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Repeat Mitral Valve Interventions After Transcatheter Edge-to-Edge Repair: The COAPT Trial



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The frequency and effectiveness of repeat mitral valve interventions (RMVI) after transcatheter edge-to-edge repair (TEER) for secondary mitral regurgitation (MR) are unknown. We aimed to examine the rate of and outcomes after RMVI after TEER in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial. Only 3.9% of COAPT trial patients required a repeat mitral valve intervention during 4-year follow-up which was successful in 90% of cases but was associated with an increased rate of heart failure (HF) hospitalizations (HFH). The COAPT trial randomized HF patients with severe secondary MR to TEER with the MitraClip device plus guideline-directed medical therapy (GDMT) versus GDMT alone. We evaluated the characteristics and outcomes of patients who had an RMVI during 4-year follow-up. A MitraClip implant was attempted in 293 patients randomized to TEER +GDMT, 10 of whom underwent an RMVI procedure (9 repeat TEER and 1 surgical mitral valve replacement) after 4 years of follow-up (cumulative incidence 3.90%, 95% confidence interval [CI] 2.08 to 7.08; median 182 days after the initial procedure). Patients with RMVI had larger mitral annular diameters, fewer clips implanted, and were more likely to have ≥ 3 +MR at discharge compared with those without RMVI. Reasons for RMVI included failed index procedure because of difficult transseptal puncture (n = 2) or tamponade (n = 1); residual or recurrent severe MR after an initially successful procedure (n = 5); partial clip detachment (n = 1); and site-assessed mitral stenosis (n = 1). RMVI was successful in 8/10 (80%) patients. Patients who underwent RMVI had higher 4-year rates of HFH but similar mortality compared with those without RMVI. The annualized incidence rates of all HFH in patients who underwent RMVI were 234 events per 100 person-years (95% CI 139 to 395) pre-RMVI and 46 per 100 person-years (95% CI 25 to 86) post-RMVI as compared with 32 events per 100 patient-years (95% CI 28 to 36) in patients without RMVI. The rate ratio of HFH was reduced after RMVI in patients who underwent RMVI (0.20, 95% CI 0.09 to 0.45). In conclusion, the cumulative incidence of RMVI after 4 years was 3.9% in patients who underwent TEER for severe secondary MR in the COAPT trial. Patients who underwent RMVI were at increased risk of HFH which was reduced after the RMVI procedure.

Clinical Trial Registration: *Clinical Trial Name:* Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial) (COAPT)

ClinicalTrial.gov Identifier: NCT01626079

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See page 13 for Declaration of Competing Interest.

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Transcatheter edge-to-edge repair (TEER) improves outcomes in selected patients with heart failure (HF) and secondary severe mitral regurgitation (MR).¹ The TEER procedure emulates the original surgical suture-based repair approach by implanting one or more clips to approximate the anterior and posterior mitral leaflets, thereby reducing the volume of regurgitation.² The safety and efficacy of the first TEER system, the MitraClip device, was demonstrated in HF patients with severe secondary MR in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT)³ trial. In COAPT, the reduction in secondary MR with the MitraClip compared with guideline-directed medical therapy (GDMT) alone led to substantial improvements in survival, reduced HF hospitalizations (HFH), and enhanced exercise performance and quality of life. Although MR reduction after the MitraClip is generally durable, some patients either initially have insufficient MR reduction or over time develop recurrent MR.^{4–7} Potential device-specific complications include single leaflet device

attachment (SLDA), device embolization, mitral stenosis, and endocarditis. Ongoing or recurrent mitral valve (MV) dysfunction in patients with HF worsens the prognosis of HF patients and may necessitate repeat mitral valve interventions (RMVI).^{8,9} However, little is known about the frequency and outcomes of RMVI after TEER, particularly in HF patients with secondary MR. We, therefore, examined the characteristics and outcomes of patients who had RMVI after their index TEER procedure in the COAPT trial.

Methods

The data that support the findings of this study may be made available from the corresponding author upon reasonable request with approval by the study leadership of the COAPT trial.

