class III/IV group.

I will give you an example: the survival in the unadjusted class I patients was 92% but, in your propensity-matched class I cohort it was only 87.3%. So, survival in the class I patients, not matched, had to be much greater than 92%. These patients you selected were sicker, and probably older. By comparison, the unmatched class III/IV patients had an unadjusted survival of 75% but in your propensity-matched cohort, the survival rose to 82%. These were the best class III/IV patients being compared with the worst class I patients. I am sure this also happened to some degree in the class II cohort-matching. About a third of the patients from class I and class II were excluded during your propensity matching. I point this out because I do not think we are quite ready to dismiss the outcome penalty of New York Heart Association functional class on survival, based on your data.

Dr McCarthy. I couldn't agree with you more. As they say, the absence of proof is not the proof of absence. My statistician and I have discussed this a few times, and he notes that this comparison is somewhat forced because the groups are so different at baseline. So, in my presentation I wanted to show the absolute difference in survival. In the propensity matching there was a trend toward a difference in survival and some of those patient numbers were pretty low after matching. If we had larger numbers, I'm sure we would have seen the difference.

Now, I have to say that is for NYHA class III and IV patients. For Dr David's paper and for ours, the difference in survival between class I and class II is not different. So we don't think that there's that much of a risk if you wait a little bit until patients get early symptoms. But the take-home message is: Don't wait until the patients are developing more advanced symptoms. Get to them early—either asymptomatic or very early class II-type symptoms.

Dr Adams. I think you are right on this point, Pat. We do not know the impact of the duration of symptoms either, but I am sure this would also influence the outcomes in many patients. I think our main emphasis should remain on interventions on all patients with any symptoms, which is consistent with the guidelines.

Dr McCarthy. I agree. Maurice Sarano wrote a compelling paper about the outcome penalty based on the Mayo Clinic experience between 1990 and 2000. During that decade, beta-blockers were introduced for patients with heart failure, angiotensin-converting enzyme inhibitors, and biventricular pacing. These days patients don't present as late. For example, the ejection fraction difference between NYHA class I and class III–IV patients in our group was only 3%—statistically, but not clinically, different. Comparing results from 1990 to today, it's a whole new world.

Dr Adams. I really commiserate how hard it is to get long-term echo follow-up, and your paper reports an 85% success-rate in getting long-term echo follow-up. Can you comment if you have done a longitudinal analysis in terms of echo results? It is a more valuable data point to have, for instance, an echo that is 7 or 8 years' postoperatively than 6 months' postoperatively. So, how are you going to handle that in your analysis?

Dr McCarthy. We have our database people focus on getting late echoes. An issue we all deal with is that the appropriate use criteria says that patients don't routinely need a follow up echo. I'd love to have them get an echo every year. But if the patient feels well and has no murmur years after repair the cardiologist frequently doesn't order one. There's no universally accepted way to report echo in follow-up. It's like reporting freedom from atrial fibrillation in follow up; it may come and go. In this case a patient may have moderate MR on one echo reading with all later reads being mild MR. We report recurrent MR 2 ways therefore. The group that have more than moderate are more concerning. Typically we wouldn't reoperate or do an intervention for moderate, but we would consider it for 3 or 4+. They likely have an organic lesion of the valve. More than moderate fortunately was very low.

Dr Adams. Pat, I will just finish by saying I know that the coronavirus disease 2019 pandemic has really changed all of our professional lives and taken away some of our usual academic exchange opportunities. It was very enjoyable to spend this time with you in the pursuit of excellence, through our discussion. I think when you are done with all of the analyses and your paper is published, it is going to become another important contribution that will be quoted and referred to often. I just want to congratulate you and your co-authors on this paper.

Dr McCarthy. Thanks, David. I appreciate the comments and we're all thinking of you in New York City during this difficult time.

Dr Adams. Well, we're getting better. Just before we leave, let me open the microphone and maybe Dr Tirone

David can make a comment. Tirone's paper last year looking at his very long-term outcomes is, in my opinion, the true benchmark and we should not leave this session without Tirone making a comment.

Dr Tirone E. David *(Toronto, Ontario, Canada)*. I don't have much to add. Maybe some questions to Patrick. How did you do these operations? Robotic, thoracotomy, sternotomy?

Dr McCarthy. These are old-fashioned sternotomy operations, Tirone. We have submitted a paper about the quantitative algorithm and measured technique that we used to create the proper coaptation without systolic anterior motion.

