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Transcatheter Aortic Valve Replacement

Outcomes of Patients With Moderate or Severe Mitral Regurgitation

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Objectives The aim of this study was to evaluate the impact of mitral regurgitation (MR) on outcomes after transcatheter aortic valve replacement (TAVR) and the impact of TAVR on MR.

Background Little is known of the influence of MR on outcomes after TAVR.

Methods The outcomes of patients with mild or less (n = 319), moderate (n = 89), and severe (n = 43) MR were evaluated after TAVR at 2 Canadian centers.

Results Patients with moderate or severe MR had a higher mortality rate than those with mild or less MR during the 30 days after TAVR (adjusted hazard ratio: 2.10; 95% confidence interval: 1.12 to 3.94; p = 0.02). However, the mortality rates after 30 days were similar (adjusted hazard ratio: 0.82; 95% confidence interval: 0.50 to 1.34; p = 0.42). One year after TAVR, moderate MR had improved in 58%, remained moderate in 17%, and worsened to severe in 1%, and 24% of patients had died. Severe MR had improved in 49% and remained severe in 16%, and 35% of patients had died. Multivariate predictors of improved MR at 1 year (vs. unchanged MR, worse MR, or death) were a mean transaortic gradient ≥40 mm Hg, functional (as opposed to structural) MR, the absence of pulmonary hypertension, and the absence of atrial fibrillation.

Conclusions Moderate or severe MR in patients undergoing TAVR is associated with a higher early, but not late, mortality rate. At 1-year follow-up, MR was improved in 55% of patients with moderate or severe MR at baseline. Improvement was more likely in patients with high transaortic gradients, with functional MR, without pulmonary hypertension and without atrial fibrillation. (J Am Coll Cardiol 2012;59:2068–74) © 2012 by the American College of Cardiology Foundation

Mitral regurgitation (MR) is present in most patients with severe aortic stenosis. In patients undergoing surgical aortic valve replacement, the reported prevalence of moderate or severe MR ranges from 13% to 74% (1–3). Such patients often undergo concomitant mitral valve repair or replacement.

Similarly, large series have reported moderate or severe MR in 22% to 48% of patients undergoing transcatheter aortic valve replacement (TAVR) (4–10), although in this setting, MR is typically left untreated. In fact, patients with severe MR have generally been excluded from formal evaluation, and outcomes in patients with MR have not been a focus of evaluation (11–13). Consequently, little is known about the impact of MR on clinical outcomes after TAVR and the impact of TAVR on MR (12,14).

Methods

Study population. Between January 2005 and July 2010, a total of 478 patients underwent TAVR for the treatment of severe symptomatic aortic stenosis at 2 Canadian centers, St. Paul's Hospital (Vancouver, British Columbia, Canada), and the Quebec Heart and Lung Institute (Quebec City, Quebec City, Canada), with the balloon expandable Cribier-Edwards, Edwards SAPIEN, or SAPIEN XT valve (Edwards

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Lifesciences, Irvine, California). Patients were excluded from analysis if they had mitral valve prostheses or received a non-balloon-expandable valves, leaving a final study population of 451 patients. All patients provided written informed consent for the procedure.

Data collection and definitions. Clinical and echocardiographic data were prospectively entered into a dedicated database at baseline, hospital discharge, 30 days, and annually. Transthoracic echocardiography was performed before TAVR, at a median of 3 days after TAVR (but before discharge), and after 1 year by senior echocardiographers according to the guidelines of the American Society of Echocardiography (15). MR severity was graded as none or trivial, mild, moderate, or severe according to the American College of Cardiology/American Heart Association/European Society of Cardiology recommendations, integrating structural, Doppler, and quantitative parameters (16). Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method. The severity of mitral annular calcification was graded according to Nair et al. (17). MR was classified on the basis of transthoracic and, in case of ambiguity, transesophageal echocardiography as predominantly functional or ischemic (no or minor associated pathology of the mitral valve leaflets, annulus, and chordate or papillary muscles on echocardiography) or predominantly structural or organic. Pulmonary hypertension was defined as a pulmonary artery systolic pressure (PASP) >60 mm Hg, as estimated by Doppler echocardiography or measured by cardiac catheterization (14). Porcelain aorta was defined as an extensive circumferential calcification of the thoracic aorta, as assessed by computed tomography and/or fluoroscopy (14). Patient–prosthesis mismatch was defined as an indexed effective orifice area ≤0.85 cm^2/m^2 (18,19). One-year follow-up was available in 131 of 132 patients (99%) with moderate or severe MR.