COAPT trial design¹⁰ and primary results³ have been published previously. In brief, COAPT was a multicenter, randomized, controlled, open-label trial of TEER with the MitraClip device (Abbott Vascular, Santa Clara, California)

Table 1
Baseline characteristics prior to the index TEER procedure

	RMVI N = 10	No RMVI N = 283	p Value
Age, years	69.1 ± 16.5	71.9 ± 11.7	0.47
Male sex	5 (50%)	192 (68%)	0.24
Body mass index, kg/m ²	31.5 ± 7.9	27.0 (5.7)	0.02
Prior stroke	1 (10%)	35 (12%)	0.85
Prior myocardial infarction	3 (30%)	150 (52%)	0.16
Coronary artery disease	7 (70%)	205 (72%)	0.87
Hypertension	9 (90%)	226 (80%)	0.43
Hypercholesterolemia	6 (60%)	155 (55%)	0.74
Chronic obstructive pulmonary disease	2 (20%)	66 (23%)	0.81
History of atrial fibrillation or flutter	6 (60%)	160 (57%)	0.83
Diabetes mellitus	5 (50%)	96 (34%)	0.29
Creatinine clearance, mL/min	60.8 ± 57.5	51.2 ± 26.7	0.26
History of anemia	3 (30%)	61 (22%)	0.53
STS replacement score	7.9 ± 4.5	7.6 ± 5.3	0.86
STS repair score	5.0 ± 3.1	5.5 ± 5.6	0.81
Prior coronary artery bypass grafting	1 (10%)	115 (41%)	0.05
Prior percutaneous coronary intervention	5 (50%)	123 (44%)	0.68
Cause of cardiomyopathy			0.94
Ischemic	6 (60%)	173 (61%)	
Non-ischemic	4 (40%)	110 (39%)	
Previous cardiac resynchronization therapy	5 (50%)	107 (38%)	0.44
Previous cardiac defibrillator therapy	7 (70%)	176 (62%)	0.62
New York Heart Association class			0.19
I	0 (0%)	1 (0.4%)	
II	1 (10%)	126 (45%)	
III	8 (80%)	139 (49%)	
IV	1 (10%)	17 (6.0%)	
KCCQ overall summary score	40.0 ± 18.0	54.1 (22.8)	0.06
6-minute walk distance, meters	211.7 ± 92.1	254.9 (123.8)	0.28

Values are mean ± standard deviation or n/N (%).

KCCQ = Kansas City Cardiomyopathy Questionnaire; RMVI = repeat mitral valve intervention; STS = Society of Thoracic Surgeons.

in patients with HF and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT. Patients had a left ventricular ejection fraction between 20% and 50%, left ventricular end-systolic dimension ≤ 70 mm, and were excluded if they had pulmonary artery systolic pressure >70 mm Hg not responsive to vasodilators or symptomatic moderate or severe right ventricular dysfunction. MR severity was graded by an echocardiographic core laboratory using a multiparametric algorithm (11) adapted from criteria recommended by the American Society of Echocardiography 2003 guidelines.¹¹ Patients were randomized 1:1 to treatment with TEER plus GDMT or GDMT alone and were followed at regular intervals through 5 years. All analyses in this study were based on 4-year follow-up. The protocol was registered at *clinicaltrials.gov* (NCT01626079) and approved by the investigational review board at each

participating center, and all patients provided written informed consent. The study conforms with the principles outlined in the Declaration of Helsinki.

Effectiveness outcomes assessed in COAPT included the 2-year rates of death, HFH, and the composite of death and HFH, and cardiovascular hospitalizations and all-cause hospitalizations. Deaths were further categorized as cardiovascular versus non-cardiovascular. Adverse outcomes including RMVI were adjudicated by an independent clinical events committee blinded to treatment assignment.

Baseline characteristics (before randomization or at the time of the index TEER procedure) are summarized with means and SDs or medians (Q1, Q3) for continuous variables and proportions for categorical variables. Continuous variables were compared between groups using unpaired *t* tests for data that were normally distributed and the Wilcoxon rank-sum test for non-normally distributed data.