Dr David. To have 100% freedom from reoperation, and only 1.5% severe MR at 10 years, is going to be very difficult to replicate by minimally invasive approaches. If I'm a patient, and I can read English, I'm going to Google, find your paper, and my dilemma is going to be: should I compromise the quality of my operation for a small scar on my chest?

The other question one is: I am amazed that you have no reoperation at all, because in my hands, preoperative functional class has no effect on the durability of the operation. On survival, yes, it's very important. It's the pathology of the mitral valve that affects long-term outcome. Posterior prolapse very seldom fails; at 20 years maybe 2% to 3% came up with disease elsewhere. In Barlow's with multiple-segment prolapse, they're tougher operations. We are doing more and more on 30-, 40-, and 50-year-old patients and they usually do not have multisegments prolapse. They frequently have more advanced myxomatous degeneration, and repair is much more complicated. And unfortunately, with many more failures—not 0 at 10 years.

Dr McCarthy. About 40% had bileaflet disease or anterior leaflet disease, so most had posterior leaflet disease only. I think it was just chance that the asymptomatic group had zero reoperations. I agree with you, it's progression of the pathology that leads to reoperation, not the patient's symptoms from 10 years earlier. If I look at my results in 20 years like you, then you'll probably see that, but we didn't see it in 10 years. The more advanced pathology likely will lead to more reoperations over time, but it's likely with the early referrals the pathology was at an earlier stage when it was repaired.

I've noticed that the patients with ruptured cords who postponed surgery for years have much more advanced disease and need a more complex repair. The tension on the non-ruptured chords over time contributes to progression of disease.

Dr David. Well, congratulations. These are quite spectacular results.

Dr Y. Joseph Woo *(Stanford, Calif)*. Pat, congratulations again on the outstanding results. I am interested in exploring the topic but in the other direction. You are comparing class I with class II and then to class III. However, if your results are that great in class 1 patients and as you conclude safe, effective, and durable, at what point do we start considering operating on class 1 asymptomatic patients who have, 3+ MR with a clear-cut structural lesion that you know will progress over time?

Dr McCarthy. If they have greater than moderate, then we will consider operating on that group. Most patients, maybe 95%, are compliant and they'll come back in 6 months, so I don't push too hard. I don't know anyone that has good data operating as early as you suggest. Perhaps it will halt progression of the disease and the repairs will be very safe, effective and durable. It's an interesting concept. By the way, Tirone regarding your comment about it being a benchmark for less invasive surgery, it's more important that it's a benchmark for transcatheter procedures. They're facing an extremely high bar with degenerative MR trying to repair or replace the valve.

Dr Matthew A. Romano *(Ann Arbor, Mich)*. Pat, that really was a great presentation. My question is, how do we educate or get this message out? I am continually surprised by how many patients I see in my mitral clinic that have had symptoms for some time, but are ultimately referred by their cardiologist when they are in class III or class IV. I was wondering when I looked at your timeline, it looks like in 2018 your volume dropped off a little bit after a steady increase. Is that reflective that still there's such uncertainty from cardiologists as to when to refer? I think we're potentially missing a huge volume of patients that we could otherwise be helping earlier in their disease and improved outcomes and it is important to get the correct message out.

Dr McCarthy. Matt, the national data would certainly indicate that it has not caught on. I happen to work in an institution where Bob Bonow and Jim Thomas wrote the guidelines. So at Northwestern, and in the region, the cardiologists are well educated about early referrals. We need more publications coming out indicating that it's not just safe for 30 days, but there's great long-term results. That's really the point of this paper.

Dr Romano. The other concern is related to your comment in regard to the transcatheter space and the push to use this technology, and that maybe willing to accept a much lower bar of success as a trade-off for a less-invasive approach.

Dr McCarthy. Well, let's hope not. Any transcatheter technique that decreases your chances for a repair because it damages the valve is contraindicated in young healthy patients.