Statistical analysis. Continuous variables are expressed as mean ± SD or as median (interquartile range) in cases of skewed distributions. Categorical variables are expressed as frequencies and percents. Differences between independent groups were tested using the Kruskal-Wallis test for 3 groups and the Wilcoxon rank sum test and *t* test for continuous variables. In cases in which the samples were paired, the Wilcoxon signed rank or paired *t* test was used. Categorical variables were compared using the chi-square test. Survival rates at 30 days and at 1 and 2 years were estimated and graphed using the Kaplan-Meier method. Variables included in the baseline characteristic and procedural tables were tested for association with 2-year survival rates and included in the model if they were univariately significant at 0.25 to estimate the risk-adjusted hazard ratio (HR). A Cox regression model was used to estimate HRs and 95% confidence intervals (CIs) to compare the patients with moderate or severe MR with those with mild or less MR for all-cause mortality. On the basis of Schoenfeld residual plots, the effect of the MR groupings appeared to

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
LVEDD = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
OR = odds ratio
PASP = pulmonary artery systolic pressure
TAVR = transcatheter aortic valve replacement

Table 1 Baseline Characteristics

	Mild or Less MR (n = 319)	Moderate MR (n = 89)	Severe MR (n = 43)	p Value
Age (yrs)	81 ± 9	82 ± 7	84 ± 8	0.03
Female	163 (51%)	52 (58%)	24 (56%)	0.44
Coronary artery disease	230 (73%)	66 (74%)	35 (81%)	0.46
Previous myocardial infarction	134 (42%)	47 (53%)	26 (61%)	0.03
Previous open-heart surgery	109 (34%)	37 (42%)	21 (49%)	0.11
Previous PCI	93 (29%)	20 (23%)	16 (37%)	0.20
Previous cerebrovascular accident	66 (21%)	19 (21%)	7 (17%)	0.81
COPD	93 (29%)	21 (24%)	11 (26%)	0.55
Diabetes	97 (30%)	21 (24%)	9 (21%)	0.24
Hypertension	252 (79%)	70 (79%)	27 (63%)	0.06
GFR <60 ml/min	194 (61%)	61 (69%)	30 (70%)	0.32
Pulmonary hypertension	42 (13%)	18 (20%)	15 (35%)	<0.01
Porcelain aorta	53 (17%)	27 (30%)	8 (19%)	0.02
Atrial fibrillation	96 (30%)	35 (39%)	29 (67%)	<0.01
NYHA functional class III or IV	283 (88%)	78 (88%)	41 (95%)	0.37
STS risk score (%)	7.5 (5.0–10.7)	8.1 (6.3–12.2)	9.7 (6.3–12.1)	0.02
Mean gradient (mm Hg)	43 ± 17	44 ± 16	43 ± 17	0.95
Aortic valve area (cm^2)	0.64 ± 0.17	0.60 ± 0.15	0.59 ± 0.14	0.02
LVEF (%)	60 (50–65)	57 (45–60)	50 (40–60)	<0.01

Values are mean ± SD, n (%), or median (interquartile range).

COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

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Table 2 Procedural and 30-Day Outcomes

	Mild or Less MR (n = 319)	Moderate MR (n = 89)	Severe MR (n = 43)	p Value
Access route				0.07
Transfemoral	163 (51%)	41 (46%)	29 (67%)	
Transapical	156 (49%)	48 (54%)	14 (33%)	
Prosthesis size (mm)				0.42
23	131 (41%)	43 (48%)	14 (33%)	
26	186 (58%)	46 (52%)	29 (67%)	
29	2 (1%)	0 (0%)	0 (0%)	
Mean gradient (mm Hg)	11 ± 5	11 ± 5	10 ± 4	0.45
Aortic valve area (cm^2)	1.6 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	0.12
Major stroke	7 (2%)	3 (3%)	1 (2%)	0.82
New permanent pacemaker	21 (7%)	8 (9%)	0 (0%)	0.14
Coronary occlusion	5 (2%)	1 (1%)	0 (0%)	0.69
Mortality	24 (8%)	12 (14%)	7 (16%)	0.07

Values are n (%) or mean ± SD.
MR = mitral regurgitation.

change at 30 days, so time-varying coefficients were included in the regression model to account for the differences in the effect of the MR grouping up to 30 days and after 30 days to 2 years. Odds ratios (ORs) and 95% CIs were calculated for multivariate predictors of improved MR at 1-year follow-up. Variables were included if they were univariately significant at 0.25 and removed in a stepwise selection process on the basis of a significance level of 0.10. Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and tested using 2-sided tests at a significance level of 0.05.

