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Transcatheter Edge-to-Edge Repair for Atrial Secondary Mitral Regurgitation

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ABSTRACT

BACKGROUND Atrial secondary mitral regurgitation (ASMR) is a subtype of SMR that has a poor prognosis, and thus far, evidence of the therapeutic options for the management of ASMR is limited.

OBJECTIVES This study aimed to investigate the effectiveness of transcatheter edge-to-edge repair (TEER) for ASMR.

METHODS The study retrospectively analyzed consecutive patients who underwent MitraClip at the Heart Center Bonn. ASMR was defined as cases that met all of the following criteria: 1) normal mitral leaflets without organic disorder; 2) left ventricular ejection fraction >50%; and 3) absence of LV enlargement and segmental abnormality. The primary outcome measure was MR reduction to ≤1+, and its predictors were explored in a logistic regression analysis.

RESULTS Among 415 patients with SMR, 118 patients met the criteria for ASMR (mean age 80 ± 8 years, 39.8% male). The technical success rate was 94.1%, and MR reduction to ≤1+ after TEER was achieved in 94 (79.7%) patients with ASMR. The in-hospital mortality rate was 2.5%. In multivariable logistic analysis, a large left atrial volume index and low leaflet-to-annulus index were associated with a lower incidence of MR reduction to ≤1+ after TEER for ASMR. In addition, the use of a newer generation of the MitraClip systems (NTR/XTR or G4 systems) was associated with a higher incidence of MR reduction to ≤1+.

CONCLUSIONS TEER is a safe and feasible therapeutic option for patients with ASMR. Assessments of left atrial volume index and leaflet-to-annulus index may assist with patient selection for TEER in patients with ASMR. (J Am Coll Cardiol Intv 2022;15:1731–1740) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Secondary mitral regurgitation (SMR) is recognized as MR that occurs in structurally normal mitral valve leaflets without organic changes and has been traditionally attributed to underlying left ventricular (LV) remodeling or dysfunction.[1] Recently, there has been increasing recognition of another type of SMR that occurs in patients with normal LV size and function.[2,3] Several studies have revealed that left atrial (LA) enlargement and subsequent mitral annulus dilation can lead to the development of SMR in this setting. This subtype of SMR has been referred to as atrial SMR (ASMR), in contrast to traditional SMR resulting from LV remodeling or dysfunction (ventricular SMR [VSMR]). According to recent observational studies, ASMR is associated with excess mortality and more frequent hospitalization due to worsening heart failure compared with the general population.[4,5] The discrimination between these 2 etiologies and more tailored management of patients with ASMR are needed; however, there is currently no robust evidence of therapeutic strategies for ASMR.

Transcatheter edge-to-edge repair (TEER) is an emerging treatment option for symptomatic SMR.[6,7]

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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

AF = atrial fibrillation

ASMR = atrial secondary mitral regurgitation

LA = left atrium

LAI = leaflet-to-annulus index

LV = left ventricular

MR = mitral regurgitation

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

VSMR = ventricular secondary mitral regurgitation

The procedural result of TEER depends on the underlying mitral valve anatomy. According to previous reports, ASMR is typically characterized as SMR with enlarged LA and mitral annulus and flattened leaflets.[2,3] These anatomical features are different from VSMR and might therefore impact the procedural results of TEER. Nonetheless, the effectiveness and durability of TEER in patients with ASMR has not yet been well studied. In the present study, we assessed the procedural outcome of TEER with MitraClip systems (Abbott Structural Heart) for ASMR and investigated the anatomical predictors of optimal MR reduction by TEER in patients with ASMR.

