



Effect of Mitral Valve Gradient After MitraClip on Outcomes in Secondary Mitral Regurgitation

Results From the COAPT Trial

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ABSTRACT

OBJECTIVES The authors sought to evaluate the association between mean mitral valve gradient (MVG) and clinical outcomes among patients who underwent MitraClip treatment for secondary mitral regurgitation (SMR) in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial.

BACKGROUND In the COAPT trial, patients with heart failure (HF) and severe SMR who remained symptomatic despite guideline-directed medical therapy had marked 2-year reductions in mortality and HF hospitalizations after treatment with MitraClip.

METHODS MitraClip-treated patients were divided into quartiles (Q) based on discharge echocardiographic MVG (n = 250). Endpoints including all-cause mortality, HF hospitalization, and health status measures at 2 years were compared between quartiles.

RESULTS Mean MVG after MitraClip was 2.1 ± 0.4 mm Hg, 3.0 ± 0.2 mm Hg, 4.2 ± 0.5 mm Hg, and 7.2 ± 2.0 mm Hg in Q1 (n = 63), Q2 (n = 61), Q3 (n = 62), and Q4 (n = 64), respectively. There was no difference across quartiles in the 2-year composite endpoint of all-cause mortality or HF hospitalization (43.2%, 49.2%, 40.6%, and 40.9%, respectively; p = 0.80), nor in improvements in New York Heart Association functional class, Kansas City Cardiomyopathy Questionnaire score, or 6-min walk time. Results were similar after adjustment for baseline clinical and echocardiographic characteristics, post-procedure MR grade, and number of clips (all-cause mortality or HF hospitalization Q4 [44.6%] vs. Q1 to Q3 [40.3%]; adjusted hazard ratio: 1.23, 95% confidence interval: 0.60 to 2.51; p = 0.57).

CONCLUSIONS Among HF patients with severe SMR, higher MVGs on discharge did not adversely affect clinical outcomes following MitraClip. These findings suggest that in select patients with HF and SMR otherwise meeting the COAPT inclusion criteria, the benefits of MR reduction may outweigh the effects of mild-to-moderate mitral stenosis after MitraClip. (J Am Coll Cardiol Interv 2021;14:879–89) © 2021 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

GDMT = guideline-directed medical therapy

HF = heart failure

HR = hazard ratio

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MVG = mitral valve gradient

MVOA = mitral valve orifice area

NYHA = New York Heart Association

ROC = receiver-operating characteristic

SMR = secondary mitral regurgitation

Secondary (also known as functional) mitral regurgitation (SMR) may develop in patients with heart failure (HF) due to malcoaptation of the mitral valve leaflets in the setting of geometric changes of the left ventricle (LV). SMR is associated with increased morbidity and mortality (1). In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, among HF patients with moderate-to-severe or severe SMR who remained symptomatic despite maximally tolerated guideline-directed medical therapy (GDMT), transcatheter mitral valve repair with the MitraClip (Abbott Vascular, Santa Clara, California) reduced the rate of HF hospitalization and improved survival compared with GDMT alone (2). In light of the COAPT trial results, the Food and Drug Administration expanded the labeled indications of the MitraClip for treatment of selected HF patients with moderate-to-severe and severe SMR (3).

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Implantation of the MitraClip in the EVEREST I pilot study (Endovascular Valve Edge-to-Edge Repair Study) and in the roll-in cohort of the randomized EVEREST II study (Pivotal Study of a Percutaneous Mitral Valve Repair System) demonstrated a reduction in the mitral valve orifice area (MVOA) by as much as 50% and an increase in the mitral valve gradient (MVG) that was not associated with clinically significant mitral stenosis (4,5). Conversely, after surgical repair for mitral regurgitation (MR), some studies have demonstrated an association of an increased MVG with reduced functional capacity (6). In the current era of transcatheter treatment of MR with multiple clips and in patients with SMR and reduced LV ejection fraction (LVEF), the effects of an elevated MVG on long-term outcomes have been conflicting (7,8). We therefore sought to evaluate the association between MVG and clinical outcomes in patients who underwent MitraClip treatment for SMR in the COAPT trial.

METHODS

STUDY POPULATION. The COAPT trial was a multicenter, randomized, open-label clinical trial of transcatheter mitral valve repair with MitraClip in HF patients with moderate-to-severe or severe SMR. Details of the study protocol and design were