Results

A total of 451 patients were analyzed. Valves implanted were the Cribier-Edwards in 56 (12%), the Edwards SAPIEN in 270 (60%), and the SAPIEN XT in 115 (28%) patients. At baseline, MR was mild or less in 319 patients (71%), moderate in 89 (20%), and severe in 43 (10%).

As shown in Table 1, moderate or severe MR was associated with increasing age, atrial fibrillation, prior myocardial infarction, porcelain aorta, a lower LVEF, smaller aortic valve area, and a higher Society of Thoracic Surgeons risk score.

Procedural outcomes and survival. Access route, prosthesis size, and procedural complications were similar regardless of the severity of MR (Table 2). Survival in patients with mild or less, moderate, and severe MR at baseline was 92.5%, 86.5%, and 83.7% at 30 days; 79.0%, 76.2%, and 64.5% at 1 year; and 66.2%, 67.9%, and 58.5% at 2 years, respectively (Fig. 1). Compared with patients with mild or less MR, those with moderate or severe MR had a higher mortality rate during the first 30 days (unadjusted HR: 2.04; 95% CI: 1.11 to 3.74; p = 0.02; and adjusted HR: 2.10; 95% CI: 1.12 to 3.94; p = 0.02) but no difference after 30 days (unadjusted HR: 0.94; 95% CI: 0.58 to 1.51; p = 0.80; and adjusted HR: 0.82; 95% CI: 0.50 to 1.34; p = 0.42) (Table 3).

New York Heart Association functional class. At 1-year follow-up, New York Heart Association functional class had generally improved, with only 6% of patients (5 of 88) with moderate MR and 5% of patients (2 of 43) with severe MR in class III or IV (Fig. 2).

MR grade. Changes over time in MR severity are shown in Figure 3.

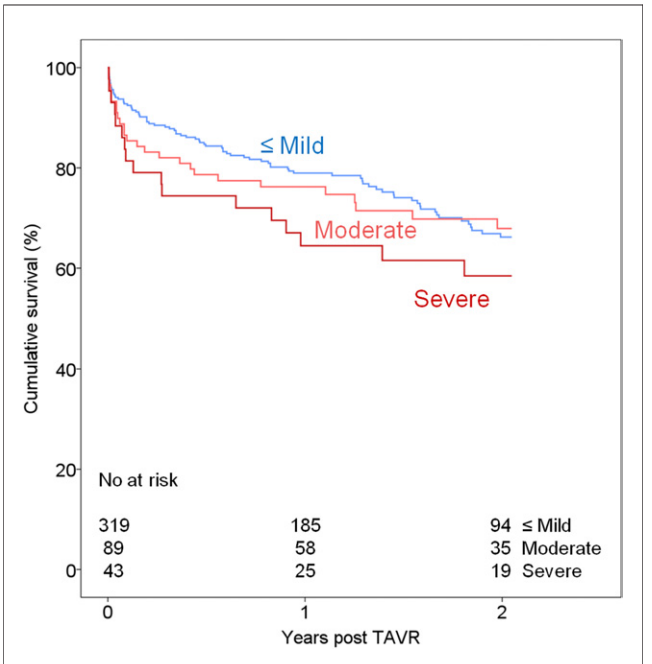

Figure 1 Kaplan-Meier Curves for All-Cause Mortality in Patients With Mild or Less, Moderate, and Severe MR at Baseline

Survival in patients with mild or less, moderate, and severe mitral regurgitation (MR) at baseline was 92.5%, 86.5%, and 83.7% at 30 days; 79.0%, 76.2%, and 64.5% at 1 year; and 66.2%, 67.9%, and 58.5% at 2 years, respectively. TAVR = transcatheter aortic valve replacement.