SEE PAGE 1741

METHODS

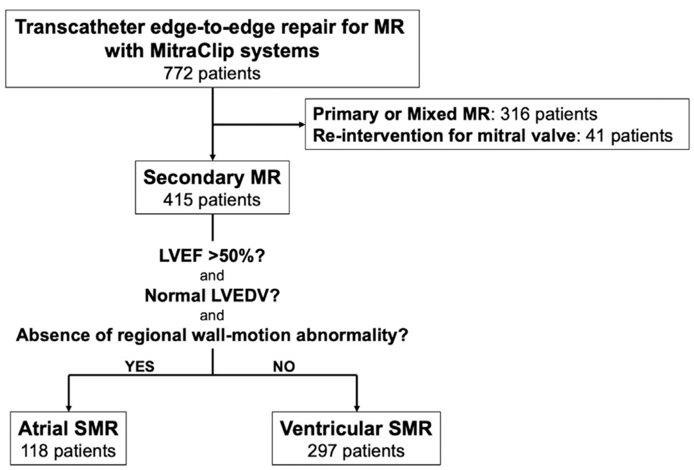
STUDY POPULATION. This study was designed as a retrospective analysis of data from the Bonn registry, which is a prospective, consecutive collection of patient data from the Heart Center Bonn. We identified consecutive patients with symptomatic MR who underwent TEER with the MitraClip system from September 2010 to September 2021. Patients with a prior history of surgical or transcatheter mitral valve interventions were excluded from this analysis. All included patients were deemed as ineligible or at high risk for conventional surgery. A standard diagnostic work-up was performed, including transthoracic and transesophageal echocardiography and left heart catheterization. The decision about the form of treatment for MR was determined by the interdisciplinary heart team at the Heart Center Bonn. The present study was approved by the institutional ethics committee and conducted in concordance with the Declaration of Helsinki. All participants in this study provided written informed consent.

The etiology of MR was evaluated based on the current guidelines and a previous study.[4] Before the procedure, the etiology of MR was prospectively classified into primary or secondary MR by experienced echocardiographers based on the current guideline. For the current analysis, patients with SMR were retrospectively divided into ASMR and VSMR with the following definition. ASMR was defined as cases that met all of the following criteria[4]: 1) normal mitral leaflets (ie, an absence of abnormal leaflet motion and organic changes); 2) normal LV systolic function (ie, LV ejection fraction >50%); and 3) absence of LV enlargement and segmental abnormality. According to the current guidelines, LV enlargement was defined as an LV end-diastolic volume >150 mL for men and >106 mL for women.[8] Patients lacking any one of the criteria were considered to have VSMR.

PROCEDURE. The procedures were performed under general anesthesia with 3-dimensional transesophageal echocardiographic and fluoroscopic guidance. This study included 4 generations of MitraClip systems: MitraClip, MitraClip NT, MitraClip NTR/XTR, and MitraClip G4. Details of the procedure have previously been well described.[9,10] The MitraClip NTR/XTR is available in 2 sizes of clips based on the different arm lengths: NTR and XTR.[9] The MitraClip G4 system is available in 4 sizes based on 2 different arm lengths and 2 different arm widths: NT, XT, NTW, and XTW.[10] Additionally, the MitraClip G4 enables independent grasping of the anterior and posterior mitral leaflets. The discretion was left up to the treating physicians as to whether multiple devices needed to be implanted.

ECHOCARDIOGRAPHIC ASSESSMENTS. All patients underwent transthoracic and transesophageal echocardiography before the MitraClip procedure. All echocardiographic assessments were performed according to current guidelines. The severity of MR was determined based on qualitative and quantitative criteria adapted from Mitral Valve Academic Research Consortium guidelines.[11] As quantitative parameters, effective regurgitant volume area and regurgitant volume were measured by proximal

FIGURE 1 Study Flowchart



LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; SMR = secondary mitral regurgitation.

isovelocity surface area method. MR was categorized as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). LA volume was assessed by the biplane area-length method at the apical 2- and 4-chamber views, and the LA volume index was calculated by dividing LA volume by body surface area. Mitral geometrical parameters were assessed using transesophageal echocardiography, such as coaptation depth and mobile posterior leaflet length. The leaflet-to-annulus index (LAI) of the mitral valve, an indicator of inadequate leaflet adaptation to mitral annulus dilatation, was evaluated as previously reported.[12] In brief, the LAI was defined as the ratio of the sum of anterior and posterior leaflet lengths in relation to the anteroposterior length of the mitral annulus in the A2-P2 segment: (anterior leaflet length + posterior leaflet length) / anteroposterior length of the mitral annulus. The measurement of the LAI was performed using the midesophageal long-axis view in a mid-systole phase. Inter- and intraobserver variabilities for the LAI measurement were evaluated in 20 cases analyzed by 2 examiners, and the results were assessed using Pearson's correlation coefficient. Echocardiographic assessments were also performed at 3 months and 1 year after TEER.

