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Prognostic Value of Increased Mitral Valve Gradient After Transcatheter Edge-to-Edge Repair for Primary Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study sought to evaluate the prognostic value of an increased mean mitral valve pressure gradient (MVG) in patients with primary mitral regurgitation (MR) after transcatheter edge-to-edge repair (TEER).

BACKGROUND Conflicting data exist regarding impact of increased mean MVG on outcomes after TEER.

METHODS This study included 419 patients with primary MR (mean age 80.6 ± 10.4 years; 40.6% female) who underwent TEER. Patients were divided into quartiles (Qs) based on discharge echocardiographic mean MVG. Primary outcome was the composite endpoint of all-cause mortality and heart failure hospitalization. Secondary outcomes included all-cause mortality and the secondary composite endpoint of all-cause mortality, heart failure hospitalization, and mitral valve reintervention.

RESULTS The median number of MitraClips used was 2 per patient. MR reduction ≤moderate was achieved in 407 (97.1%) patients. Mean MVG was 1.9 ± 0.3 mm Hg, 3.0 ± 0.1 mm Hg, 4.0 ± 0.1 mm Hg, and 6.0 ± 1.2 mm Hg in Q1, Q2, Q3, and Q4, respectively. There was no significant differences across quartiles in the primary outcome (15.4%, 19.6%, 22.0%, and 21.9% in Q1-Q4, respectively; $P = 0.63$), all-cause mortality (15.9% vs 18.6% vs 19.4% vs 17.1%, respectively; $P = 0.91$), and the secondary composite endpoint at 2 years (33.3% vs 29.5% vs 22.0% vs 31.6%, respectively; $P = 0.37$). After multivariate adjustment for baseline clinical and procedural variables, the mean MVG in Q4 compared with Q1 to Q3 was not independently associated with the primary outcome (HR: 1.22; 95% CI: 0.82-1.83; $P = 0.33$), all-cause mortality, and the secondary composite endpoint.

CONCLUSIONS Increased mean MVG was not independently associated with adverse events after TEER in patients with primary MR. (J Am Coll Cardiol Intv 2022;15:935-945) © 2022 by the American College of Cardiology Foundation.

Transcatheter edge-to-edge repair (TEER) of the mitral valve (MV) using the MitraClip device (Abbott Vascular) has become the standard alternative treatment for symptomatic patients with primary mitral regurgitation (MR) who are at prohibitive or high surgical risk.[1] TEER using the MitraClip approximates the MV leaflets and creates a double orifice MV, which improves leaflet coaptation and reduces MR but often results in increased mean MV pressure gradient (MVG).[2] The patients with an

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ABBREVIATIONS AND ACRONYMS

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

MVG = mitral valve pressure gradient

NYHA = New York Heart Association

Q = quartile

STS = Society of Thoracic Surgeons

TEER = transcatheter edge-to-edge repair

increased mean MVG after TEER are a unique subset with increased preload caused by underlying MR and nonrigid MV. In addition, their mean MVG typically remained with mild to moderate and does not exceed 10 mm Hg.[2,3] There is conflicting evidence regarding the impact of increased mean MVG after TEER on clinical outcomes.[4-7] In the current study, we aimed to evaluate the prognostic value of increased mean MVG on discharge in patients who underwent TEER for primary MR.

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METHODS

PATIENT POPULATION. Consecutive patients with moderate-to-severe and severe primary MR who underwent TEER were included in this analysis. Baseline demographic and clinical data as well as echocardiographic measurements were collected using the hospital records and were analyzed retrospectively. Patients at prohibitive or high surgical risk were selected for TEER after discussion in the multidisciplinary heart team.[8] All TEER procedures were conducted in accordance with local guidelines using standard techniques and MitraClip devices (Abbott Vascular) were implanted. This retrospective analysis of clinically acquired data was approved by the Institutional Review Boards, and the need for patient written informed consent was waived caused by the retrospective nature of the study. In the present study, patients were divided into quartiles (Qs) (Q1, Q2, Q3, and Q4) based on their mean MVG on discharge transthoracic echocardiography.

ECHOCARDIOGRAPHIC ASSESSMENT. Using commercially available ultrasound systems, 2-dimensional, color, pulsed, and continuous-wave Doppler images were obtained from the apical and parasternal views according to current recommendations with the patient at rest in the left lateral decubitus position.[9] From the parasternal long-axis view, left ventricular (LV) dimensions were assessed. LV end-diastolic and end-systolic volumes were evaluated from the apical 2- and 4-chamber views, and the LV ejection fraction was calculated according to the Simpson's biplane method. The severity of MR and tricuspid regurgitation was graded according to a multiparametric approach, as recommended.[10-14] The right ventricular pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation. The right atrial pressure was determined by the inspiratory collapse and diameter of the inferior vena cava. The systolic pulmonary arterial pressure was estimated by the sum of right ventricular pressure and right atrial pressure.[9,15] From the short-axis view, MV area was measured with planimetry in diastole at the time of the peak valve opening. Mean MVG was measured from continuous-wave Doppler of the mitral inflow in diastole by tracing the entire forward flow contour from the apical views, as recommended by the American Society of Echocardiography guidelines.[16]