Table 3 HRs for Moderate or Severe Versus Mild or Less MR

	HR (95% CI)	p Value
Unadjusted		
≤30 days	2.04 (1.11–3.74)	0.02
>30 days	0.94 (0.58–1.51)	0.94
Risk adjusted		
≤30 days	2.10 (1.12–3.94)	0.02
>30 days	0.82 (0.50–1.34)	0.42

The risk-adjusted HRs were adjusted for Society of Thoracic Surgeons risk score, mean gradient, porcelain aorta, site, access route, New York Heart Association functional class, atrial fibrillation, prior cerebrovascular accident, kidney function, pulmonary hypertension, chronic obstructive pulmonary disease, and sex.

CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation.

After TAVR, moderate MR improved in 62%, remained moderate in 27%, and worsened to severe in 5%. At 1 year, MR had improved in 58%, remained moderate in 17%, and worsened to severe in 1%, and 24% of patients had died. In patients with severe MR at baseline, MR improved in 60% and remained severe in 33% after TAVR. At 1 year, MR had improved in 49% and remained severe in 16%, and 35% of patients had died (Fig. 3).

Predictors of improved MR. Table 4 compares baseline and procedural characteristics in patients with improved MR with those with unchanged or worse MR or patients who died before 1-year follow-up. For stepwise multivariate analysis, absence of atrial fibrillation, a mean gradient ≥40 mm Hg, PASP <60 mm Hg, LVEF <50%, mitral annular calcification grade 2 or 3, and the presence of functional MR (all with p values <0.25) were included in the initial step of the model-building process. Only the following significant predictors remained in the final model: mean transaortic gradient ≥ 40 mm Hg (OR: 2.92; 95% CI: 1.20 to 6.60; p = 0.01), the presence of functional MR (OR: 2.85; 95% CI: 1.27 to 6.39; p = 0.01), the absence of pulmonary hypertension (OR: 2.57; 95% CI: 1.07 to 6.16; p = 0.03), and the absence of atrial fibrillation (OR: 2.55; 95% CI: 1.19 to 5.46; p = 0.02) (Table 5).

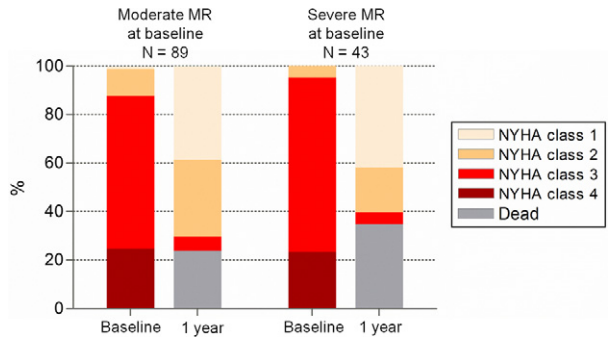

Figure 2 NYHA Functional Class at Baseline and 1-Year Follow-Up in Patients With Moderate or Severe MR

At 1-year follow-up, New York Heart Association (NYHA) functional class had improved, with only 6% of patients with moderate mitral regurgitation (MR) and 5% of patients with severe MR in NYHA class III or IV.

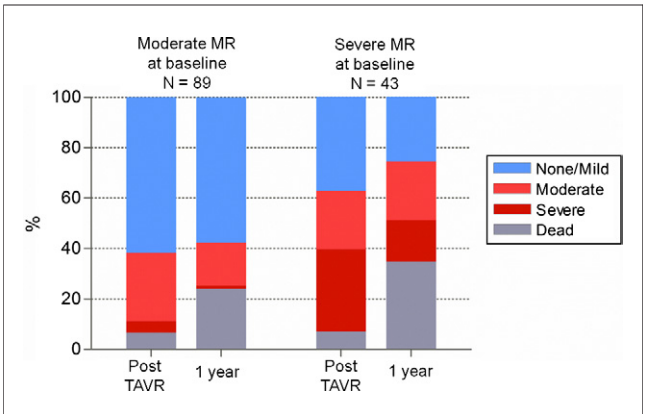

Figure 3 Degree of MR After TAVR and at 1-Year Follow-Up in Patients With Moderate or Severe MR at Baseline

One year after transcatheter aortic valve replacement (TAVR), moderate mitral regurgitation (MR) had improved by ≥1 grade in 58% of patients, remained the same in 17%, and worsened in 1%. Severe MR had improved by ≥1 grade in 49% and remained severe in 16%.