STUDY ENDPOINT. The primary endpoint was a reduction of MR to ≤1+ after TEER using echocardiographic assessments before discharge. Secondary endpoints were in-hospital mortality, technical success, and device success, according to the Mitral Valve Academic Research Consortium criteria.[13]

STATISTICS. Continuous variables are presented as mean ± SD or median (IQR) and were compared using *t*-tests or the Mann-Whitney test. Changes in continuous variables between baseline and postprocedure were analyzed using paired *t* tests or Wilcoxon signed rank tests. Proportions of categorical data were presented as numbers with percentages and compared using the chi-square test or Fisher exact test. Bowker's test was used to analyze changes in categorical variables between baseline and postprocedure. A logistic regression analysis was conducted to examine predictors of the reduction of MR to ≤1+. The OR and 95% CI for each covariate are provided. In a multivariable logistic regression analysis, we included the covariates that were significant ($P < 0.05$) upon the univariate analysis. The factors associated with the reduction of MR to ≤1+ were also examined in a subgroup of patients with moderate-to-severe or severe MR. Receiver-operating characteristic analysis was performed to determine the cutoff value of continuous variables to predict the reduction of MR to ≤1+. By using these cutoffs, we established a scoring system that predicted the MR reduction to ≤1+. As a sensitivity analysis, we explored the association between the device generation (ie, MitraClip, MitraClip NT, MitraClip NTR/XTR, and MitraClip G4) and the reduction of MR after TEER. Statistical significance was set as a 2-sided $P < 0.05$. All analyses were conducted using Stata/SE 15.1 (StataCorp).

TABLE 1 Baseline Patient Characteristics in ASMR and VSMR

	ASMR (n = 118)	VSMR (n = 297)	*P* Value
Age, y	80 ± 8	76 ± 8	<0.001
Male	47 (39.8)	193 (65.0)	<0.001
BMI, kg/m^2	26.5 ± 5.1	26.3 ± 5.0	0.942
Diabetes mellitus	34 (28.8)	88 (29.9)	0.822
Hypertension	89 (75.4)	223 (75.1)	0.957
CAD	66 (55.9)	191 (64.3)	0.100
Prior myocardial infarction	16 (13.6)	131 (44.1)	<0.001
Prior PCI	45 (38.1)	137 (46.1)	0.133
Prior CABG	21 (17.8)	86 (29.0)	0.020
Prior cardiac surgery	28 (23.7)	98 (33.0)	0.064
COPD	21 (17.8)	53 (17.8)	0.956
NYHA functional class			0.012
II	13 (11.0)	66 (22.5)	
III	85 (72.0)	172 (57.9)	
IV	20 (17.0)	59 (19.9)	
Atrial fibrillation	107 (90.7)	215 (73.1)	<0.001
Paroxysmal	31 (26.3)	84 (28.6)	0.638
Persistent or permanent	76 (64.4)	131 (44.6)	<0.001
CIED	27 (22.9)	162 (54.5)	<0.001
eGFR, mL/min/m^2	37.1 ± 14.3	34.6 ± 13.9	0.105
NT-proBNP, pg/mL	2,041 (1,324-4,073)	4,118 (2,082-8,492)	<0.001
EuroSCORE II, %	3.40 (2.01-4.92)	4.79 (2.91-8.11)	<0.001

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

ASMR = atrial secondary mitral regurgitation; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CIED = cardiac implantable electronic device; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; VSMR = ventricular secondary mitral regurgitation.

RESULTS

STUDY POPULATION. Among 415 patients with SMR who underwent TEER with the MitraClip system, 118 (28.4%) patients met the criteria for ASMR, while 297 (61.6%) patients were considered as having VSMR (Figure 1). The baseline clinical and echocardiographic characteristics are summarized in Tables 1 and 2. Patients with ASMR were older, were more frequently women, and had a higher prevalence of atrial fibrillation (AF) than those with VSMR. In patients with ASMR, the mean LV ejection fraction was 59.7% ± 6.3%; the median LA volume index was 53.1 mL/m^2

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SEPTEMBER 12, 2022:1731-1740