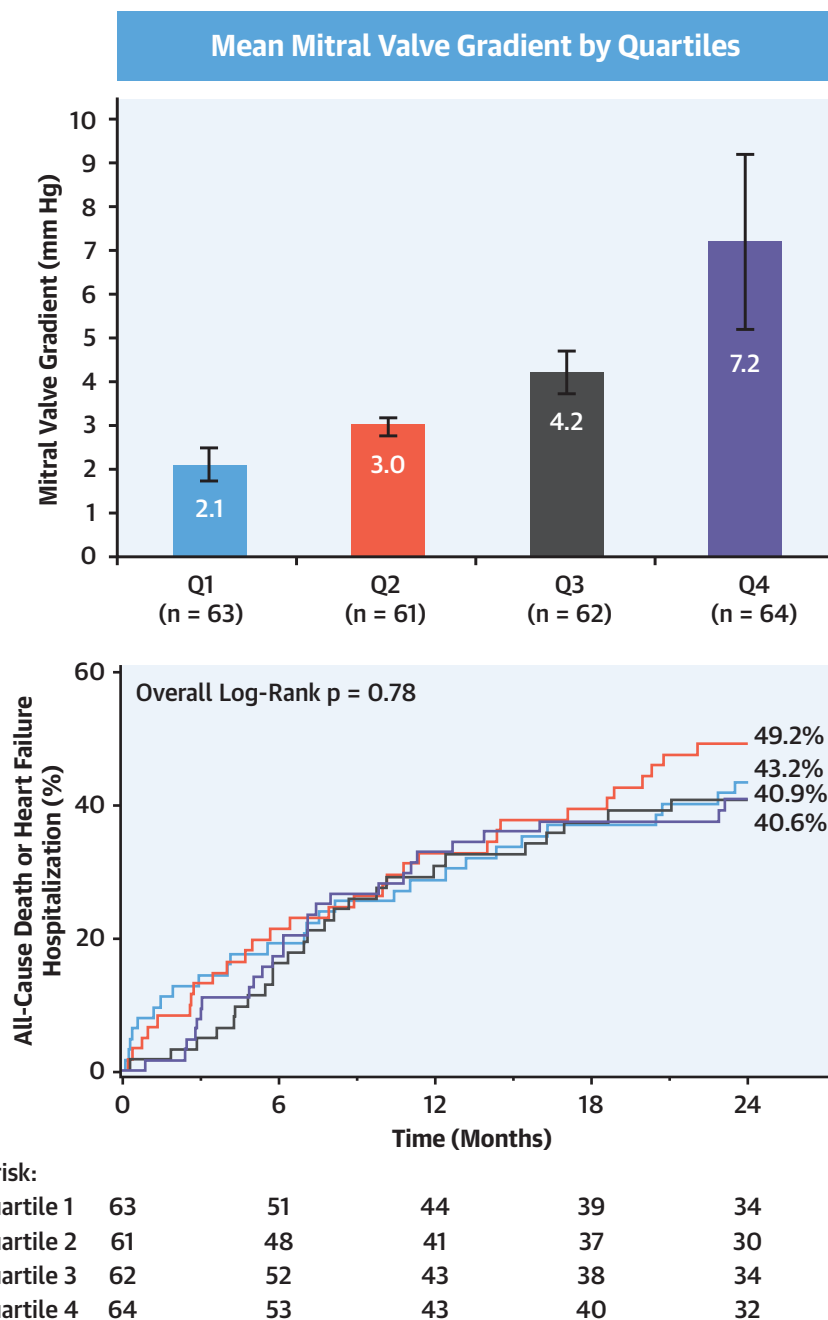
previously published (2). In brief, The COAPT trial enrolled patients with HF and moderate-to-severe or severe (3+ or 4+) SMR who remained symptomatic despite maximally tolerated GDMT and cardiac resynchronization therapy when applicable. The severity of MR was graded according to American guidelines (9). Eligible patients had either ischemic or nonischemic cardiomyopathy. Heart teams at the participating centers identified patients for whom surgery was not the standard of care and with mitral valve anatomy suitable for MitraClip intervention. Inclusion criteria included LVEF between 20% and 50% and LV end-systolic dimension ≤ 70 mm. Exclusion criteria included a primary (degenerative) etiology of MR and MVOA < 4 cm², among others (2). Eligible patients were randomized in a 1:1 ratio to either MitraClip in addition to GDMT or GDMT alone. Institutional review board/ethics committee approval was obtained from all sites that participated in the COAPT trial, and all patients signed informed consent.

For the present study, patients randomized to the MitraClip arm in whom the device was implanted were divided into quartiles (Q1, Q2, Q3, and Q4) based on their MVG on discharge echocardiography. Follow-up duration was 24 months. Adverse events in COAPT were adjudicated by an independent clinical events committee. Echocardiographic findings were assessed by an independent echocardiographic core laboratory. 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, on 3 consecutive beats whenever available (5 consecutive beats if the patient was in atrial fibrillation), and the average was reported.

ENDPOINTS. For the present report, the principal endpoint of interest was the time to the first occurrence of all-cause mortality or HF hospitalization within 2 years. Additional analyses were performed for quality of life and functional status measures, including 6-min walk distance (6MWD), New York Heart Association (NYHA) functional class, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score. Missing values for the 6MWD were imputed according to the protocol (2). Subjects who expired due to an adjudicated HF death before the 2 years' follow-up time or were unable to walk due to cardiac reasons were included in the analysis and assigned a distance of 0.

STATISTICAL PLAN. Continuous data are expressed as mean $\pm$ SD and were compared with Student's *t*-tests or the Wilcoxon rank sum test for non-

CENTRAL ILLUSTRATION Post MitraClip-Treatment Mitral Valve Gradients and Clinical Outcomes



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Upper: Mean (and SD) of mitral valve gradient by quartile in patients assigned to and treated with the MitraClip as assessed by pre-discharge echocardiography. **Lower:** Two-year rates of all-cause mortality or hospitalization for heart failure in the 4 quartiles of MitraClip-treated patients. There was no difference across quartiles in the 2-year composite endpoint of all-cause mortality or heart failure hospitalization.

TABLE 1 Baseline Clinical and Core Laboratory Echocardiographic Characteristics by MVG Quartile