Table 2
Baseline laboratory echocardiographic characteristics

	RMVI N= 10	No RMVI N= 283	p Value
Mitral regurgitation severity			0.56
Moderate-to-severe (3+)	4/10 (40%)	140 /283(50%)	
Severe (4+)	6/10 (60%)	143/283 (51%)	
Effective regurgitant orifice area - by PISA (cm ²)	0.41 $\pm$ 0.13	0.42 (0.15)	0.95
Anterior-posterior mitral annulus diameter (cm)	3.54 $\pm$ 0.52	3.25 $\pm$ 0.39	0.02
Intercommissural mitral annulus diameter (cm)	3.49 $\pm$ 0.43	3.56 (0.40)	0.57
Anterior mitral valve leaflet length (cm)	2.40 $\pm$ 0.18	2.27 $\pm$ 0.36	0.35
Posterior mitral valve leaflet length (cm)	1.33 $\pm$ 0.21	1.34 $\pm$ 0.24	0.91
Coaptation to septum distance (cm)	3.96 $\pm$ 0.42	4.06 $\pm$ 0.45	0.48
Tenting height (cm)	1.08 $\pm$ 0.26	0.99 $\pm$ 0.24	0.23
Tenting area (cm ²)	2.64 $\pm$ 0.90	2.27 (0.36)	0.03
Tethering location			0.49
None	0/8 (0.0%)	6/210 (2.9%)	
P1	2/8 (25%)	21/210 (10%)	
P1-P2	0/8 (0.0%)	60/210 (29%)	
P2	5/8 (63%)	85/210 (41%)	
P2-P3	1/8 (13 %)	29/210 (14%)	
P3	0/8 (0%)	8/210 (3.8%)	
All	0/8 (0%)	1/210 (0.5%)	
Anterior papillary muscle to MV annulus distance (cm)	3.74 $\pm$ 0.74	3.82 $\pm$ 0.65	0.87
Posterior papillary muscle to MV annulus distance (cm)	4.34 $\pm$ 0.93	4.03 $\pm$ 0.55	0.35
Basal mitral anterior leaflet angle (ALA _{base}) (degree)	33 $\pm$ 7	31 $\pm$ 7	0.53
Distal mitral anterior leaflet angle (ALA _{dist}) (degree)	17 $\pm$ 3	19 $\pm$ 6	0.39
Posterior mitral leaflet angle (degree)	44 $\pm$ 10	38 $\pm$ 9	0.059
LV ejection fraction, %	33.9 $\pm$ 6.2	31.3 $\pm$ 9.2	0.38
LV end-systolic dimension, cm	5.3 $\pm$ 0.7	5.3 $\pm$ 0.9	0.94
LV end-diastolic dimension, cm	6.3 $\pm$ 0.7	6.2 $\pm$ 0.7	0.64
LV end-systolic volume, mL	121.2 $\pm$ 49.8	136.3 $\pm$ 56.8	0.41
LV end-diastolic volume, mL	183.3 $\pm$ 74.4	194.9 $\pm$ 69.5	0.59
LV end-systolic volume index, mL/m ²	59.8 $\pm$ 22.2	71.8 $\pm$ 28.7	0.19
LV end-diastolic volume index, mL/m ²	90.5 $\pm$ 33.2	102.8 $\pm$ 33.9	0.26
Regurgitant fraction, %	49.0 $\pm$ 12.3	37.8 $\pm$ 13.6	0.16
Pulmonary artery systolic pressure, mmHg	45.7 $\pm$ 12.9	43.9 $\pm$ 13.6	0.70
Left atrial volume, mL	94.1 $\pm$ 21.1	91.2 $\pm$ 36.1	0.81
(3+) Moderate/severe tricuspid regurgitation	0/10 (0%)	2/280 (0.7%)	0.79
(4+) Severe tricuspid regurgitation	0/10 (0%)	0/280 (0%)	N/A
Peak pulmonary venous flow diastole, cm/s	84.3 $\pm$ 22.2	66.8 $\pm$ 18.8	0.03
E wave/A wave ratio	1.8 $\pm$ 0.9	2.2 $\pm$ 1.1	0.40

Values are mean $\pm$ standard deviation or n/N (%).