TABLE 2 Echocardiographic Findings in Patients With ASMR and VSMR

	ASMR (n = 118)	VSMR (n = 294)	*P* Value
LVEF, %	59.7 ± 6.3	37.0 ± 12.1	<0.001
LVEDV, mL	75 (58-97)	165 (123-210)	<0.001
LVESV, mL	30 (22-41)	101 (69-139)	<0.001
LA volume index, mL/m^2	63.9 (47.3-84.3)	51.7 (41.6-68.7)	<0.001
MR severity			0.047
2+	12 (10.2)	21 (7.1)	
3+	55 (46.6)	109 (36.7)	
4+	51 (43.2)	167 (56.2)	
EROA, mm^2	34.4 ± 9.4	34.6 ± 13.2	0.890
Regurgitant volume, mL	55.9 ± 18.3	56.1 ± 16.8	0.615
Mean transmitral gradient, mm Hg	1.4 (1.0-1.9)	1.5 (1.1-2.0)	0.100
Anteroposterior annulus diameter, mm	35.4 ± 5.1	33.8 ± 5.2	0.012
Anterior leaflet length, mm	27.1 ± 4.5	27.5 ± 6.9	0.634
Posterior leaflet length, mm	12.6 ± 3.2	12.2 ± 3.2	0.330
LAI	1.14 ± 0.15	1.17 ± 0.15	0.174
Mobile posterior leaflet length, mm	11.1 ± 2.6	12.8 ± 3.4	<0.001
<10 mm	39 (33.0)	60 (20.2)	0.005
Coaptation depth, mm	4.5 ± 1.6	8.3 ± 3.1	<0.001
>11 mm	1 (0.8)	51 (17.2)	<0.001
Coaptation length, mm	3.4 (2.4-4.4)	3.1 (1.7-4.2)	0.074
<2 mm	23 (19.5)	60 (20.2)	0.895
SPAP, mm Hg	42 ± 17	42 ± 14	0.865
TAPSE, mm	19 ± 5	17 ± 5	0.011
TR			<0.001
None/mild	23 (19.5)	93 (31.3)	
Moderate	38 (32.2)	125 (42.1)	
Severe or more	57 (48.3)	79 (26.6)	

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

EROA = effective regurgitant orifice area; LA = left atrium; LAI = leaflet-to-annulus index; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; other abbreviations as in Table 1.

(IQR: 43.3-68.5 mL/m^2). Patients with ASMR had a larger mitral annulus diameter, shorter mobile posterior leaflet length, and smaller coaptation depth compared with those with VSMR, while the LA volume index and LAI were comparable between the 2 groups. The intraobserver and interobserver reliabilities of the LAI measurement were acceptable (0.846 and 0.811, respectively).

PROCEDURAL FINDINGS AND PROCEDURAL OUTCOME. The procedural findings of TEER for ASMR are listed in Table 3. The median number of implanted clips per patient was 1 (IQR: 1-2), and technical success was achieved in 94.1%, with no statistical difference to VSMR (95.6%) (P = 0.519). The procedure was aborted without clip implantation in 7 (5.9%) patients with ASMR because of an increased transmitral pressure gradient after clip placement (n = 3), insufficient MR reduction despite adequate clip positioning (n = 3), and the inability to perform transseptal puncture in an appropriate height from the mitral valve annulus (n = 1). Single-leaflet device attachment occurred in 1 (0.8%) patient requiring reintervention before discharge. During the hospitalization, 3 (2.5%) patients died after the procedure due to gastrointestinal bleeding (n = 1) or sepsis (n = 2), while no cardiovascular deaths occurred.

The echocardiographic assessment before discharge showed that the severity of MR significantly improved compared with that at baseline in patients with ASMR (P < 0.001) (Figure 2A, Central Illustration). The median transmitral pressure gradient was 3.7 mm Hg (IQR: 2.8-4.8 mm Hg). The device success rate was 90.7%, and the reduction of MR to ≤1+ was achieved in 79.7% of patients with ASMR, which was comparable to those with VSMR (71.4%) (Figure 2B).

The MR reduction by TEER was sustained at 3 months and 1 year after TEER (n = 76 and n = 51, respectively) (Figure 2A, Supplemental Table 1). In addition, the LA volume index decreased at 3 months and 1 year after TEER compared with baseline (58.0 [IQR: 45.3-71.5] mL/m^2; P < 0.001, and 53.0 [IQR: 39.6-65.3] mL/m^2; P < 0.001, respectively), while LV ejection fraction and volumes were comparable between baseline and the follow-ups.