	Quartile 1 (n = 63)	Quartile 2 (n = 61)	Quartile 3 (n = 62)	Quartile 4 (n = 64)	Overall p Value
Baseline characteristics					
Age, yrs	73.1 ± 11.8	73.3 ± 10.3	71.3 ± 10.6	68.6 ± 13.6	0.09
Female	17.5 (11/63)	24.6 (15/61)	29.0 (18/62)	57.8 (37/63)	<0.001
Race					
White or Caucasians	76.2 (48/63)	80.3 (49/61)	80.6 (50/62)	68.8 (44/64)	0.36
African-American	11.1 (7/63)	6.6 (4/61)	14.5 (9/62)	25.0 (16/64)	0.02
Hispanic or Latino	9.5 (6/63)	6.6 (4/61)	1.6 (1/62)	3.1 (2/64)	0.19
Asian	1.6 (1/63)	1.6 (1/61)	3.2 (2/62)	1.6 (1/64)	0.89
Native Hawaiian or other Pacific Islander	0.0 (0/63)	0.0 (0/61)	0.0 (0/62)	0.0 (0/64)	-
American Indian or Alaska Native	0.0 (0/63)	0.0 (0/61)	0.0 (0/62)	0.0 (0/64)	-
Other	1.6 (1/63)	4.9 (3/61)	0.0 (0/62)	1.6 (1/64)	0.26
Body mass index, kg/m ²	26.1 ± 5.2	26.4 ± 4.3	27.1 ± 5.3	29.4 ± 8.2	0.008
Heart rate, beats per min	72.2 ± 12.3	73.4 ± 13.6	76.3 ± 13.4	78.4 ± 10.7	0.02
Systolic blood pressure, mm Hg	111.1 ± 19.2	113.5 ± 17.6	110.0 ± 15.6	110.9 ± 16.5	0.72
Diastolic blood pressure, mm Hg	66.7 ± 10.3	65.5 ± 9.1	64.8 ± 9.9	64.7 ± 9.7	0.65
Hemoglobin, g/dl	12.3 ± 1.8	12.1 ± 1.8	12.1 ± 1.5	12.3 ± 1.7	0.86
Creatinine clearance, ml/min	49.0 ± 25.5	50.5 ± 23.7	50.9 ± 25.1	55.9 ± 34.4	0.53
Chronic kidney disease, CrCl ≤60 ml/min	77.8 (49/63)	68.3 (41/60)	71.0 (44/62)	69.4 (43/62)	0.64
NT-proBNP, pg/ml	4,067 ± 2,801	6,090 ± 8,253	3,914 ± 3,118	4,131 ± 3,501	0.60
Etiology of cardiomyopathy					
Ischemic	54.0 (34/63)	67.2 (41/61)	66.1 (41/62)	51.6 (33/64)	0.16
Nonischemic	46.0 (29/63)	32.8 (20/61)	33.9 (21/62)	48.4 (31/64)	0.16
Coronary artery disease	65.1 (41/63)	80.3 (49/61)	75.8 (47/62)	67.2 (43/64)	0.19
Chronic obstructive pulmonary disease	25.4 (16/63)	24.6 (15/61)	17.7 (11/62)	29.7 (19/64)	0.48
History of atrial fibrillation or flutter	60.3 (38/63)	59.0 (36/61)	54.8 (34/62)	48.4 (31/64)	0.53
Diabetes	28.6 (18/63)	32.8 (20/61)	29.0 (18/62)	43.8 (28/64)	0.23
Baseline echocardiographic measures					
Mitral regurgitation					
Moderate to severe, 3+	47.6 (30/63)	44.3 (27/61)	45.2 (28/62)	54.7 (35/64)	0.64
Severe, 4+	52.4 (33/63)	55.7 (34/61)	54.8 (34/62)	45.3 (29/64)	0.64
Mitral regurgitation EROA by PISA, cm ²	0.40 ± 0.16	0.42 ± 0.13	0.44 ± 0.18	0.42 ± 0.16	0.57
Mitral regurgitation regurgitant volume, ml	55.9 ± 19.9	60.6 ± 20.8	60.9 ± 26.6	62.9 ± 20.5	0.35
LV ejection fraction, %	30.9 ± 9.2	31.7 ± 10.4	30.0 ± 8.7	33.6 ± 8.9	0.18
LV end-diastolic dimension, cm	6.4 ± 0.7	6.0 ± 0.7	6.3 ± 0.8	6.0 ± 0.8	0.01
LV end-diastolic volume index, ml/m ²	205.0 ± 76.5	185.7 ± 52.1	207.6 ± 73.8	183.5 ± 75.2	0.13
Mitral valve orifice area, cm ²	5.4 ± 1.5	5.0 ± 0.9	5.3 ± 1.3	4.9 ± 1.4	0.08
Mitral valve area indexed to BSA, cm ² /m ²	2.9 ± 0.8	2.7 ± 0.6	2.8 ± 0.6	2.6 ± 0.7	0.09
Mitral valve mean gradient, mm Hg	1.9 ± 0.8	2.3 ± 0.7	2.2 ± 0.8	3.2 ± 1.2	<0.001
Right ventricular systolic pressure, mm Hg	47.2 ± 14.0	45.4 ± 14.0	44.5 ± 13.5	40.8 ± 14.1	0.13
Tricuspid regurgitation					
Moderate, 2+	16.1 (10/62)	20.0 (12/60)	11.3 (7/62)	9.5 (6/63)	0.33
Moderate-to-severe, 3+	0.0 (0/62)	0.0 (0/60)	1.6 (1/62)	0.0 (0/63)	0.39
Severe, 4+	0.0 (0/62)	0.0 (0/60)	0.0 (0/62)	0.0 (0/63)	N/A

Values are mean ± SD or % (n/N).

BSA = body surface area; CrCl = creatinine clearance; EROA = effective regurgitant orifice area; LV = left ventricular; MVG = mitral valve gradient; NT-proBNP = N-terminal Pro-B-type natriuretic peptide; PISA = proximal isovelocity surface area.

normally distributed data. Categorical variables are summarized as percentages and were compared using the chi-square or Fisher exact test as appropriate. The primary endpoint, composite of all-cause death and HF hospitalization, is analyzed as time-to-first event. Time-to-event variables are summarized as Kaplan-Meier event rates and were compared by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using Cox proportional hazards regression. Multivariable analyses were performed with adjustment for the following

variables: age, sex, body mass index, chronic obstructive pulmonary disease, history of atrial fibrillation or flutter, diabetes, chronic kidney disease, baseline LV end-diastolic volume index, baseline effective regurgitant orifice area, ischemic versus nonischemic etiology of MR, baseline LVEF, baseline MVG, number of MitraClips, post-procedural MR grade, and final MVG. The relationship between discharge MVG and risk of interested outcomes was further explored by entering the logarithmic MVG measurement as a nonlinear term (penalized spline

TABLE 2 Procedural Characteristics and Discharge Core Laboratory Echocardiographic Measures by MVG Quartile

	Quartile 1 (n = 63)	Quartile 2 (n = 61)	Quartile 3 (n = 62)	Quartile 4 (n = 64)	Overall p Value
Procedural characteristics					
Average number of MitraClips implanted	1.7 ± 0.6	1.5 ± 0.6	1.8 ± 0.7	1.8 ± 0.7	0.04
None	1.6 (1/63)	0.0 (0/61)	0.0 (0/62)	1.6 (1/64)	0.58
1 clip	34.9 (22/63)	52.5 (32/61)	33.9 (21/62)	29.7 (19/64)	0.05
2 clips	57.1 (36/63)	44.3 (27/61)	51.6 (32/62)	57.8 (37/64)	0.40
3 clips	6.3 (4/63)	3.3 (2/61)	14.5 (9/62)	10.9 (7/64)	0.13
Echocardiographic measures on discharge					
Mitral regurgitation					
None, 0	3.4 (2/59)	0.0 (0/61)	1.6 (1/62)	0.0 (0/62)	0.28
Mild, 1+	83.1 (49/59)	83.6 (51/61)	79.0 (49/62)	83.9 (52/62)	0.88
Moderate, 2+	10.2 (6/59)	13.1 (8/61)	14.5 (9/62)	12.9 (8/62)	0.91
Moderate to severe, 3+	1.7 (1/59)	1.6 (1/61)	4.8 (3/62)	1.6 (1/62)	0.58
Severe, 4+	1.7 (1/59)	1.6 (1/61)	0.0 (0/62)	1.6 (1/62)	0.79
Moderate or less, ≤2+	96.6 (57/59)	96.7 (59/61)	95.2 (59/62)	96.8 (60/62)	0.96
Left ventricular ejection fraction	25.9 ± 9.4	27.6 ± 9.6	26.2 ± 7.8	30.0 ± 7.8	0.08
Values are mean ± SD or % (n/N). MVG = mitral valve gradient.					

with 2 degrees of freedom) in Cox proportional hazards regression models. A 2-sided p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

DATA AVAILABILITY. At the present time, there are no plans to make the individual patient data or aggregate data from the COAPT trial publicly available, although the sponsor and principal investigators welcome outside interest for academic collaboration. The publications committee will consider requests from non-study-related investigators for secondary analyses. Such analyses, if approved, will be run by the Cardiovascular Research Foundation.