LVEF, left ventricular diameter, and PASP. At 1 year, patients with moderate or severe MR had significant improvements in LVEF, left ventricular end-diastolic diameter (LVEDD), and PASP, but 28% of the patients had died. In patients with moderate MR at baseline, median LVEF increased from 57% (interquartile range: 45% to 60%) to 60% (interquartile range: 55% to 65%) (p = 0.03), mean LVEDD dimension decreased from 49 ± 8 mm to 46 ± 6 mm (p < 0.01), and mean PASP decreased from 49 ± 8 mm Hg to 41 ± 11 mm Hg (p < 0.01). In patients with severe MR at baseline, median LVEF increased from 50% (interquartile range: 40% to 60%) to 60% (interquartile range: 54% to 65%) (p = 0.01), mean LVEDD decreased from 53 ± 7 mm to 51 ± 6 mm (p = 0.17), and mean PASP decreased from 55 ± 18 mm Hg to 49 ± 13 mm Hg (p < 0.01).

Discussion

Moderate or severe MR in patients undergoing TAVR was associated with reduced survival. The mortality rate was higher during the first 30 days but not thereafter. The 30-day mortality rate in patients with moderate or severe MR was approximately double that in patients with no or mild MR, but mortality rates were similar from 30 days up to 2 years. MR diminished in 61% of patients with moderate or severe MR at baseline after TAVR. At 1-year follow-up MR, had improved in 55%, remained unchanged in 16%, and worsened in 1%; the remaining 28% had died. LVEF and LVEDD had improved at 1-year follow-up, suggesting positive remodeling. Patients with high transaortic gradients, with functional (as opposed to structural) MR, without pulmonary hypertension, and without atrial fibrillation were more likely to have reductions in MR at 1-year follow-up.

Survival. From published surgical research, it is known that combining mitral with aortic valve surgery is associated

Table 4 Baseline Characteristics of Patients With Moderate or Severe MR at Baseline With Reduced and Unchanged or Worsened MR at 1-Year Follow-Up

	Reduced MR (n = 71)	Unchanged or Worsened MR (n = 59)	Univariate p Value
Age (yrs)	83 ± 6	82 ± 8	0.26
Female	43 (61%)	33 (56%)	0.59
Coronary artery disease	52 (73%)	48 (81%)	0.27
Previous myocardial infarction	41 (58%)	32 (54%)	0.69
Previous open-heart surgery	32 (45%)	25 (42%)	0.76
Previous cerebrovascular accident	14 (20%)	12 (20%)	0.96
COPD	18 (25%)	14 (24%)	0.83
Hypertension	55 (78%)	41 (70%)	0.30
GFR <60 ml/min	49 (69%)	41 (70%)	0.95
Pulmonary hypertension	12 (17%)	21 (36%)	0.02
Porcelain aorta	21 (30%)	14 (24%)	0.45
Atrial fibrillation	27 (38%)	37 (63%)	<0.01
NYHA functional class III or IV	65 (92%)	52 (88%)	0.52
STS risk score (%)	8.5 (6.3–12.1)	8.4 (6.1–12.2)	0.87
Mean gradient ≥40 mm Hg	50 (70%)	30 (51%)	0.02
Aortic valve area (cm^2)	0.58 ± 0.14	0.61 ± 0.15	0.26
Ejection fraction <50%	18 (25%)	27 (46%)	0.02
Functional MR	45 (64%)	28 (48%)	0.06
MAC grade 2 or 3	29 (41%)	32 (54%)	0.13
Transfemoral access	39 (55%)	29 (49%)	0.51
Valve size ≥26 mm	37 (52%)	36 (61%)	0.31
Patient–prosthesis mismatch	41 (59%)	24 (51%)	0.37

Values are mean ± SD, n (%), or median (interquartile range).
MAC = mitral annular calcification; other abbreviations as in Table 1.

with increased postoperative mortality and morbidity (20,21). A few studies have reported the impact of untreated MR on isolated surgical aortic valve replacement. Some (1,22), but not all (23), found increases in morbidity and mortality in patients with moderate MR. In contrast to surgical aortic valve replacement, concurrent mitral valve repair or replacement has not been an option in patients undergoing TAVR, although new transcatheter mitral therapies offer options in the future (24).