ECHOCARDIOGRAPHIC PREDICTORS OF OPTIMAL MR REDUCTION. In patients with ASMR, we evaluated the association of echocardiographic parameters with the reduction of MR to ≤1+ after TEER (Table 4). In the univariate logistic regression analysis, LA volume index, LAI, and short mobile posterior leaflet length (<10 mm) were associated with the reduction of MR to ≤1+. In the multivariable model, LA volume index (adjusted OR per 1-mL/m^2 increase: 0.98; 95% CI: 0.97-0.99) and LAI (adjusted OR per 0.1-increase: 1.98; 95% CI: 1.13-3.45) remained significant.

The generation of MitraClip systems (G4 or other generations) did not interact with the association of the LA volume index and LAI with the reduction of MR to ≤1+ (P for interaction = 0.409 and 0.991, respectively).

In the subgroup of patients with moderate-to-severe or severe MR, the reduction of MR to ≤1+ was achieved in 77.4%, and the LA volume index and LAI were also associated with the reduction of MR to ≤1+ (Supplemental Table 2).

Receiver-operating characteristic analysis showed that the values of LA volume index and LAI are needed to discern the incidence of the reduction of MR to ≤1+ were 85 mL/m^2 (C-statistic = 0.646; P = 0.007) and 1.10 (C-statistic = 0.709; P = 0.01),

TABLE 3 Procedural Findings in Patients With ASMR (N = 118)

Number of clips per patient	
0	7 (5.9)
1	61 (51.7)
2	44 (37.3)
3	6 (5.1)
Number of implanted clips per patient	1 (1-2)
Distribution of MitraClip generations	
MitraClip	25 (21.2)
MitraClip NT	32 (27.1)
MitraClip NTR/XTR	42 (35.6)
MitraClip G4	19 (16.1)
Number of clips per patient in each generation	
MitraClip	
0	1 (4.0)
1	12 (48.0)
2	10 (40.0)
3	2 (8.0)
MitraClip NT	
0	2 (6.3)
1	11 (34.4)
2	15 (46.9)
3	4 (12.5)
MitraClip NTR/XTR	
0	4 (9.5)
1	26 (61.9)
2	12 (28.6)
MitraClip G4	
1	12 (63.2)
2	7 (36.8)
Independent grasping[a]	10 (52.6)

Values are n (%) or median (IQR). [a]Independant grasping only possible with MitraClip G4.

respectively (Supplemental Figure 1). According to these cutoff values, 29 (24.6%) patients had a larger LA volume index (>85 mL/m²), and 45 (38.1%) had a lower LAI (<1.10).

By combining these 2 echocardiographic parameters, patients with ASMR could be stratified according to the incidence of the reduction of MR to ≤1+ (**Figure 3,** Supplemental Figure 2). If patients had none of these echocardiographic characteristics, the reduction of MR to ≤1+ was achieved in 90.7% (n = 54) of cases. With either a large LA volume index or a low LAI, the incidences of MR reduction to ≤1+ were 76.0% (n = 50). Notably, patients with both large LA volume index and low LAI had a low incidence of MR reduction to ≤1+ (41.7% [n = 12]).

DIFFERENCE IN THE REDUCTION OF MR BETWEEN THE MitraClip GENERATIONS. The distribution of MitraClip generations and the number of implanted clips per patient in each generation are summarized in **Table 3**. MitraClip NTR/XTR and G4 systems were used in 42 (35.6%) and 19 (16.1%) patients with ASMR, respectively. The number of implanted clips was likely to be less in the newer generation of MitraClip systems (ie, NTR/XTR or G4), in which all cases were treated with <3 clips. In particular, patients treated with MitraClip G4 experienced no implantation failure. Smaller clips (ie, NTR, NT, and NTW) were more frequently used than larger clips (ie, XTR, XT, and XTW), and NTW was the most frequently implanted device of the MitraClip G4 system (**Figure 4A**). The independent grasping feature was used in 10 (52.6%) of our 19 cases with the MitraClip G4 system. Postprocedural echocardiographic assessments showed that the reduction of MR to ≤1+ was more frequently achieved in patients treated with MitraClip NTR/XTR or G4 systems than those treated with the older generations (ie, MitraClip or MitraClip NT system) (**Figure 4B**). In a logistic regression analysis, the use of newer generations of MitraClip (ie, NTR/XTR or G4 systems) was independently associated with the reduction of MR to ≤1+ (adjusted OR: 4.65; 95% CI: 1.67-13.00).