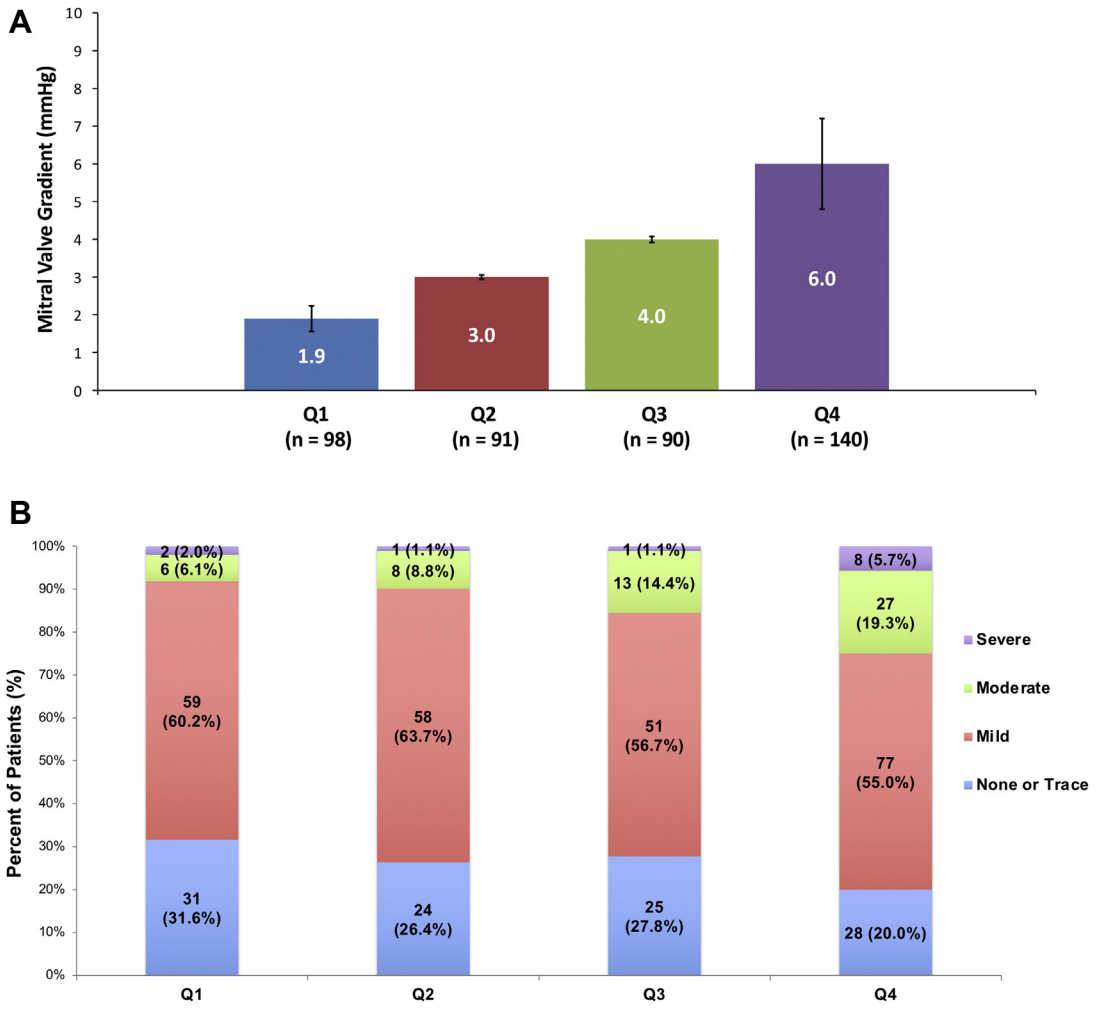
OUTCOMES AND DATA COLLECTION. The primary outcome of the present study was the composite endpoint of all-cause mortality and heart failure hospitalization. Secondary outcomes included all-cause mortality, and the composite of all-cause mortality, heart failure hospitalization, and surgical or transcatheter MV reintervention. Follow-up was obtained by clinical visits or through telephone contacts at prespecified time points (1, 6, and 12 months and yearly thereafter). Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (IQR) and compared with analysis of variance or Kruskal-Wallis test as appropriate. Categorical variables are provided with percentages and were compared with the chi-square or Fisher exact test. Cumulative event rates were calculated using the Kaplan-Meier survival analysis, and the log-rank test was used for comparison across the groups. The estimated HR with 95% CI was provided by the Cox proportional hazards regression. To assess the association between mean MVG at discharge and clinical outcomes, multivariate analyses were performed with adjustment for the following variables: age, sex, New York Heart Association (NYHA) functional class IV symptoms, estimated glomerular filtration rate, chronic lung disease, prior atrial fibrillation, LV ejection fraction, pulmonary artery pressure (≥50 mm Hg), tricuspid regurgitation (≥ moderate), and residual MR (≥ moderate). The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. All statistical analyses were performed using SPSS software version 24.0 (IBM Corp) and Stata version 14.2. A 2-sided P value <0.05 was selected as the threshold for statistical significance.

RESULTS

PATIENT CHARACTERISTICS. A total of 436 patients with primary MR who underwent TEER with the

FIGURE 1 Mean MVG and Residual Mitral Regurgitation



(A) Mean values and SD of mitral valve pressure gradient (MVG) according to the quartiles (Qs). **(B)** Residual mitral regurgitation in the 4 Qs.

MitraClip at Cedars-Sinai Medical Center between March 2007 and August 2019 were included. After excluding 17 patients (6 patients with aborted procedure; 4 lost to follow-up; 7 with postprocedural echocardiographic images not available or suboptimal quality), 419 patients were included in this analysis. Discharge echocardiography was performed on the next day of the procedure for 360 (94.7%) patients. The mean values of the mean MVG Qs were 1.9 ± 0.3 mm Hg, 3.0 ± 0.1 mm Hg, 4.0 ± 0.1 mm Hg, and 6.0 ± 1.2 mm Hg in Q1, Q2, Q3, and Q4, respectively (**Figure 1A**). One (0.2%) patient had mean MVG of 10 mm Hg, and no patients showed mean MVG higher than 10 mm Hg. There was a modest correlation between mean MVG on discharge transthoracic echocardiography and mean MVG on intraprocedural transesophageal echocardiography (Supplemental Figure 1). Of the study population, 170 (40.6%) patients were female with a mean age of 80.6 years and a Society of Thoracic Surgeons (STS) score of 7.7% (**Table 1**). Patients in Q4 were more likely to be female with NYHA functional class IV symptoms, whereas there were no significant differences in STS score and other baseline clinical characteristics across the 4 Qs. In terms of baseline echocardiographic data, LV systolic volume index was smaller and pulmonary artery pressure ≥50 mm Hg was more frequent in the Q4, while there were no significant differences in LV ejection fraction, and moderate or severe tricuspid regurgitation. Baseline mean MVG was higher and MV area was smaller in Q4. Procedural and