ALA = anterior leaflet angle; LV = left ventricular; MV = mitral valve; PAD = peripheral arterial disease; PISA = proximal isovelocity hemispheric surface area; RMVI = repeat mitral valve intervention.

The chi-square or Fisher's exact test was used to compare categorical variables. Time-to-event rates were estimated by the Kaplan-Meier method and were compared with Cox regression. Poisson regression analysis was performed to assess annualized incidence rates of all HFH per 100 person-years with 95% confidence intervals (CI) for patients who underwent RMVI both before and after the RMVI procedure and also for patients without RMVI. The relative risk of HFH pre- and post-RMVI was assessed from the Poisson regression analysis. All p values are 2-tailed, and $p < 0.05$ was considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Of 302 patients randomized to TEER+GDMT, a TEER procedure was attempted in 293, 10 of whom underwent RMVI (9 repeat TEER and 1 surgical MV replacement) with a cumulative incidence of RMVI of 3.90%, 95% CI 2.08 to 7.08; after 4 years of follow-up. Compared with patients who did not undergo RMVI, RMVI patients had larger body mass index and were more often in New York Heart Association class III or IV at baseline (Table 1).

Table 3
Procedural characteristics of the index procedure

	RMVI N = 10	No RMVI N = 283	p Value
Number of MitraClip devices implanted			<0.0001
None	3 (30%)	3 (1.1%)	
1 clip	5 (50%)	101 (36%)	
2 clips	2 (20%)	155 (55%)	
3 clips	0/10 (0%)	23 (8.1%)	
4 clips	0 (0%)	1 (0.4%)	
Procedure duration (minutes)	143.9 ± 52.6	165.9 ± 113.3	0.54
Length of stay in hospital (days)	2.8 ± 2.1	2.5 ± 2.3	0.64

Values are mean ± standard deviation or n/N (%).

RMVI = repeat mitral valve intervention.

RMVI patients also had larger anterior-posterior mitral annulus diameters and larger tenting areas, but otherwise similar echocardiographic characteristics (Table 2). At the index procedure, patients requiring RMVI had fewer clips implanted and were more likely to have >2+MR at discharge compared with patients who did not require RMVI during follow-up (Table 3).

RMVI was performed at a median of 182 days (interquartile range 29 to 329 days) after initial TEER (range 17 to 629 days; Figure 1). Reasons for RMVI included failed index procedure because of difficulties with transseptal puncture (n = 2) or tamponade (n = 1); residual 3+ MR post-procedure with no improvement in HF symptoms (n = 1); recurrent severe MR after an initially successful procedure with worsening of HF symptoms (n = 4); SLDA (n = 1); and ongoing symptoms with site assessment of mitral stenosis (n = 1) (Table 4). MR severity was 3+ or 4+ in 9 patients before RMVI and was ≤2+ in 8 patients after RMVI (Figure 2, Table 4). One patient developed cardiogenic shock after RMVI and died before discharge although the RMVI procedure was technically successful.

In unadjusted analysis, patients who underwent RMVI had higher 4-year rates of HFH but similar mortality compared with those without RMVI (Table 5). The annualized incidence rates of all HFH in patients who underwent RMVI were 234 events per 100 person-years (95% CI 139 to 395) pre-RMVI and 46 per 100 person-years (95% CI 25 to 86) post-RMVI as compared with 32 events per 100 patient-years (95% CI 28 to 36) in patients without RMVI. The relative risk of HFH decreased after RMVI in patients who underwent RMVI (0.20, 95% CI 0.09 to 0.45).