RESULTS

COMPARISON OF MVG QUARTILES. One or more MitraClips were implanted in 287 of 302 randomized patients, 260 of whom underwent pre-discharge transthoracic echocardiography. Among these patients, the MVG measured at discharge was evaluable in the echocardiographic core laboratory in 250 patients, comprising the current study population. The mean (range) of the MVG quartiles were 2.1 ± 0.4 (1.0 to 2.6) mm Hg, 3.0 ± 0.2 (2.7 to 3.4) mm Hg, 4.2 ± 0.5 (3.5 to 5.0) mm Hg, and 7.2 ± 2.0 (5.1 to 13.2) mm Hg in Q1, Q2, Q3, and Q4, respectively (**Central Illustration**). Baseline characteristics in the different quartiles are shown in **Table 1**. Female sex was more prevalent in Q4, whereas the proportion of patients of African-American race was higher in Q4. Patients in Q4 had a higher body mass index as compared with other

quartiles. There was no difference in baseline hemoglobin across quartiles (p = 0.86); the mean ± SD for baseline hemoglobin was 12.3 ± 1.8 g/dl in Q1, 12.1 ± 1.8 g/dl in Q2, 12.1 ± 1.5 g/dl in Q3, and 12.3 ± 1.7 g/dl in Q4. Procedural characteristics and echocardiographic outcomes are shown in **Table 2**. The mean number of clips implanted per patient was slightly greater in Q3 and Q4 (1.8 in each) than in Q1 and Q2 (1.7 and 1.5, respectively). Reduction in MR severity to ≤2+ on discharge echocardiography was achieved in 96.3% of patients and did not differ across quartiles. On the pre-discharge echocardiogram, the rates of moderate-to-severe (3+) and severe (4+) MR were 2.5% and 1.2%, respectively. At 1 year, the rates of moderate-to-severe and severe MR were 3.3%, and 0.6%, respectively. At 2 years, moderate-to-severe MR was present in 0% of patients and severe MR was present in 0.7%. There were no significant differences between groups according to MVG (**Table 3**).

EFFECT OF MVG QUARTILE ON CLINICAL OUTCOMES.

The results of the clinical endpoints are shown in the **Central Illustration, Figure 1, and Table 3**. At 2 years, there were no significant differences in the composite endpoint of all-cause mortality or HF hospitalization across the 4 quartiles (43.2%, 49.2%, 40.6%, and 40.9% in Q1 through Q4, respectively; p = 0.78). Compared with Q1 to Q3, Q4 was associated with similar rates of all-cause mortality, cardiovascular mortality, HF hospitalization, annualized HF hospitalization, and all-cause rehospitalization in unadjusted analyses. After multivariable adjustment for baseline clinical and procedural variables, including number of clips and post-procedural residual MR,

TABLE 3 Clinical Endpoints and Core Laboratory Echocardiographic Measures by MVG Quartile at 2 Years

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Overall p Value
Clinical endpoints					
Patients	63	61	62	64	
Mortality or hospitalization for heart failure*	43.2 (27)	49.2 (30)	40.6 (25)	40.9 (26)	0.78
All-cause mortality*	24.0 (15)	30.1 (18)	29.0 (18)	25.4 (16)	0.91
Heart failure hospitalization*	33.4 (19)	42.0 (24)	34.2 (20)	25.5 (15)	0.42
Annualized rate of heart failure hospitalizations, n events/total N patient-year*	33.0 (35/105.1)	36.3 (37/101.9)	31.8 (33/103.6)	31.8 (34/107.0)	0.92
All-cause rehospitalization*	67.8 (41)	76.5 (46)	63.6 (38)	69.6 (44)	0.41
LVAD implantation or heart transplantation*	5.8 (3)	1.9 (1)	5.9 (3)	2.1 (1)	0.57
6-min walk distance†					
Total distance, m	272.2 ± 164.3	196.3 ± 182.7	224.4 ± 145.8	230.7 ± 169.8	0.25
Change from baseline, m	−23.0 ± 142.3	−53.9 ± 158.0	−46.9 ± 136.6	−34.2 ± 137.8	0.60
KCCQ summary score	22.8 ± 22.1	9.8 ± 30.3	15.7 ± 26.7	13.3 ± 24.2	0.20
NYHA functional class					
I	23.8 (10/42)	19.4 (6/31)	13.2 (5/38)	7.5 (3/40)	0.21
II	50.0 (21/42)	41.9 (13/31)	55.3 (21/38)	52.5 (21/40)	0.72
III	23.8 (10/42)	32.3 (10/31)	23.7 (9/38)	30.0 (12/40)	0.79
IV	2.4 (1/42)	6.5 (2/31)	7.9 (3/38)	10.0 (4/40)	0.56
III or IV	26.2 (11/42)	38.7 (12/31)	31.6 (12/38)	40.0 (16/40)	0.53
Echocardiographic measures					
Patients	38	32	34	36	
Mitral valve gradient, mm Hg	2.9 ± 1.4	3.1 ± 1.4	4.2 ± 1.9	4.7 ± 1.9	<0.001
Mitral regurgitation					
None, 0	2.6 (1/38)	3.1 (1/32)	0.0 (0/34)	0.0 (0/36)	0.56
Mild, 1+	71.1 (27/38)	71.9 (23/32)	79.4 (27/34)	77.8 (28/36)	0.81
Moderate, 2+	26.3 (10/38)	21.9 (7/32)	20.6 (7/34)	22.2 (8/36)	0.94
Moderate to severe, 3+	0.0 (0/38)	0.0 (0/32)	0.0 (0/34)	0.0 (0/36)	-
Severe, 4+	0.0 (0/38)	3.1 (1/32)	0.0 (0/34)	0.0 (0/36)	0.33
Moderate or less, ≤2+	100.0 (38/38)	96.9 (31/32)	100.0 (34/34)	100.0 (36/36)	0.33
Left ventricular ejection fraction	25.2 ± 9.0	27.9 ± 7.6	27.2 ± 9.3	31.0 ± 10.6	0.15

Values are n, % (n), mean ± SD, or % (n/N), unless otherwise indicated. *Event rates are Kaplan-Meier estimated rates expressed as % (n of events). †Missing values for the 6-min walk distance were imputed according to the protocol pre-defined rules. Subjects who expired due to an adjudicated heart failure death prior to the 2 years follow-up time or were unable to walk due to cardiac reasons were included and assigned a distance of 0.