TABLE 1 Baseline Clinical and Echocardiographic Characteristics

	Overall (N = 419)	Quartile 1 (n = 98)	Quartile 2 (n = 91)	Quartile 3 (n = 90)	Quartile 4 (n = 140)	*P* Value
Baseline characteristics						
Age, y	80.6 ± 10.4	80.3 ± 11.1	81.3 ± 10.5	81.6 ± 9.3	79.7 ± 10.7	0.51
Female	170 (40.6)	27 (27.6)	34 (37.6)	34 (37.8)	75 (53.6)	<0.001
Body surface area, m^2	1.78 ± 0.28	1.78 ± 0.23	1.80 ± 0.28	1.79 ± 0.30	1.77 ± 0.29	0.85
NYHA functional class IV	179 (42.7)	64 (38.3)	47 (43.9)	26 (37.1)	42 (56.0)	0.05
STS score for mitral valve replacement, %	7.7 ± 6.8	7.1 ± 6.9	8.2 ± 6.3	8.3 ± 8.7	7.4 ± 5.4	0.56
Hypertension	333 (79.5)	73 (74.5)	71 (78.0)	72 (80.0)	117 (83.6)	0.38
Diabetes mellitus	66 (15.8)	14 (14.3)	13 (14.3)	16 (17.8)	23 (16.4)	0.90
Creatinine, μmol/L	1.5 ± 1.6	1.4 ± 1.3	1.5 ± 2.2	1.4 ± 1.3	1.5 ± 1.6	0.82
eGFR, mL/min/1.73 m^2	65.3 ± 25.8	65.3 ± 25.9	67.1 ± 26.8	65.9 ± 24.5	63.6 ± 26.1	0.78
Dialysis	11 (2.6)	2 (2.0)	2 (2.2)	2 (2.2)	5 (3.6)	0.87
Peripheral vascular disease	29 (6.9)	7 (7.1)	8 (8.8)	3 (3.3)	11 (7.9)	0.48
Chronic lung disease	31 (7.4)	5 (5.1)	10 (11.0)	9 (10.0)	7 (5.0)	0.21
Prior stroke	19 (4.5)	5 (5.1)	4 (4.4)	2 (2.2)	8 (5.7)	0.68
Prior myocardial infarction	27 (6.4)	6 (6.1)	7 (7.7)	5 (5.6)	9 (6.4)	0.96
Prior percutaneous coronary intervention	75 (17.9)	17 (17.3)	16 (17.6)	17 (18.9)	25 (17.9)	0.99
Prior coronary artery bypass surgery	63 (15.0)	13 (13.3)	14 (15.4)	13 (14.4)	23 (16.4)	0.92
Prior atrial fibrillation	218 (52.0)	49 (50.0)	50 (54.9)	50 (55.6)	69 (49.3)	0.72
Prior ICD	11 (2.6)	2 (2.0)	4 (4.4)	1 (1.1)	4 (2.9)	0.62
Prior aortic valve replacement	41 (9.8)	10 (10.2)	8 (8.8)	7 (7.8)	16 (11.4)	0.81
Baseline echocardiographic data						
LV end-diastolic diameter, mm	49.9 ± 7.9	51.6 ± 7.9	50.4 ± 7.3	49.9 ± 8.7	48.2 ± 7.5	0.01
LV end-systolic diameter, mm	32.5 ± 7.6	34.1 ± 8.2	33.0 ± 6.9	32.7 ± 7.8	30.9 ± 7.2	0.013
LV end-diastolic volume index, mL/m^2	53.7 ± 24.1	57.9 ± 31.4	51.2 ± 18.1	55.5 ± 22.7	51.3 ± 22.0	0.12
LV end-systolic volume index, mL/m^2	20.7 ± 12.1	22.7 ± 14.4	20.0 ± 9.9	22.2 ± 14.1	18.8 ± 9.7	0.046
LV ejection fraction, %	62.1 ± 11.0	61.7 ± 10.9	61.4 ± 12.1	60.5 ± 10.6	63.8 ± 10.4	0.11
Pulmonary artery pressure, mm Hg	46.4 ± 18.3	43.0 ± 17.7	45.4 ± 17.7	47.8 ± 17.7	48.6 ± 19.2	0.099
Pulmonary artery pressure ≥50 mm Hg	160 (38.2)	25 (25.5)	37 (40.7)	37 (41.1)	61 (43.6)	0.03
Tricuspid regurgitation ≥ moderate	169 (40.3)	32 (32.7)	37 (40.7)	38 (42.2)	62 (44.3)	0.33
Mean MVG, mm Hg	2.8 ± 1.6	2.1 ± 1.0	2.4 ± 1.3	3.1 ± 1.7	3.3 ± 1.8	<0.001
MV area, cm^2	5.3 ± 1.8	6.2 ± 2.0	5.5 ± 1.7	5.3 ± 1.7	4.7 ± 1.4	<0.001

Values are mean ± SD or n (%).

eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LV = left ventricular; MV = mitral valve; MVG = mitral valve pressure gradient; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

echocardiographic outcomes are summarized in Table 2. There were no patients who required conversion to open-heart MV surgery after TEER; however, 4 patients died during the index hospitalization. Three of them presented in cardiogenic shock requiring emergent TEER, and the remaining patient died caused by exacerbation of chronic obstructive pulmonary disease despite excellent results of TEER. The median number of MitraClips used was 2 per patient without significant difference between the groups. At discharge, reduction of MR ≤moderate was achieved in 407 (97.1%) patients. Moderate or greater residual MR was more prevalent in Q4 compared with Q3 to Q1 (25.0% vs 15.6% vs 9.9% vs 8.2%; $P = 0.001$) (Figure 1B).