Discussion

Since receiving United States Food and Drug Administration approval for treatment of secondary MR in HF patients in 2019, the use of TEER for this indication has increased.¹² As such, characterizing the durability and long-term outcomes of TEER and RMVI in this patient cohort is essential. The major findings from the present

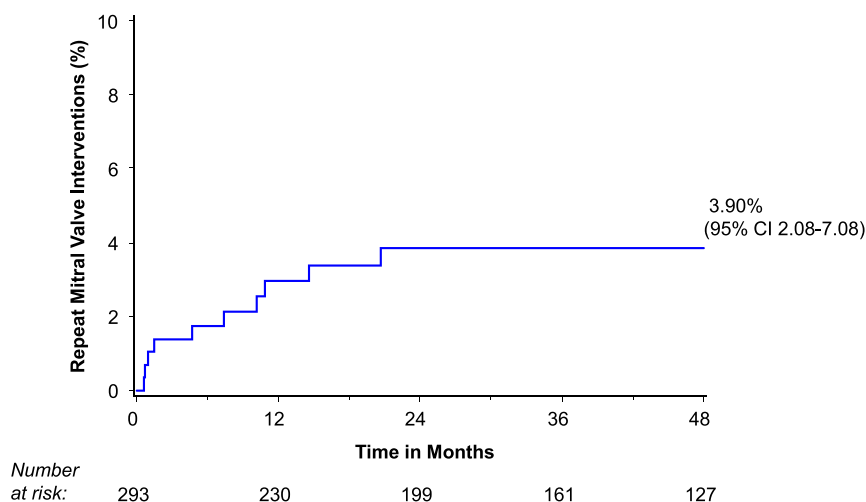


Figure 1. Cumulative incidence of repeat mitral valve interventions.

Table 4
Case summary of patients undergoing repeat mitral valve interventions

Case #	Index procedure			RMVI procedure						
	# of clips	MR severity at baseline	MR severity at discharge	Reason for RMVI	RMVI procedure	Days to RMVI	# of clips	Leaflets clipped	MR Severity Pre-procedure	MR Severity Post- Procedure
#1	1	Moderate to severe (3+)	Mild (1+)	No improvements of HF symptoms	MitraClip	442	1	A2-P2	Severe (4+)	Moderate (2+)
#2	0	Moderate to severe (3+)	Moderate to severe (3+)	Unsuccessful first procedure (difficult transseptal puncture)	MitraClip	17	2	A2-P2	Moderate to severe (3+)	Moderate (2+)
#3	1	Severe (4+)	Mild (1+)	Recurrent MR	MitraClip	309	2	A1-P1	Severe (4+)	Moderate to severe (3+)
#4	0	Moderate to severe (3+)	Moderate to severe (3+)	Tamponade	MitraClip	29	2	A2-P2	Moderate to severe (3+)	Moderate (2+)
#5	0	Moderate to severe (3+)	Moderate to severe (3+)	Unsuccessful first procedure (difficult transseptal puncture)	MitraClip	21	0	Unknown	Moderate to severe (3+)	Moderate to severe (3+)
#6	1	Severe (4+)	Mild (1+)	Worsening HF symptoms	MitraClip	223	2	Unknown	Moderate to severe (3+)	Mild or less ($\leq 1+$)
#7	1	Severe (4+)	Mild (1+)	Site-assessed mitral valve stenosis*	Mitral valve surgery	141	N/A	N/A	Mild (1+)	Mild or less ($\leq 1+$)
#8	2	Moderate to severe (3+)	Mild (1+)	Single leaflet device attachment	MitraClip	629	2	A2-P2	Moderate to severe (3+)	Mild or less ($\leq 1+$)
#9	2	Severe (4+)	Moderate to severe (3+)	Worsening of HF symptoms	MitraClip	329	1	A2-P2	Moderate to severe (3+)	Mild or less ($\leq 1+$)
#10	1	Severe (4+)	Mild (1+)	No improvement of HF symptoms	MitraClip	44	2	A2-P2	Severe (4+)	Mild or less ($\leq 1+$)

* Mitral valve area determined by echocardiographic core laboratory was 2.9 cm², larger than the pre-specified core laboratory criterion for mitral stenosis (<1.5 cm²).

HF = heart failure; MR = mitral regurgitation; RMVI = repeat mitral valve intervention.