Limited information is available with regard to the impact of MR on outcomes after TAVR. A Canadian registry reported that severe MR was present in 17% of patients who died within 30 days after TAVR but only 7% of those who survived (14). The Italian CoreValve (Medtronic, Inc., Minneapolis, Minnesota) registry reported that grade 3+ or 4+ MR was present in 13.2% of patients who died but only 4.9% of those who survived at a median of 69 days after the procedure (HR: 4.62) (12). Interesting data come from the PARTNER (Placement of Aortic Transcatheter Valves) studies suggesting that patients with moderate or severe MR may derive a large benefit from TAVR compared with both medical management and surgical aortic valve replacement (5,25). In the PARTNER B study, subgroup analysis showed that the number needed to treat to prevent 1 death at 1 year was 3 in patients with moderate or severe MR, compared with 7 in patients without. In the PARTNER A study, 1-year mortality of patients with moderate or severe MR was 24.2% after TAVR (similar to the 27.7% in our study) and as high as 35% after surgical aortic valve replacement.

Table 5 Multivariate Predictors of Reduced MR at 1-Year Follow-Up

	Multivariate Odds Ratio (95% CI)	Multivariate p Value
Pulmonary pressure <60 mm Hg	2.68 (1.09–6.58)	0.03
Absence of atrial fibrillation	2.55 (1.17–5.55)	0.02
Mean gradient ≥40 mm Hg	2.71 (1.19–6.18)	0.02
Functional MR	2.61 (1.15–5.93)	0.02

Variables initially included in the model were pulmonary artery systolic pressure <60 mm Hg, absence of atrial fibrillation, mean transaortic gradient ≥40 mm Hg, functional MR, mitral annular calcification grade 2 or 3, and left ventricular ejection fraction <50%.
CI = confidence interval; MR = mitral regurgitation.

Predictors of MR reduction. In line with our study, the absence of atrial fibrillation (26) and functional (as opposed to structural) MR (27) have been identified as predictors for reduction of MR in patients undergoing isolated surgical aortic valve replacement. Left atrial size (3,28), left ventricular mass index (28), mitral valve tenting area (26), left ventricular fractional area change (29), and less mitral annular calcification (28) have also been reported to predict MR reduction after surgical aortic valve replacement.

Little information is available with regard to changes in MR after TAVR. Durst et al. (30) reported improvement in mild to moderate MR after TAVR with the SAPIEN valve in 12 of 35 patients (34%). The absence of mitral annular calcification was associated with improved MR. Tzikas et al.

(31) reported reduction in moderate to severe MR after TAVR with the CoreValve prosthesis, improving in 6 of 10 patients (60%), remaining unchanged in 3 patients (30%), and worsening in 1 patient (10%). A worse LVEF was associated with reduced MR. It has been suggested that the effects of the 2 transcatheter valves may differ because of a possible increased risk of the longer CoreValve prosthesis interfering with the anterior mitral leaflet apparatus (32).

Mechanisms of benefit. The severity of MR depends primarily on regurgitant orifice area and the systolic pressure gradient between the left ventricle and the left atrium (33). After aortic valve replacement, MR is expected to diminish immediately because of a reduction in afterload and may diminish further in the mid and long terms, should positive left ventricular remodeling occur (34). Reductions in left ventricular volumes may lead to improved coaptation of the leaflets. As shown in this and other (27,28) studies, MR reduction may be less likely in patients with structural mitral valve disease, such as might occur in the presence of deformed leaflets or moderate or severe annular calcification. Patient–prosthesis mismatch and prosthesis size were not significant predictors of MR reduction in our study.

Study limitations. Our data represent the experience of 2 centers rather than outcomes of a clinical trial, and they are self-reported, with no external independent data adjudication. Changes in LVEF, left ventricular diameter, and PASP may be subject to survivor bias and may therefore be overestimated.

Conclusions

If left untreated, patients with severe aortic stenosis and concomitant moderate or severe MR have a very poor prognosis. TAVR procedural mortality is increased in patients with advanced MR. Nevertheless, these findings demonstrate late functional benefit in survivors and are consistent with, but do not prove, a possible late survival benefit. MR was reduced in more than one-half of patients at 1-year follow-up. Various clinical factors may assist in identifying which patients may benefit from isolated aortic valve replacement. TAVR may be a reasonable strategy in carefully selected patients with combined aortic and mitral valve disease.

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