OUTCOMES ACCORDING TO MVG AFTER MitraClip. Over a median follow-up duration of 550 (IQR: 355-1,091 days), 101 patients died, and 112 patients reached the primary composite endpoint (all-cause mortality and heart failure hospitalization), while 148 patients reached the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and surgical or transcatheter MV reintervention). The 2-year event rates of the primary outcome, all-cause mortality, the secondary composite endpoint, and each component are shown in Supplemental Table 1 and Figure 2. With a medial duration of 322 (IQR: 94-612) days from the index TEER, 38 patients had MV reintervention (10 patients for surgical MV replacement or repair; 28 patients for transcatheter MV reintervention). The indications for MV reintervention were recurrent MR (n = 34), detachment of the MitraClip (n = 3), and endocarditis (n = 1).

There was no significant difference in the primary outcome at 2 years (all-cause mortality or heart failure hospitalization) across the 4 Qs (15.4%, 19.6%, 22.0%, and 21.9% in Q1-Q4, respectively; $P = 0.63$)

TABLE 2 Procedural and Echocardiographic Outcomes

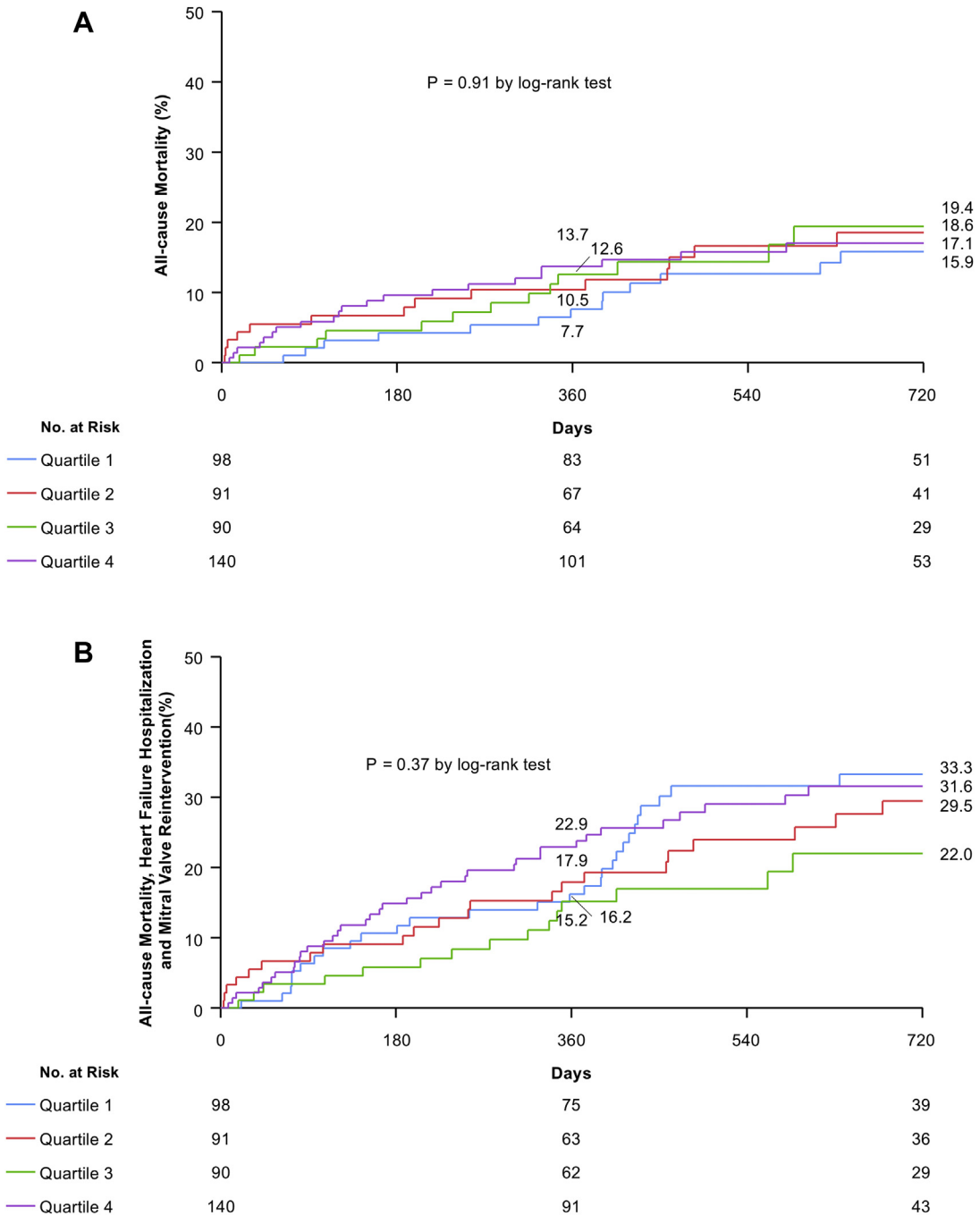
	Overall (N = 419)	Quartile 1 (n = 98)	Quartile 2 (n = 91)	Quartile 3 (n = 90)	Quartile 4 (n = 140)	*P* Value
Procedural data						
In-hospital mortality	4 (1.0)	0 (0)	3 (3.3)	0 (0)	1 (0.7)	0.12
Conversion to open mitral valve surgery	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Duration of hospitalization, d	1 (1-1)	1 (1-1)	1 (1-2)	1 (1-1.25)	1 (1-1)	0.087
Fluoroscopy time, min	19.6 (14.0-28.1)	19.0 (12.7-26.0)	19.5 (14.6-28.9)	20.0 (13.0-25.0)	20.0 (15.0-30.1)	0.36
Procedure time, min	110.0 (91.0-143.5)	104.0 (84.0-130.5)	118.0 (91.0-143.0)	117.5 (95.0-149.5)	128.9 (92.8-150.0)	0.098
Number of clips	2 (1, 2)	1 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)	0.12
2 or more	227 (54.2)	46 (46.9)	52 (57.1)	54 (60.0)	75 (53.6)	0.30
3 or more	41 (9.8)	4 (4.1)	6 (6.6)	14 (15.6)	17 (12.1)	0.028
Echocardiographic findings						
Heart rate, beats/min	72.1 ± 14.4	66.3 ± 11.9	72.6 ± 13.4	73.8 ± 16.4	75.1 ± 14.0	0.002
LV end-diastolic diameter, mm	47.1 ± 8.4	48.2 ± 8.4	47.6 ± 8.5	47.1 ± 8.2	45.9 ± 8.3	0.23
LV end-systolic diameter, mm	33.2 ± 8.1	34.4 ± 8.2	33.2 ± 7.9	33.7 ± 8.2	31.9 ± 8.0	0.14
LV ejection fraction, %	55.9 ± 12.3	53.5 ± 11.3	54.0 ± 12.9	55.3 ± 13.2	59.3 ± 11.3	0.001
Residual MR ≥ moderate	66 (15.8)	8 (8.2)	9 (9.9)	14 (15.6)	35 (25.0)	0.001
Mean MVG at 1 mo, mm Hg	4.0 ± 2.2	2.6 ± 1.3	3.1 ± 1.7	4.0 ± 1.6	5.3 ± 2.5	<0.001
Mean MVG at 6 mo, mm Hg	3.8 ± 2.2	2.2 ± 1.3	3.0 ± 1.7	4.0 ± 1.6	5.1 ± 2.5	<0.001