KCCQ = Kansas City cardiomyopathy questionnaire; LVAD = left ventricular assist device; MVG = mitral valve gradient; NYHA = New York Heart Association.

MVG in Q4 compared with Q1 to Q3 was not independently associated with the 2-year rates of all-cause mortality or HF hospitalization (HR: 1.23; 95% CI: 0.60 to 2.51; $p = 0.57$). Nor was higher MVG an independent predictor of all-cause mortality, cardiovascular mortality, or HF hospitalization alone (Table 4). Furthermore, discharge MVG had no significant impact on the improvement in 6MWD, NYHA functional class, or KCCQ after MitraClip treatment (Table 3).

Patients were further classified into 4 groups based on different combinations of discharge MVG quartiles and residual MR (group 1: MVG Q1 to Q3 and MR <2+ [n = 152]; group 2: MVG Q4 and MR <2+ [n = 52]; group 3: MVG Q1 to Q3 and MR ≥2+ [n = 30]; and group 4: MVG Q4 and MR ≥2+ [n = 10]). There was no difference in outcomes of all-cause mortality or HF hospitalization between groups 1 and 2 (HR: 0.98; 95% CI: 0.60 to 1.61; $p = 0.94$) or between groups 3 and 4 (HR: 1.50; 95% CI: 0.56 to 4.01; $p = 0.42$) (overall log-rank test $p = 0.07$). There was also no

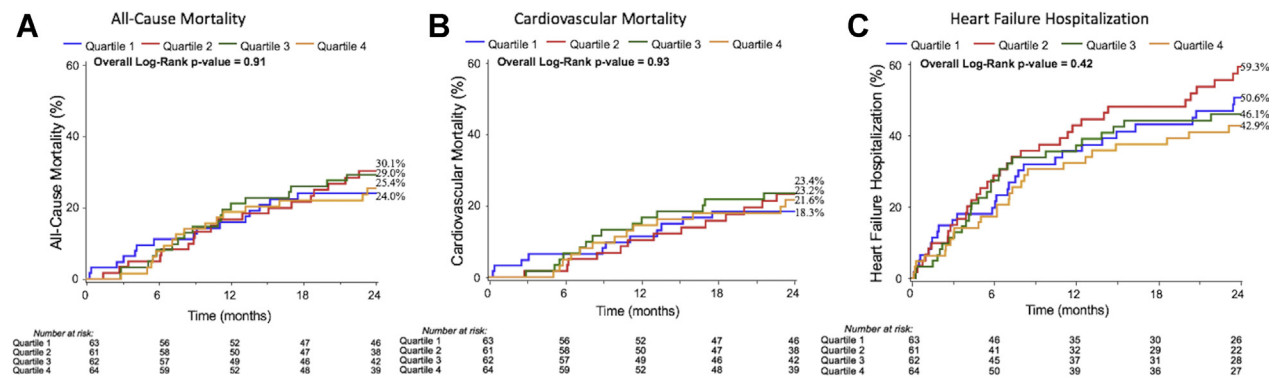
difference in outcomes in the 2 extremes of combinations of MVG and residual MR, between groups 1 and 4 (HR: 0.76; 95% CI: 0.31 to 1.89; $p = 0.56$).

ADDITIONAL MVG ANALYSES. Effect of MVG as a continuous variable on clinical outcomes.

We used spline regression to assess whether there was a nonlinear relationship between MVG measured on discharge echocardiography as a continuous variable and clinical endpoints; no nonlinear associations were found (all $p > 0.05$) (Figure 2). In addition, a sensitivity analysis excluding patients with residual MR ≥2+ was performed, and a receiver-operating characteristic (ROC) curve for prediction of the composite outcome of 2-year all-cause death or HF hospitalization was obtained. The ROC curve suggests no predictive capacity of post-MitraClip MVG for the composite outcome (ROC area under the curve 0.49, 95% CI: 0.41 to 0.57) (Supplemental Figure 1).

Effect of MVG cutoff value of 5 mm Hg on clinical outcomes. An additional analysis was performed using

FIGURE 1 Kaplan-Meier Curves of Clinical Outcome Measures During 2-Year Follow-Up According to Post MitraClip-Treatment MVG by Quartile



(A) All-cause mortality; (B) cardiovascular mortality; (C) heart failure hospitalization. There were no significant differences in clinical outcomes according to post-MitraClip mitral valve gradient (MVG).

MVG cutoff at a value of 5 mm Hg instead of quartiles. In multivariate Cox regression analyses, discharge MVG ≥ 5 mm Hg was not associated with a higher risk of all-cause death (HR: 0.83; 95% CI: 0.35 to 1.98; $p = 0.68$), HF hospitalization (HR: 0.87; 95% CI: 0.47 to 1.60; $p = 0.65$), or the composite endpoint of all-cause death or HF hospitalization (HR: 1.00; 95% CI: 0.51 to 1.97; $p = 0.99$) at 2 years compared with MVG < 5 mm Hg (Table 5). In addition, the interaction between discharge MVG ≥ 5 mm Hg and residual MR $\geq 2+$ was not statistically significant for the composite endpoint of all-cause death or HF hospitalization ($p = 0.85$). Supplemental Figure 2 shows the Kaplan-Meier curves for the outcome of HF hospitalization or all-cause death by groups with different combinations of MVG (≥ 5 mm Hg vs. < 5 mm Hg) and residual MR ($\geq 2+$ vs. $< 2+$). The overall comparison log-rank for these groups was not statistically different. The only binary comparison that was statistically different was the comparison showing the group with the combination of MVG < 5 mm Hg and residual MR $\geq 2+$ had a higher rate of HF hospitalization or all-death at 2 years versus patients with

MVG ≥ 5 mm Hg and residual MR $< 2+$ (HR: 2.10; 95% CI: 1.13 to 3.91; $p = 0.017$).

DISCUSSION

The major findings of this study are as follows: 1) Approximately 25% of patients with HF and SMR treated with the MitraClip in the COAPT trial had an elevated MVG > 5 mm Hg at discharge. These patients were more likely female, African-American, and obese; 2) Nonetheless, patients with an elevated MVG measured at discharge after MitraClip treatment had similar rates of mortality, HF hospitalization, and measures of functional status, including 6MWD, NYHA functional class, and KCCQ score during 2-year follow-up compared with those with absent or lesser MVGs.