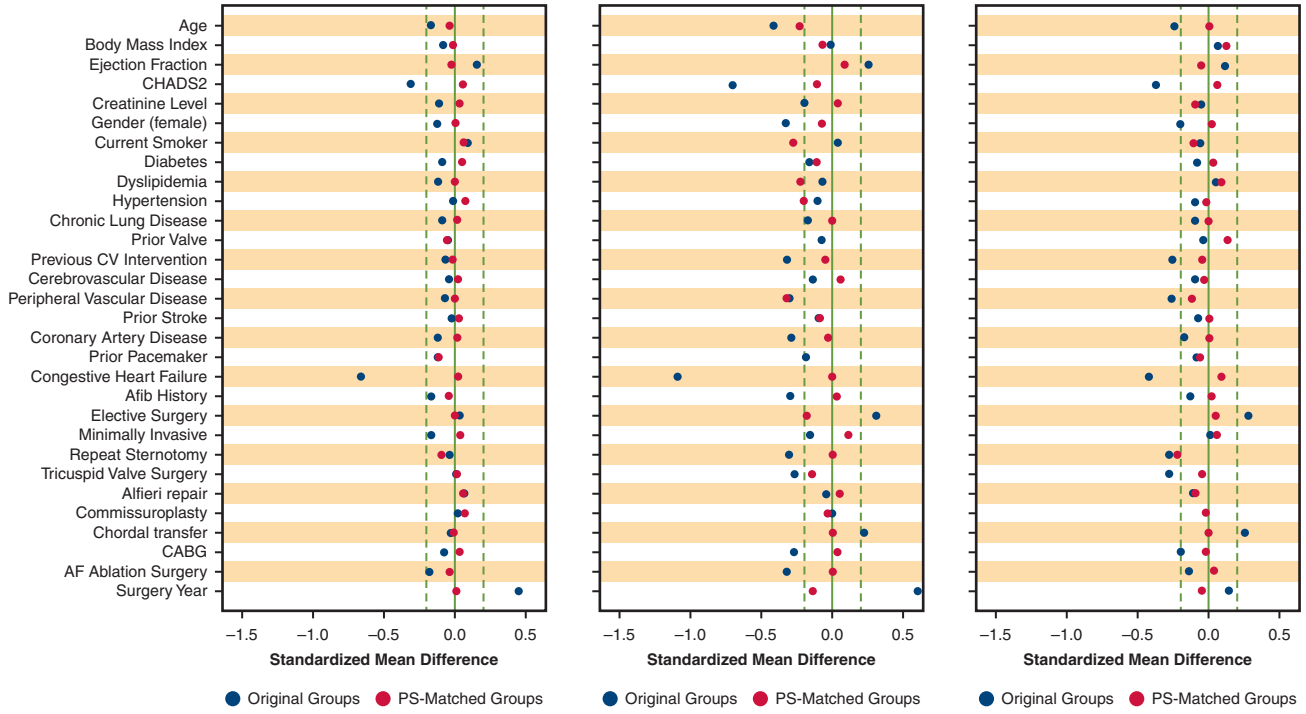


FIGURE E1. Standardized mean differences for NYHA pairwise comparisons. Baseline covariates for PS-matched pairs NYHA I versus NYHA II (A) and NYHA II versus NYHA III/IV (C) were well balanced, except for repeat sternotomy (C). In B (NYHA II vs III/IV), some residual imbalances were remained for current smoker status, dyslipidemia, and peripheral vascular disease. *PS*, Propensity-score; *CHADS2*, congestive heart failure, hypertension, age, diabetes, stroke; *CV*, cardiovascular; *Afib*, atrial fibrillation; *CABG*, coronary artery bypass graft; *AF*, atrial fibrillation.