Values are n (%), median (IQR), or mean ± SD.
Abbreviations as in Table 1.

(Central Illustration). Similarly, there were no significant differences in all-cause mortality (15.9% vs 18.6% vs 19.4% vs 17.1% in Q1-Q4, respectively; $P = 0.91$) and the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and MV reintervention) across the 4 Qs (33.3% vs 29.5% vs 22.0% vs 31.6% in Q1-Q4, respectively; $P = 0.37$) (Figures 2A and 2B). After multivariate adjustment with baseline clinical and procedural variables, the mean MVG in Q4 compared with Q1 to Q3 was not independently associated with the primary outcome (HR: 1.22; 95% CI: 0.82-1.83; $P = 0.33$), all-cause mortality (HR: 1.14; 95% CI: 0.74-1.75; $P = 0.56$), and the secondary composite endpoint (HR: 1.16; 95% CI: 0.81-1.66; $P = 0.42$) (Table 3). However, the residual MR ≥ moderate was independently associated with adverse events (Supplemental Tables 2 to 4). When mean MVG was evaluated as a continuous variable, multivariate analysis showed that the mean MVG was not independently associated with the primary outcome (HR per increase of mm Hg: 1.07; 95% CI: 0.95-1.19; $P = 0.27$), all-cause mortality (HR per increase of mm Hg: 1.03; 95% CI: 0.91-1.16; $P = 0.63$), and the secondary composite outcome (HR per increase of mm Hg: 1.01; 95% CI: 0.92-1.12; $P = 0.78$). Further analyses were performed using a mean MVG cutoff value of 5 mm Hg. There were no significant differences between patients with MVG <5 mm Hg and 5 mm Hg or more in 2-year events rates of the primary outcome (18.8% vs 21.9%; $P = 0.39$), all-cause mortality (17.9% vs 17.1%; $P = 0.80$), and the secondary composite endpoint (28.9% vs 31.6%; $P = 0.32$) (Supplemental Figures 2 and 3). On multivariate analysis, mean MVG ≥5 mm Hg was not independently associated with an increased risk of the primary outcome (HR: 1.22; 95% CI: 0.82-1.83; $P = 0.33$), all-cause mortality (HR: 1.14; 95% CI: 0.74-1.75; $P = 0.56$), and the secondary composite endpoint (HR: 1.16; 95% CI: 0.81-1.66; $P = 0.42$).

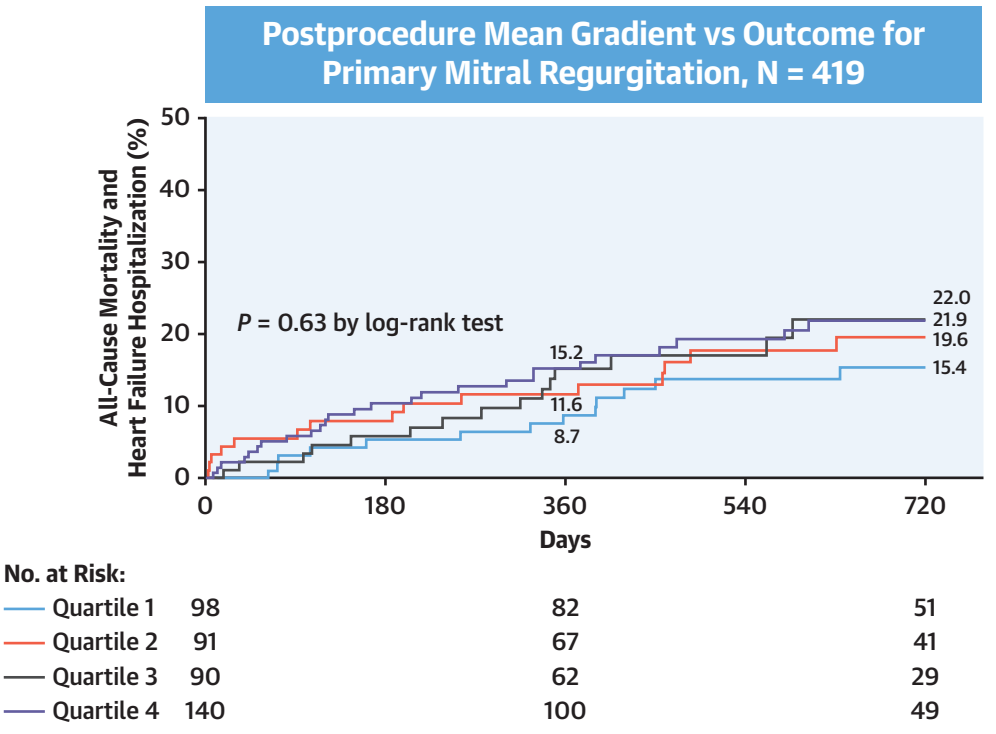
OUTCOMES ACCORDING TO MEAN MVG AND RESIDUAL MR. Patients were classified into 4 groups according to discharge mean MVG Qs and residual MR (group 1: mean MVG Q1-Q3 and residual MR <moderate [n = 248]; group 2: mean MVG Q4 and residual MR <moderate [n = 105]; group 3: mean MVG Q1-Q3 and residual MR ≥ moderate [n = 31]; group 4: mean MVG Q4 and residual MR ≥ moderate [n = 35]). There were no significant differences in the primary outcome (all-cause mortality or heart failure hospitalization) between groups 1 and 2 (HR: 1.38; 95% CI: 0.89-2.16; $P = 0.15$), whereas groups 3 and 4 had higher risk compared with group 1 (group 3, HR: 2.39; 95% CI: 1.33-4.31; $P = 0.004$; group 4, HR: 2.07; 95% CI: 1.13-3.80; $P = 0.019$) (Figure 3A). These findings were consistent for all-cause mortality and the secondary composite endpoint (Figures 3B and 3C). However, group 3 tended to have higher risk of the primary outcome (HR: 1.72; 95% CI: 0.91-3.27; $P = 0.096$), all-cause mortality (HR: 1.98; 95% CI: 1.00-3.91; $P = 0.050$), and the secondary composite endpoint (HR: 2.03; 95% CI: 1.16-3.53; $P = 0.013$) compared with group 2.