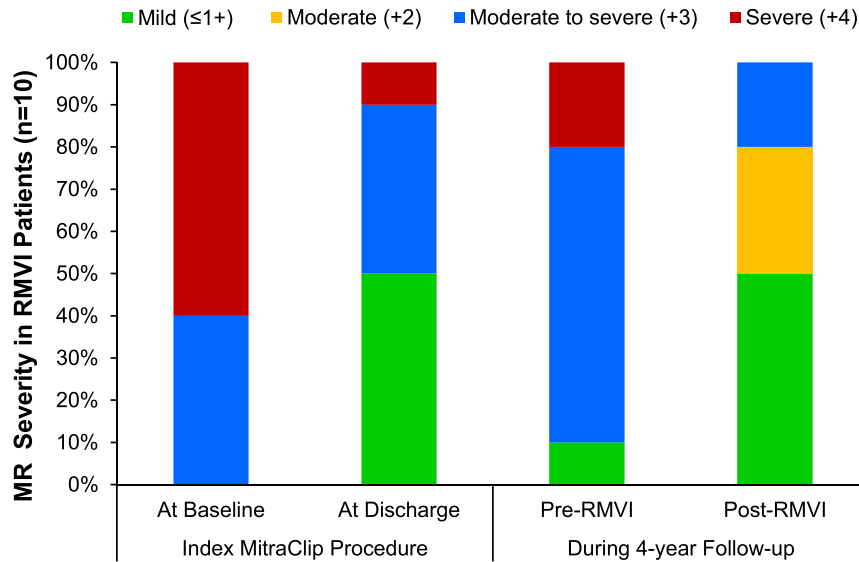


Figure 2. Changes in mitral regurgitation severity in patients who underwent repeat mitral valve interventions.

study from the COAPT trial are as follows: (1) Only 10 of 293 patients in whom a MitraClip procedure was initially attempted required RMVI within 4 years after the initial procedure (median time RMVI was 6 months, and all cases were within 2 years); (2) The most common reason for RMVI was residual MR with lack of improvement or recurrent MR with worsening of HF symptoms; (3) MR severity after RMVI was reduced in most cases; and (4) In patients who underwent RMVI, the annualized incidence rates of all HFH decreased after RMVI compared with before RMVI. However, both rates were higher than those observed in patients who did not undergo RMVI, and mortality within 4 years was not increased in this cohort.

The incidence of RMVI in the present study is comparable to that previously reported from several single-center MitraClip series.^{13–15} However, the 3.9% cumulative incidence rate of RMVI after 4 years in COAPT was lower than the incidence of severe residual or recurrent MR after TEER. In the 302 patients assigned to MitraClip in COAPT, 293 (97.0%) underwent a clip implant procedure, and one or more clips were implanted in 289 (98.0% of attempted procedures, 96% of all MitraClip group-assigned patients). In 260 patients with a predischARGE echocardiogram, 13

patients (5.0%) still had $\geq 3+$ MR. Thus, MR was reduced from $\geq 3+$ at baseline to $\leq 2+$ in $\sim 90\%$ of patients, similar to the rate seen in the Society of Thoracic Surgeons-American College of Cardiology Transcatheter Valve Therapy registry.¹⁶ In addition, by 30 days, 7.4% of MitraClip-assigned patients had $\geq 3+$ MR (9). Given the poor prognosis associated with severe residual MR after TEER (9), predicting those patients in whom TEER is likely to be unsuccessful either immediately after the index procedure or during follow-up might identify a group better served by alternative approaches.

Although the modest sample size precluded identifying independent predictors of RMVI, several baseline characteristics (beyond not initially reducing severe MR to $\leq 2+$) were associated with an increased risk of RMVI, including a larger anterior-posterior mitral annulus diameter and larger tenting areas. These anatomic factors may directly impair the ability of the TEER procedure to reduce MR or affect the durability of the implant by increasing strain on the TEER tissue bridge.^{17–19} Alternatively, greater mitral annular dilatation may be a marker of a more chronic or severe cardiomyopathy, with ongoing ventricular remodeling leading to progression of MR and a poor prognosis, even after TEER.