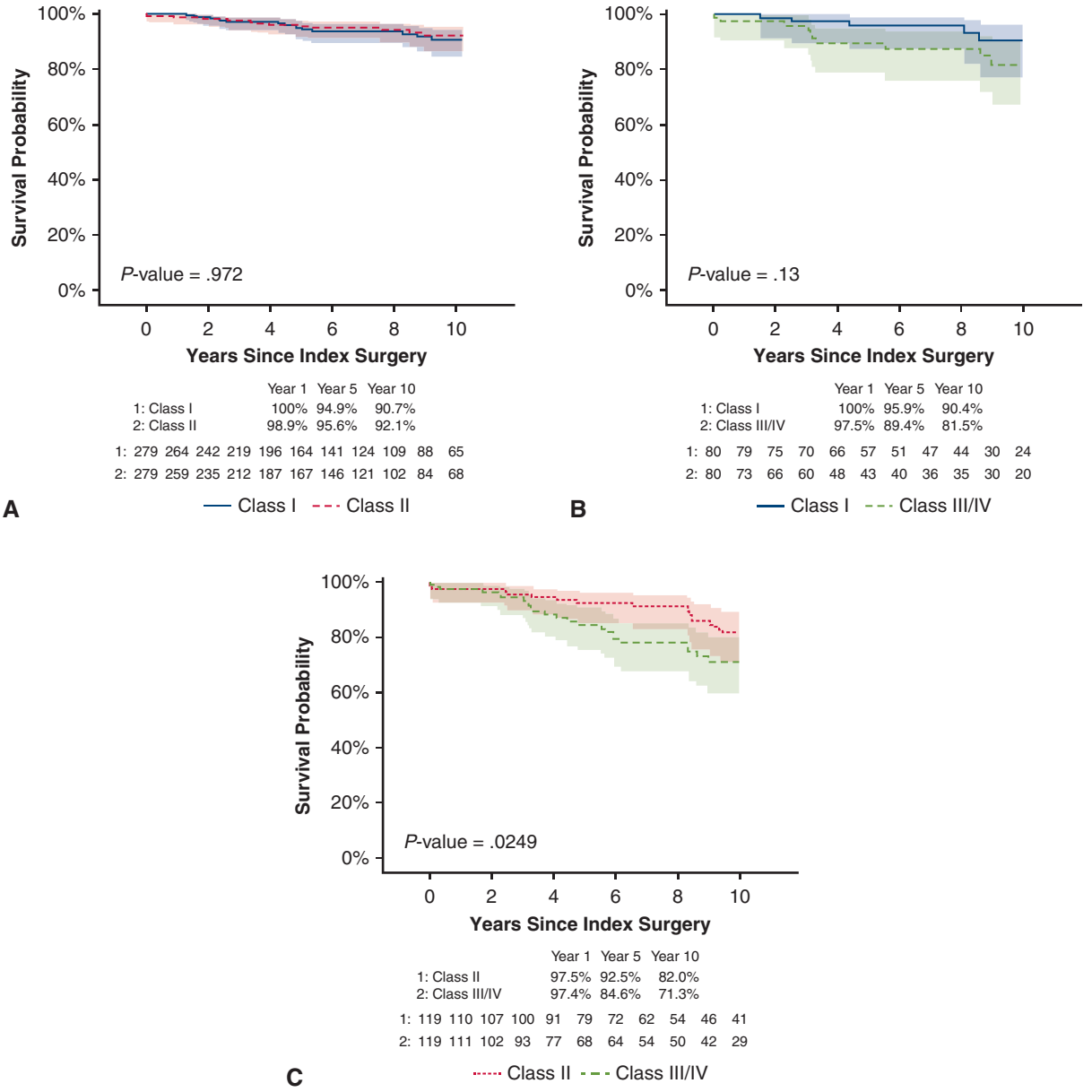
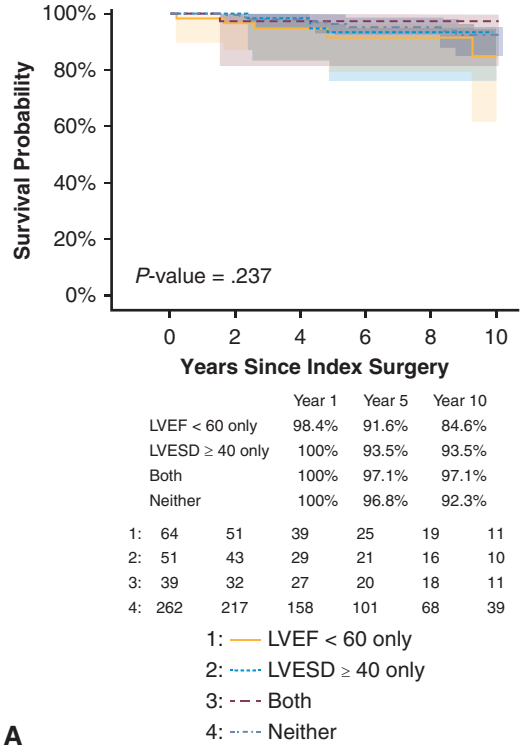


FIGURE E2. Comparison of overall survival by NYHA class in pairwise propensity score-matched comparisons. Near-identical survival is seen between NYHA I versus NYHA II (A, $P = .972$) and significantly superior survival in class II compared with III/IV (C, $P = .025$). Despite reduced sample sizes, data suggest that a difference may exist between NYHA I vs III/IV (B, $P = .13$). *NYHA*, New York Heart Association.