FIGURE 2 **Time-to-Event Curves According to Mean Mitral Valve Pressure Gradient**



Time-to-event curves for **(A)** all-cause mortality and **(B)** the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and mitral valve reintervention) according to the mean mitral valve pressure gradient by quartiles. Event rates were calculated with Kaplan-Meier analysis and were compared using the log-rank test.

CENTRAL ILLUSTRATION **All-Cause Mortality and Heart Failure Hospitalization According to Mean Mitral Valve Pressure Gradient**



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Time-to-event curves for the primary outcome (all-cause mortality and heart failure hospitalization) according to the mean mitral valve pressure gradient by quartiles. Event rates were calculated with Kaplan-Meier analysis and were compared using the log-rank test.

DISCUSSION

This is the first large-scale study that evaluated the prognostic value of increased mean MVG in patients with primary MR who underwent TEER. The major findings of the present study are as follows: 1) among 419 patients at prohibitive or high surgical risk who underwent TEER for primary MR, reduction of MR ≤moderate was achieved in 97.1% of patients; 2) patients with the highest Q of mean MVG at discharge (Q4) were more likely to be female with NYHA functional class IV symptoms and showed higher baseline mean MVG and smaller MV area, and importantly, moderate or greater residual MR after TEER was more frequent in Q4; and 3) mean MVG at discharge was not independently associated with the primary outcome (all-cause mortality and heart failure hospitalization), all-cause mortality, and the secondary

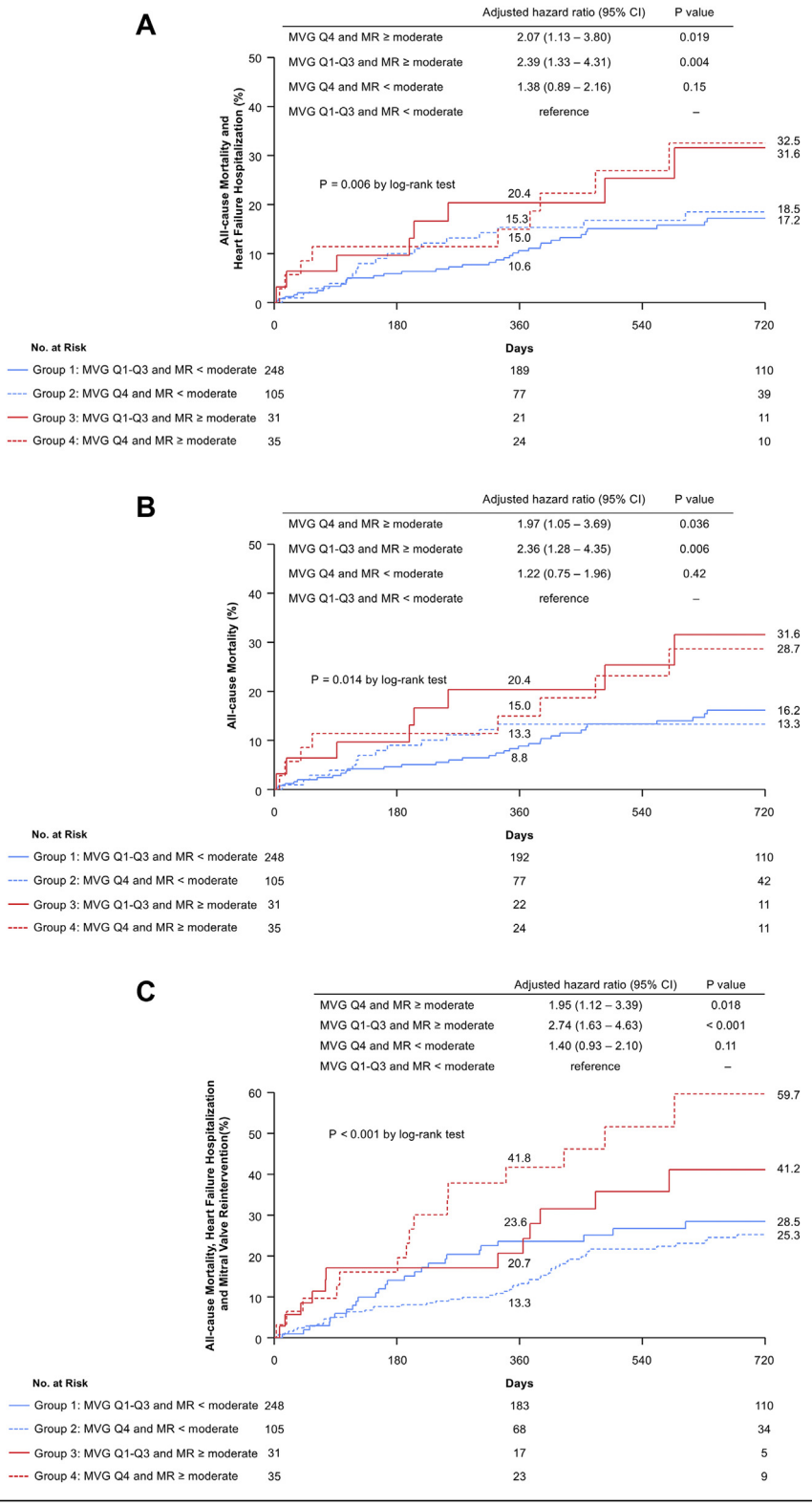
TABLE 3 **Cox Regression Analysis of Primary Outcomes (All-Cause Mortality and Heart Failure Hospitalization)**