Table 5

Four-year rates of adverse outcomes in patients with and without RMVI

Outcomes	RMVI N = 10	No RMVI N = 283	Unadjusted HR (95% CI)	p Value
Death or hospitalization for heart failure	80.0% (8)	65.2% (182)	2.49 (1.22, 5.08)	0.009
Death, all-cause	34.4% (3)	48.5% (133)	0.64 (0.20, 2.01)	0.44
Cardiovascular death	34.4% (3)	40.9% (104)	0.82 (0.26, 2.59)	0.74
Non-cardiovascular death	0.0% (0)	12.9% (29)	-	0.31
Hospitalization for heart failure	80.0% (8)	53.1% (129)	3.53 (1.72, 7.25)	0.0002
All-cause hospitalization	100.0% (10)	84.4% (228)	3.01 (1.58, 5.73)	0.0006
Cardiovascular hospitalization	100.0% (10)	70.4% (179)	5.14 (2.67, 9.90)	<0.0001
Non-cardiovascular hospitalization	60.0% (5)	61.7% (152)	0.92 (0.38, 2.24)	0.85

Rates are Kaplan-Meier estimates and include time before and after RMVI, % (n).

CI = confidence interval; HR = hazard ratio; RMVI = repeat mitral valve intervention.

The RMVI procedure was successful (residual MR $\leq 2+$) in 8 of 10 cases. All 6 patients who had an initial successful TEER at the index procedure had also a successful RMVI, with 5 patients who underwent repeat TEER for residual MR and one having mitral valve surgery for site-assessed mitral stenosis. Of the 3 patients who had an unsuccessful initial TEER because of a failed transeptal puncture ($n = 2$) or tamponade ($n = 1$), 2 had a successful TEER. Only 1 of 10 patients underwent RMVI because of SLDA. In contrast, SLDA was the cause of $\sim 50\%$ RMVI procedures in previous single-center series.^{13–15} The low prevalence of SLDA in COAPT might be explained by improved patient selection and greater experience of the COAPT interventionalists and imaging specialists.

Mortality was not increased in patients who underwent RMVI in COAPT, but RMVI was associated with HFH both before and after the procedure. Clinical outcomes of patients who underwent RMVI in previous reports have been variable. With follow-up between 3 months and 1 year, mortality rates ranging between 10% and 62% and HFH rates ranging between 12% and 50% have been reported after RMVI.^{13–15}

This study has some limitations. Although these data were collected from a contemporary dataset that was closely monitored and in which all events were adjudicated, the number of patients with RMVI was small, and thus our findings on the predictors of RMVI, its durability and possible impact on mortality should be considered exploratory. In addition, changes in health status and exercise capacity were not routinely assessed pre-RMVI and post-RMVI. The present results also only apply to RMVI after MitraClip procedures in HF patients with secondary MR; whether similar results would be obtained with other TEER devices or other transcatheter MV repair or replacement systems or in patients with primary MR is unknown.

In conclusion, in patients who underwent TEER for severe secondary MR in the COAPT trial, the cumulative incidence rate of RMVI after 4 years was only 3.9%. Although the technical success rate of RMVI was favorable and long-term survival was not affected, patients with RMVI had higher rates of HFH both before and after the procedure compared with those without RMVI. Larger numbers of patients and longer-term follow-up are needed to assess the durability of and clinical outcomes after RMVI. The Society of Thoracic Surgeons-American College of Cardiology Transcatheter Valve Therapy Registry or other international registries may be well suited for this purpose.

Declaration of competing interest

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CRediT authorship contribution statement

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Ben-Yehuda: Writing – review & editing, Methodology, Conceptualization. **Saibal Kar:** Writing – review & editing, Methodology, Conceptualization. **D. Scott Lim:** Writing – review & editing, Methodology, Conceptualization. **John T. Saxon:** Writing – review & editing, Methodology, Conceptualization. **Zhipeng Zhou:** Methodology, Formal analysis, Data curation, Conceptualization. **Joann Lindenfeld:** Writing – review & editing, Methodology, Conceptualization. **William T. Abraham:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Michael J. Mack:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gregg W. Stone:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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