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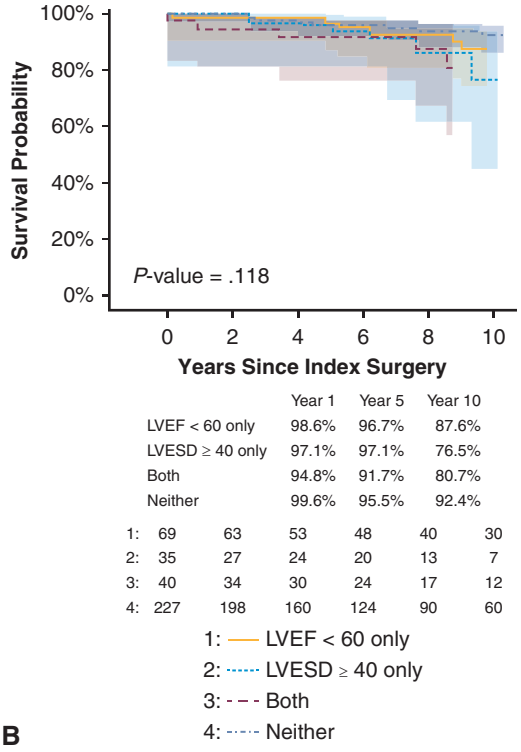

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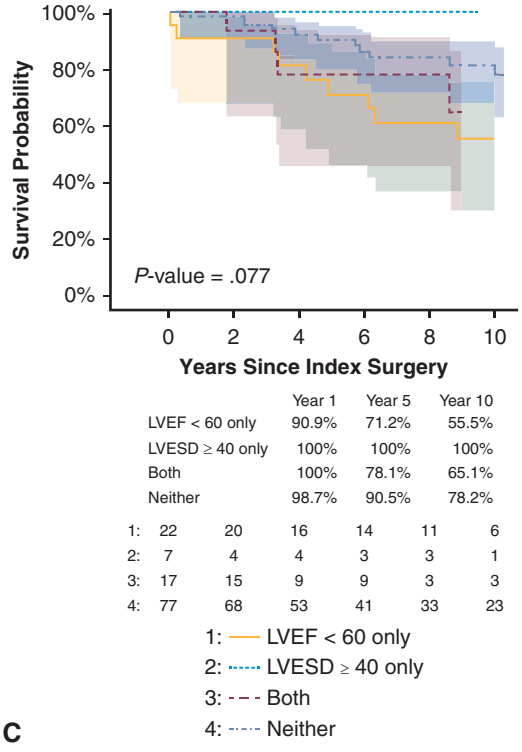

C

FIGURE E3. Overall survival by NYHA class and indication. Data suggest a lack of statistically significant survival differences by indication within NYHA class I (A, $P = .237$), NYHA II (B, $P = .118$), or NYHA class III/IV patients (C, $P = .077$), although definitive conclusions are not possible due to small sample sizes. *LVEF*, Left ventricular ejection fraction; *LVESD*, left ventricular end-systolic diameter.

TABLE E1. Summary of MW-weighted standardized mean differences among by New York Heart Association classes