	Univariable Model		Multivariable Model	
Clinical Outcome Measure	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause mortality or heart failure hospitalization	1.36 (0.93-1.99)	0.12	1.22 (0.82-1.83)	0.33
All-cause mortality	1.23 (0.82-1.84)	0.33	1.14 (0.74-1.75)	0.56
All-cause mortality, heart failure hospitalization, or mitral valve reintervention	1.37 (0.98-1.92)	0.064	1.16 (0.81-1.66)	0.42

To assess the association between MVG (quartile 4 vs quartiles 1-3) and clinical outcomes, multivariable analyses were performed adjustment for the following variables: age, sex, NYHA functional class IV symptoms, eGFR lung disease, prior atrial fibrillation, LV ejection fraction, pulmonary artery pressure ≥50 mm Hg, tricuspid regurgitation ≥ moderate, and residual MR ≥ moderate. Age, eGFR, and LV ejection fraction were used as continuous variables.

Abbreviations are as in Table 1.

FIGURE 3 Time-to-Event Curves According to Mean MVG and Residual Mitral Regurgitation



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composite endpoint (all-cause mortality, heart failure hospitalization, and MV reintervention).

TEER using the MitraClip mimics the Alfieri stitch, a technique of edge-to-edge surgical repair.[17] The MitraClip pulls the anterior and posterior leaflets together and creates a double orifice MV, which improves the coaptation and reduces MR but also potentially limits the flow, leading to increased mean MVG. The MR reduction ≤moderate was achieved in 93% from the STS/American College of Cardiology Transcatheter Valve Therapy Registry and 97.8% from the German transcatheter mitral valve interventions registry.[18,19] In the present study, 407 (97.1%) patients had residual MR ≤moderate, while the mean MVG discharge ranged from 3 mm Hg to 5 mm Hg, consistent with previous studies.[2,4,5,18] The impact of increased mean MVG on clinical outcomes after the MitraClip procedure has been debated. Neuss et al[4] reported that increased mean MVG (>4.4 mm Hg) was associated with adverse events in a cohort of 215 patients with mixed MR etiology (primary MR 35%; secondary MR 65%). Patzelt et al[6] confirmed these findings only in patients with primary MR but not with secondary MR. From the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, Halaby et al[7] reported that discharge mean MVG was not associated with the composite of all-cause mortality and heart failure hospitalization in patients with secondary MR. The present study, including 419 patients with primary MR, confirmed that an increased mean MVG at discharge transthoracic echocardiography was not independently associated with primary outcomes (all-cause mortality and heart failure hospitalization), all-cause mortality, and the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and MV reintervention). These results were consistent when the mean MVG was evaluated as a continuous variable or by using a cutoff value for mean MVG of 5 mm Hg. The reasons for the conflicting results among different studies regarding the impact of mean MVG on outcomes are unclear. The mean MVG is influenced by the MV area as well as other factors that influence transmitral flow, such as heart rate, cardiac output, and associated MR.[20] Smaller baseline MV area and more clips used in Q3 and Q4 might suggest a reduced MV area after TEER with limited the transmitral flow, causing an increased mean MVG. Nonetheless, the higher rate of moderate or greater residual MR after TEER in Q4 versus Q1 to Q3 in the present cohort suggests that an increased mean MVG after TEER does not necessarily indicate a limited transmitral flow. It is possible that increased blood flow over the MV caused by residual MR causes an increased mean MVG in patients with primary MR.

The data from a pivotal randomized clinical trial (EVEREST [Endovascular Valve Edge-to-Edge Repair Study] II trial) and prospective registries showed the safety of TEER but limited its efficacy, particularly in terms of residual MR.[1,21] Nonetheless, with technical advances of the device and increased operator experiences, TEER has been increasingly utilized for patients with primary MR at prohibitive or high surgical risk.[22-24] Given the improved outcomes of the contemporary TEER studies, the prospective, randomized REPAIR MR (Percutaneous MitraClip Device or Surgical Mitral Valve REpair in PAtients With PrImaRy MItral Regurgitation Who Are Candidates for Surgery) clinical trial (NCT04198870) will enroll 500 patients with primary MR who are deemed at intermediate risk for surgery and compare the effectiveness of TEER with surgical MV repair. For further expansion of the application of this minimally invasive technology toward younger and lower-risk patients, the outcomes of TEER should be optimal. Multivariable analyses showed that there was no association between increased mean MVG and clinical outcomes, whereas residual MR (≥moderate) was independently associated with increased risk of adverse events. The present study also showed the higher adverse event rates in patients with significant residual MR (≥moderate) without increased mean MVG (Q1-Q3) compared with those patients with increased mean MVG (Q4) without residual MR. Therefore, elimination of MR may be prioritized despite a mild to moderately increased mean MVG during TEER. The present study, along with the findings of the COAPT trial, demonstrated that the benefits of MR reduction might outweigh the adverse effects of mild-to-moderate increased mean MVG in patients with moderate-severe and severe MR, regardless of its etiology. Nonetheless, further