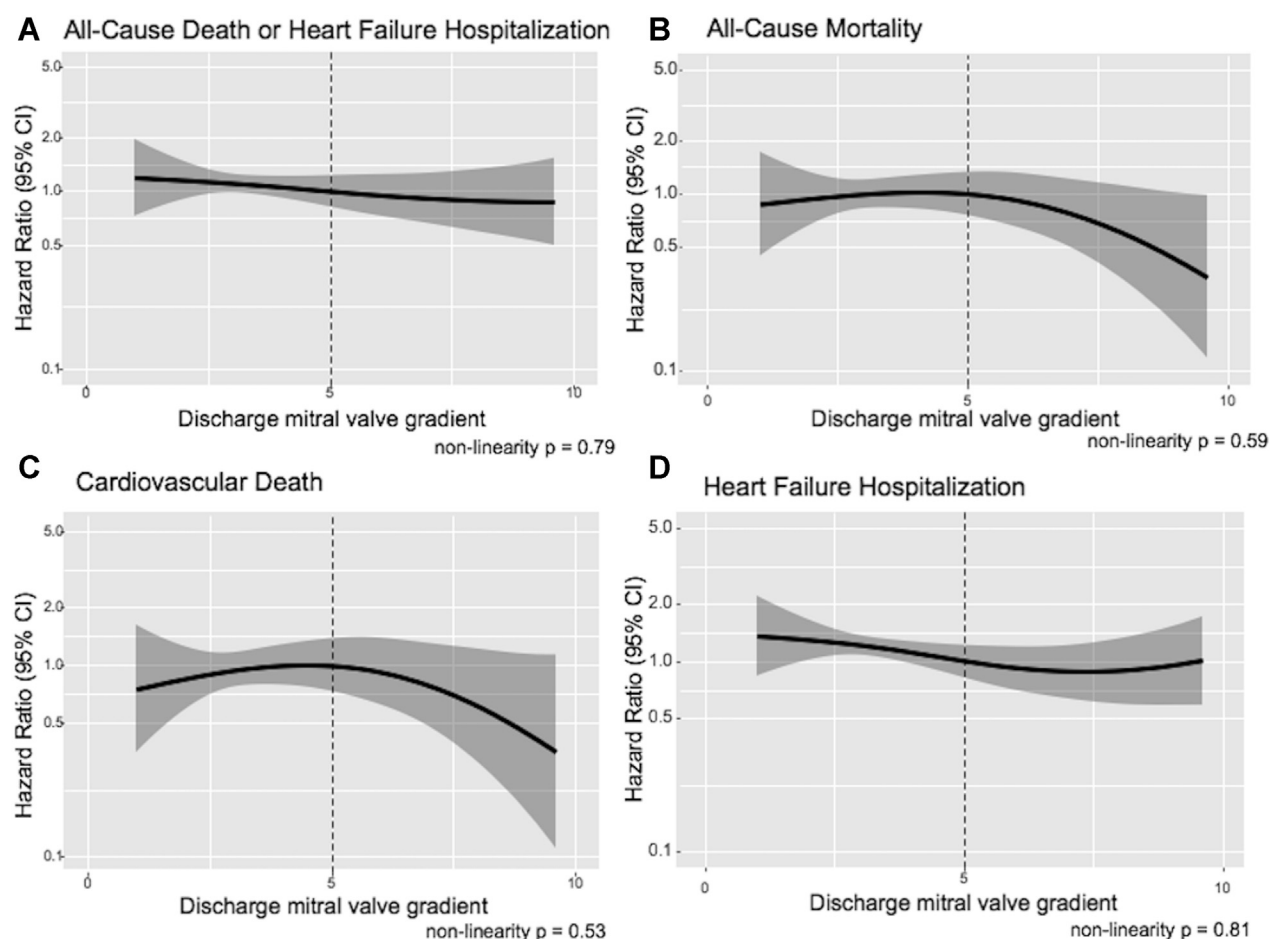
In the COAPT trial, the reduction of moderate-to-severe and severe SMR with the MitraClip in HF patients resulted in substantial improvements in prognosis compared with GDMT alone (2). The lack of an association between an elevated MVG following MitraClip implantation and worse outcomes of mortality, HF hospitalization, and measures of functional

TABLE 4 Multivariable Adjusted Clinical Outcomes at 2 Years According to Quartile of Discharge MVG After MitraClip Treatment

2-Year Outcome Measure	Q4	Q1 to Q3	Adjusted Hazard Ratio (95% CI) Q4 vs. Q1 to Q3	Adjusted p Value
All-cause mortality	25.4 (16)	27.6 (51)	0.90 (0.37 to 2.19)	0.82
Cardiovascular mortality	21.6 (13)	21.6 (38)	0.90 (0.34 to 2.36)	0.83
Hospitalization for heart failure	25.5 (15)	36.5 (63)	1.00 (0.52 to 1.90)	0.99
Cardiovascular mortality or hospitalization for heart failure	37.5 (23)	41.6 (75)	1.21 (0.58 to 2.54)	0.61
All-cause mortality or hospitalization for heart failure	40.9 (26)	44.3 (82)	1.23 (0.60 to 2.51)	0.57

Event rates are Kaplan-Meier estimated rates expressed as % (n of events).
CI = confidence interval; MVG = mitral valve gradient.

FIGURE 2 Spline Regression Analysis of Post MitraClip-Treatment MVG and Clinical Outcome Measures



There were no significant correlations between mitral valve gradient (MVG) as a continuous variable and clinical outcomes as assessed by spline regression. The vertical dotted line indicates the reference point of a discharge mitral valve gradient of 5 mm Hg that corresponds to a hazard ratio of 1. CI = confidence interval.

status provides important guidance regarding MR reduction in COAPT eligible patients. Residual MR after MitraClip is associated with worse outcomes (10–12); often, placement of additional clips is considered when residual MR is substantial. Further reducing the severity of MR with additional clips while avoiding mitral stenosis can be challenging. Most guidelines recommend avoiding a post-MitraClip gradient of >5 mm Hg (9). However, in the COAPT trial population, the clinical benefits of SMR reduction were preserved despite 25% of MitraClip-treated patients having a post-procedure MVG in this range (mean 7.2 mm Hg, range 5.1 to 13.2 mm Hg). Thus, although avoiding a substantial post-treatment MVG is desirable, the present study suggests that the benefits of MR reduction outweigh the effects of mild-to-moderate mitral stenosis after MitraClip

treatment in select HF patients who remain symptomatic despite maximally-tolerated GDMT and cardiac resynchronization therapy if appropriate.