Variable	Original data summaries			MW-weighted data summaries		
	Class I vs II	Class I vs III/IV	Class II vs III/IV	Class I vs II	Class I vs III/IV	Class II vs III/IV
Age, y	0.170	0.416	0.245	0.048	0.026	0.073
Body mass index, kg/m^2	0.079	0.015	0.065	0.080	0.003	0.088
Ejection fraction	0.156	0.257	0.115	0.102	0.020	0.076
CHADS2	0.308	0.704	0.372	0.051	0.053	0.000
Creatinine level	0.113	0.201	0.051	0.026	0.067	0.090
Sex (female)	0.124	0.326	0.200	0.018	0.127	0.109
Current smoker	0.095	0.037	0.058	0.049	0.060	0.012
Diabetes	0.086	0.165	0.081	0.040	0.003	0.043
Dyslipidemia	0.117	0.068	0.048	0.055	0.049	0.104
Hypertension	0.009	0.107	0.098	0.031	0.012	0.019
Chronic lung disease	0.088	0.177	0.091	0.092	0.043	0.134
Previous valve	0.047	0.081	0.037	0.039	0.089	0.059
Previous CV intervention	0.067	0.318	0.253	0.100	0.032	0.132
Cerebrovascular disease	0.040	0.135	0.095	0.054	0.061	0.007
Previous stroke	0.020	0.094	0.075	0.025	0.036	0.011
Coronary artery disease	0.057	0.280	0.212	0.034	0.027	0.007
Previous pacemaker	0.120	0.191	0.085	0.007	0.149	0.154
Congestive heart failure	0.661	1.089	0.422	0.017	0.023	0.005
Atrial fibrillation history	0.163	0.297	0.133	0.154	0.091	0.062
Elective surgery	0.036	0.307	0.279	0.059	0.022	0.081
Minimally invasive	0.169	0.160	0.009	0.034	0.042	0.076
Repeat sternotomy	0.036	0.307	0.279	0.041	0.102	0.141
Tricuspid valve surgery	0.010	0.266	0.276	0.024	0.066	0.043
Alfieri repair	0.066	0.048	0.114	0.105	0.140	0.035
Commissuroplasty	0.018	0.006	0.024	0.038	0.121	0.084
Chordal transfer	0.029	0.225	0.254	0.003	0.025	0.023
CABG	0.074	0.272	0.199	0.012	0.078	0.066
Atrial fibrillation Ablation surgery	0.180	0.320	0.139	0.130	0.068	0.062
Surgery year	0.449	0.598	0.144	0.038	0.017	0.054

MW, Matching weights; *CHADS2*, congestive heart failure, hypertension, age, diabetes, sex; *CV*, cardiovascular; *CABG*, coronary artery bypass grafting.

TABLE E2. Survival differences among New York Heart Association classes with and without application of matching weights

Cox regression model	N/events	NYHA class	HR (95% CI)	*P* value
Unadjusted, unweighted	1005/84	I	0.26 (0.15-0.45)	<.001
		II	0.36 (0.22-0.59)	<.001
		III/IV	REF	REF
Adjusted, unweighted	988/84	I	0.57 (0.29-1.14)	.11
		II	0.49 (0.28-0.85)	.011
		III/IV	REF	REF
Unadjusted, M-weighted	985/83	I	0.72 (0.27-1.96)	.52
		II	0.65 (0.24-1.79)	.41
		III/IV	REF	REF
Adjusted, M-weighted	985/83	I	0.72 (0.24-2.20)	.57
		II	0.50 (0.17-1.50)	.22
		III/IV	REF	REF

Summaries of unadjusted (marginal) and covariate-adjusted (conditional) Cox regression models with unweighted and M-weighted observations. Summaries shown are HRs and corresponding 95% CIs for NYHA classes I and II compared with NYHA class III/IV (reference). *NYHA*, New York Heart Association; *HR*, hazard ratio; *CI*, confidence interval; *REF*, reference.

TABLE E3. Hazard ratios and confidence intervals among New York Heart Association class I, II, or III/IV groups

Cox regression model	NYHA class I vs II (REF)			NYHA class I vs III/IV (REF)			NYHA class II vs III/IV (REF)		
	N/events	HR (95% CI)	*P* value	N/events	HR (95% CI)	*P* value	N/events	HR (95% CI)	*P* value
Original groups, unadjusted	878/55	0.71 (0.41-1.23)	.22	597/50	0.25 (0.14-0.45)	<.001	535/63	0.36 (0.22-0.59)	<.001
PS-matched groups, unadjusted	558/34	1.01 (0.52-1.98)	.97	160/17	0.47 (0.17-1.28)	.14	238/42	0.49 (0.26-0.92)	.028
Original groups, adjusted	861/55	1.17 (0.62-2.27)	.63	586/50	0.72 (0.31-1.64)	.43	529/63	0.50 (0.28-0.88)	.017
PS-matched groups, adjusted	558/34	1.33 (0.64-2.75)	.45	160/17	0.51 (0.16-1.63)	.25	238/42	0.46 (0.23-0.93)	.031

Summaries of HRs and corresponding 95% CIs based on pairwise comparisons among NYHA classes I, II, or III/IV. Results are shown in the original groups and the PS-matched groups, summarizing both unadjusted (marginal) and covariate-adjusted (conditional) effects. *NYHA*, New York Heart Association; *REF*, reference; *HR*, hazard ratio; *CI*, confidence interval; *PS*, propensity score.