FIGURE 3 Continued

Patients were divided in 4 groups according to the mean mitral valve pressure gradient (MVG) (the highest quartile [quartile 4 (Q4)] and the remaining 3 Qs [Q1-Q3]) and residual mitral regurgitation (MR) (≥ moderate or ≤ mild). Time-to-event curves for **(A)** the primary outcome (composite endpoint of all-cause mortality and heart failure hospitalization), **(B)** all-cause mortality, and **(C)** the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and mitral valve reintervention) are shown. Event rates were calculated with Kaplan-Meier analysis and were compared by the log-rank test.

studies are needed to evaluate the long-term outcomes of patients with mild-to-moderate increased mean MVG after TEER.

STUDY LIMITATIONS. First, this is a single-center study, and therefore, the current findings need to be validated in future studies. Second, increased mean MVG was mostly modest in the current study, and thus the clinical impact of severely increased mean MVG (≥10 mm Hg) is unclear. Third, mean MVG was highly dependent on heart rate, which should be considered for interpretation of this study. Fourth, this study evaluated the impact of increased mean MVG on clinical outcomes in patients with primary MR who underwent TEER with the MitraClip. Accordingly, the current findings should not be extrapolated to patients with secondary MR or the use of other MV devices.

CONCLUSIONS

Increased mean MVG on discharge echocardiography was not independently associated with adverse events in patients with primary MR who underwent TEER.

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PERSPECTIVES

WHAT IS KNOWN? There is conflicting evidence regarding the impact of increased mean MVG after TEER on clinical outcomes in patients with primary MR.

WHAT IS NEW? In patients with primary MR who underwent TEER, an increased mean MVG was not independently associated with the primary outcomes (all-cause mortality and heart failure hospitalization) as well as with all-cause mortality and the secondary composite endpoint (all-cause mortality, heart failure hospitalization, and MV reintervention).

WHAT IS NEXT? Future studies are needed to evaluate the long-term prognosis in patients with increased mean MVG after TEER for primary MR.

REFERENCES

1. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395-1406.

2. Herrmann HC, Rohatgi S, Wasserman HS, et al. Mitral valve hemodynamic effects of percutaneous edge-to-edge repair with the MitraClip™ device for mitral regurgitation. *Catheter Cardio Interv*. 2006;68:821-828.

3. Howard CH, Subrata K, Robert JS, et al. Effect of percutaneous mitral repair with the MitraClip® device on mitral valve area and gradient. *EuroIntervention*. 2009;4:437-442.

4. Neuss M, Schau T, Isotani A, Pilz M, Schopp M, Butter C. Elevated mitral valve pressure gradient after MitraClip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. *J Am Coll Cardiol Intv*. 2017;10:931-939.

5. Utsunomiya H, Itabashi Y, Kobayashi S, et al. Effect of percutaneous edge-to-edge repair on mitral valve area and its association with pulmonary hypertension and outcomes. *Am J Cardiol*. 2017;120:662-669.

6. Patzelt J, Zhang W, Sauter R, et al. Elevated mitral valve pressure gradient is predictive of long-term outcome after percutaneous edge-to-edge mitral valve repair in patients with degenerative mitral regurgitation (MR), but not in functional MR. *J Am Heart Assoc*. 2019;8:e011366.

7. Halaby R, Herrmann HC, Gertz ZM, et al. Effect of mitral valve gradient after MitraClip on outcomes in secondary mitral regurgitation: results from the COAPT trial. *J Am Coll Cardiol Intv*. 2021;14:879-889.

8. Writing Committee M, Otto CM, Nishimura RA, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25-e197.

9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39.e14.

10. Zoghbi WA, Adams D, Bonow RO, 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;30:303-371.

11. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2019;32:431-475.

12. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64:2792-2801.

13. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association

of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611–644.

14. Cavalcante JL, Rodriguez LL, Kapadia S, Tuzcu EM, Stewart WJ. Role of echocardiography in percutaneous mitral valve interventions. *J Am Coll Cardiol Img*. 2012;5:733–746.

15. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713. quiz 786–788.

16. Biaggi P, Felix C, Gruner C, et al. Assessment of mitral valve area during percutaneous mitral valve repair using the MitraClip system: comparison of different echocardiographic methods. *Circ Cardiovasc Imaging*. 2013;6:1032–1040.

17. Fucci C, Sandrelli L, Pardini A, Torracca L, Ferrari M, Alfieri O. Improved results with mitral valve repair using new surgical techniques. *Eur J Cardiothorac Surg*. 1995;9:621–627.

18. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry report. *J Am Coll Cardiol*. 2017;70:2315–2327.

19. Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J*. 2016;37:703–712.

20. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE Recommendations for Clinical Practice. *J Am Soc Echocardiogr*. 2009;22:1–23. quiz 101–102.

21. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol*. 2014;64:172–181.

22. Chhatriwalla AK, Vemulapalli S, Holmes DR, et al. Institutional experience with transcatheter mitral valve repair and clinical outcomes: insights from the TVT Registry. *J Am Coll Cardiol Intv*. 2019;12:1342–1352.

23. Praz F, Braun D, Unterhuber M, et al. Edge-to-edge mitral valve repair with extended clip arms: early experience from a multicenter observational study. *J Am Coll Cardiol Intv*. 2019;12:1356–1365.

24. Raschpichler M, Woitek FJ, Chakravarty T, et al. Valve-in-valve for degenerated transcatheter aortic valve replacement versus valve-in-valve for degenerated surgical aortic bioprostheses: a 3-center comparison of hemodynamic and 1-year outcome. *J Am Heart Assoc*. 2020;9:e013973.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.