In the surgical published reports, the data on the effect of post-surgical MVG following mitral valve repair or replacement are conflicting (6,13–19). Development of early mitral stenosis after surgical repair can be caused by multiple factors, such as surgical technique, resection of redundant leaflet tissue, and undersizing of the annuloplasty ring (20). Some studies have suggested that post-operative elevated MVG may result in lower exercise capacity and poorer quality of life in patients with primary MR (6,18). There are limited data on the clinical and long-term effects of an elevated MVG after surgical repair of SMR; 1 study demonstrated a decrease in 6MWD (19), although most others reported no deleterious effects (13,14,16).

Herrmann et al. (4,5) first investigated the effects of MitraClip on mitral valve area and gradient in the early EVEREST trials. By planimetry, mean MVOA decreased from 6.0 cm² at baseline to 3.6 cm² after MitraClip implantation, and mean MVG increased from 1.7 to 4.1 mm Hg. These changes were similar in patients with 1 and 2 clips, in patients with primary and secondary MR, and were not associated with the need for surgery during 2-year follow-up. In these studies, patients with a baseline MVOA <4.0 cm² were excluded, and most patients received a single clip. Other series yielded conflicting results (7,8,11). Neuss et al. (7) evaluated the impact of high MVG following MitraClip on the combined endpoint of all-cause mortality, unsuccessful implantation, mitral valve surgery, LV assist device implantation, or repeat procedures in a retrospective study of 216 patients (70% SMR) from a single center in Germany. A MVG of >5 mm Hg measured invasively or >4.4 mm Hg by echocardiographic estimation, both assessed during the procedure under anesthesia, were associated with a higher rate of the combined endpoint (unadjusted HR: 2.3, 95% CI: 1.4 to 3.8; *p* < 0.002). A nonsignificant trend for increased mortality with elevated MVG was noted. Patients with MVG >5 mm Hg had a higher number of clips (1.50 ± 0.72 vs. 1.29 ± 0.54; *p* = 0.02). The investigators also found that baseline MVOA ≤4.0 cm² was associated with a higher MVG after MitraClip (odds ratio: 3.41; *p* = 0.003). Notably, 12% of patients had an initial MVOA ≤4.0 cm², one-half of whom developed significant mitral stenosis after the MitraClip procedure. In addition, patients with residual MR ≥2+ had worse outcomes, especially when accompanied with an elevated MVG. On the basis of these results, the investigators recommended against accepting a higher MVG as a tradeoff for better MR reduction. In contrast to these findings, not only did our study find comparable clinical outcomes in the different MVG quartiles, we also observed no significant difference in all-cause death or HF hospitalization between patients with MR ≥2+ plus elevated MVG (Q4) compared with those with MR <2+ and lower MVG (Q1 to Q3). However, the number of patients with the combination of elevated MVG in the highest quartile and MR ≥2+ was too small (*n* = 10) to draw definitive conclusions. It is also worth noting that the COAPT trial excluded patients with baseline MVOA ≤4.0 cm², which likely contributed to a lower post-procedural MVG than that in the study of Neuss et al. (7). Finally, Neuss et al. did not differentiate between primary MR and SMR in their analysis, whereas the COAPT trial exclusively enrolled SMR patients.

TABLE 5 Multivariable Adjusted Clinical Outcomes at 2 Years According to Discharge MVG ≥5 mm Hg vs. <5 mm Hg After MitraClip Treatment

Clinical Outcomes at 2 Years	Adjusted Hazard Ratio (95% Confidence Interval) for Mitral Valve Gradient ≥5 mm Hg vs. <5 mm Hg	Adjusted p Value
All-cause death	0.83 (0.35–1.98)	0.68
Heart failure hospitalization	0.87 (0.47–1.60)	0.65
All-cause death or heart failure hospitalization	1.00 (0.51–1.97)	0.99

Multivariable analyses were performed with adjustment for the following variables: age, sex, body mass index, chronic obstructive pulmonary disease, history of atrial fibrillation or flutter, diabetes, chronic kidney disease, baseline left ventricular end-diastolic volume index, baseline effective regurgitant orifice area, ischemic versus nonischemic etiology of mitral regurgitation, baseline left ventricular ejection fraction, baseline mitral valve gradient, number of MitraClips, post-procedural mitral regurgitation grade, and discharge mitral valve gradient (MVG).

MR is a diverse disease with numerous etiologies and phenotypes. Specifically, primary MR and SMR have different physiologies, LV features, and hemodynamic characteristics. The effect of a post-procedural elevated MVG may be tolerated differently in patients with primary MR in whom LV function is usually preserved and HF patients with SMR in whom LVEF is typically impaired, comorbidities are common, and baseline functional capacity is reduced. Patzelt et al. (8) evaluated the effect of elevated MVG after MitraClip stratified by the type of MR in a retrospective study of 255 patients (59% SMR). Reduction of MR severity ≤2+ was accomplished in 98.4% of patients. Post-MitraClip MVG >4.4 mm Hg measured on echocardiography was associated with worse combined endpoint of all-cause mortality, mitral valve surgery, left ventricular assist device implantation, or repeat procedures in primary MR, but not in SMR. By contrast, there was no correlation between elevated MVG and 6MWD in either primary or SMR. Conversely, in a smaller study of 78 patients, reduction in MR appeared to be more important for HF hospitalization than a MVG >5 mm Hg, regardless of MR etiology (12).

It is important to note increasing experience with MitraClip placement has resulted in improved procedural outcomes. MitraClip treatment had a 93% success rate in reducing MR to ≤2+ in the COAPT trial, substantially higher than in the early EVEREST trials. Given the substantial contribution of severe SMR to the poor prognosis of patients with HF who remain symptomatic despite GDMT, the significant improvement in MR with the MitraClip in a high proportion outweighed any detrimental effect of iatrogenic mild or moderate mitral stenosis in the COAPT study population.

Our study has several strengths relative to prior ones. It is the largest such study to assess the impact of MVG at discharge after treatment of severe SMR in HF. All events

were monitored and adjudicated by a central committee. An independent core laboratory was utilized for the echocardiographic assessment of MR and MVG. In addition, these values were measured at discharge rather than under general anesthesia during the procedure. Although this study might be underpowered to ascertain differences in outcomes between patient groups with different combinations of MVG and residual MR, we showed with different analytic approaches (using MVG quartiles, MVG cutoff value of 5 mm Hg, ROC curve, and MVG as a continuous variable in spline regression) that there was no association between discharge MVG gradient and long-term outcomes in the study population. Finally, the patients included were a homogenous group with HF and SMR who met defined inclusion and exclusion criteria of the COAPT trial.

STUDY LIMITATIONS. Our results cannot be generalized to patients who do not meet the inclusion and exclusion criteria of the COAPT trial, particularly those with baseline MVOA ≤ 4.0 cm² and those with unfavorable leaflet anatomy that may preclude MitraClip implantation. Our results are also not applicable to a healthier, more active patient population with primary MR in whom mild mitral stenosis may not be well tolerated, especially during exercise. Second, MVG is flow dependent and can vary depending on the heart rate, loading conditions, and cardiac output at the time of the gradient measurement, as well as on the existence of concomitant MR. Changes of the MVG with exertion were not assessed in this study, although the fact that functional and quality of life measures such as 6MWD, NYHA functional class, and KCCQ summary score were not adversely impacted by a mild to moderate increase in MVG is reassuring. We also did not use MVOA to assess the effects of MitraClip. Mitral area is subject to variability in measurement after MitraClip (21) and was not recorded in most patients in our study. In this regard, previous studies have demonstrated that mean MVG is a reasonable surrogate for MVOA (22). Third, intraprocedural hemodynamic data were not collected; as such, it is possible that the intraprocedural MVG might have affected the decision to implant additional clips. Finally, the individual group sizes are small, adding some imprecision. In particular, the number of patients with an elevated MVG was modest, and the adjusted confidence interval for the comparison between Q4 and Q1 to Q3 was wide (0.60 to 2.51). As such, we cannot exclude a deleterious effect of an increased MVG (especially if a residual MR grade of $\leq 2+$ cannot be achieved), and the results of the present study should thus be considered hypothesis generating.

CONCLUSIONS

Among HF patients with severe SMR who remained symptomatic despite maximally tolerated GDMT in the COAPT trial, a higher MVG measured on discharge echocardiography did not impair the benefits of MR reduction following MitraClip treatment. Thus, although an elevated MVG should be avoided if possible, these findings suggest that the benefits of MR reduction may outweigh the effects of mild-to-moderate mitral stenosis after MitraClip treatment in select patients with HF and severe SMR.

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PERSPECTIVES

WHAT IS KNOWN? The effects of an elevated mitral valve gradient on long-term outcomes after MitraClip treatment of heart failure patients with secondary mitral regurgitation and reduced left ventricular ejection fraction have been conflicting.

WHAT IS NEW? In the COAPT trial, patients with an elevated mitral valve gradient following mitral valve repair with MitraClip had similar 2-year rates of death, heart failure hospitalization, and measures of functional status as compared to those with lower gradients. These findings suggest that, in the context of physician-directed

decision-making, the benefits of mitral regurgitation reduction may outweigh the effects of mild-to-moderate mitral stenosis after MitraClip treatment in select patients with heart failure and severe secondary mitral regurgitation.

WHAT IS NEXT? Additional research is needed to understand whether our findings translate to patients with severe mitral regurgitation treated with the MitraClip who do not otherwise meet the eligibility criteria of the COAPT trial.

REFERENCES

1. Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *J Am Coll Cardiol HF* 2017;5:652–9.
2. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379:2307–18.
3. U.S. Food and Drug Administration. FDA Approves New Indication for Valve Repair Device to Treat Certain Heart Failure Patients With Mitral Regurgitation 2019. FDA News Release, 2019. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-valve-repair-device-treat-certain-heart-failure-patients-mitral>. Accessed January 20, 2020.
4. 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 Cardiovasc Interv* 2006;68:821–8.
5. Herrmann HC, Kar S, Siegel R, et al. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. *Euro-Intervention* 2009;4:437–42.
6. Chan KL, Chen S-Y, Chan V, Hay K, Mesana T, Lam BK. Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. *Circ Cardiovasc Imaging* 2013;6:1041–7.
7. 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;10:931–9.
8. 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.
9. 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. *J Am Soc Echocardiogr* 2019;32:431–75.
10. Kaneko H, Neuss M, Weissenborn J, Butter C. Impact of residual mitral regurgitation after MitraClip implantation. *Int J Cardiol* 2017;227:813–9.
11. Ailawadi G, Lim DS, Mack MJ, et al. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation* 2019;139:37–47.
12. Cheng R, Dawkins S, Tat E, et al. Relation of residual mitral regurgitation despite elevated mitral gradients to risk of heart failure hospitalization after MitraClip repair. *Am J Cardiol* 2017;120:1595–600.
13. Tomsic A, Hiemstra YL, Arabkhan B, et al. Risk factors and clinical significance of elevated mitral valve gradient following valve repair for degenerative disease. *Eur J Cardiothorac Surg* 2019;57:293–9.
14. Rubino AS, Onorati F, Santarpia G, et al. Impact of increased transmitral gradients after undersized annuloplasty for chronic ischemic mitral regurgitation. *Int J Cardiol* 2012;158:71–7.
15. Kainuma S, Taniguchi K, Daimon T, et al. Does stringent restrictive annuloplasty for functional mitral regurgitation cause functional mitral stenosis and pulmonary hypertension? *Circulation* 2011;124 Suppl:S97–106.
16. Williams ML, Daneshmand MA, Jollis JG, et al. Mitral gradients and frequency of recurrence of mitral regurgitation after ring annuloplasty for ischemic mitral regurgitation. *Ann Thorac Surg* 2009;88:1197–201.
17. Bertrand PB, Gutermann H, Smeets CJP, et al. Functional impact of transmitral gradients at rest and during exercise after restrictive annuloplasty for ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2014;148:183–7.
18. Mesana TG, Lam B-K, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. *J Thorac Cardiovasc Surg* 2013;146:1415–8.
19. Magne J, Senechal M, Mathieu P, Dumesnil JG, Dagenais F, Pibarot P. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. *J Am Coll Cardiol* 2008;51:1692–701.
20. Shabsigh M, Lawrence C, Rosero-Britton BR, et al. Mitral valve stenosis after open repair surgery for non-rheumatic mitral valve regurgitation: a review. *Front Cardiovasc Med* 2016;3:8.
21. 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;6:1032–40.
22. Nishimura RA, Rihal CS, Tajik AJ, Holmes DRJ. Accurate measurement of the transmitral gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol* 1994;24:152–8.

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