DISCUSSION

The current study investigated the effectiveness of TEER with the MitraClip systems in patients with ASMR. The main findings can be summarized as follows.

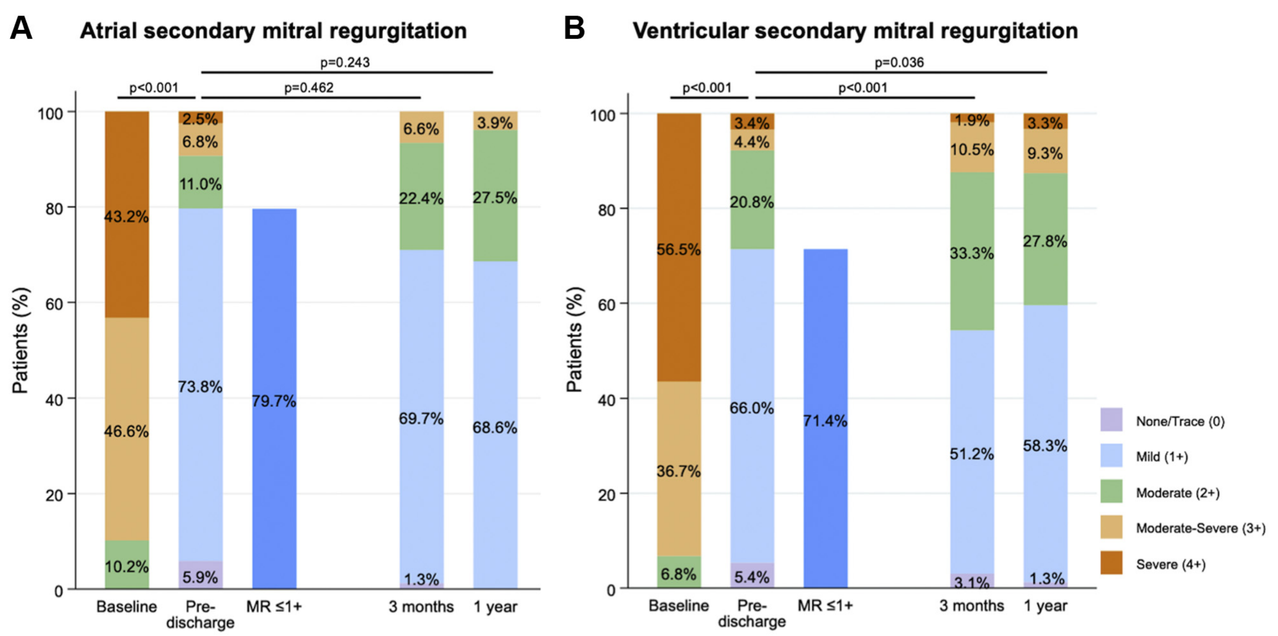
First, in our cohort, 28% of SMR patients were considered to have ASMR. Reduction of MR to ≤1+ by TEER with the MitraClip system was achieved in 79.7% of ASMR patients, which was comparable to that in VSMR patients.

Second, smaller LA volume index and higher LAI were associated with a higher incidence of MR reduction to ≤1+ after TEER in patients with ASMR. A combination of these echocardiographic characteristics could stratify patients with ASMR according to the incidence of MR reduction to ≤1+.

Third, the new generations of the MitraClip system (NTR/XTR and G4 systems) were associated with a greater MR reduction compared with the previous systems.

ASMR has been an increasingly recognized as a subtype of SMR, and its prognostic impacts have been revealed.[4] Despite the prognostic impact of ASMR, robust evidence about the therapeutic options for the management of ASMR is still limited. Recently, clinical and echocardiographic results of surgical repair for ASMR were reported[14,15];

FIGURE 2 Changes in the Severity of MR After Transcatheter Edge-to-Edge Repair



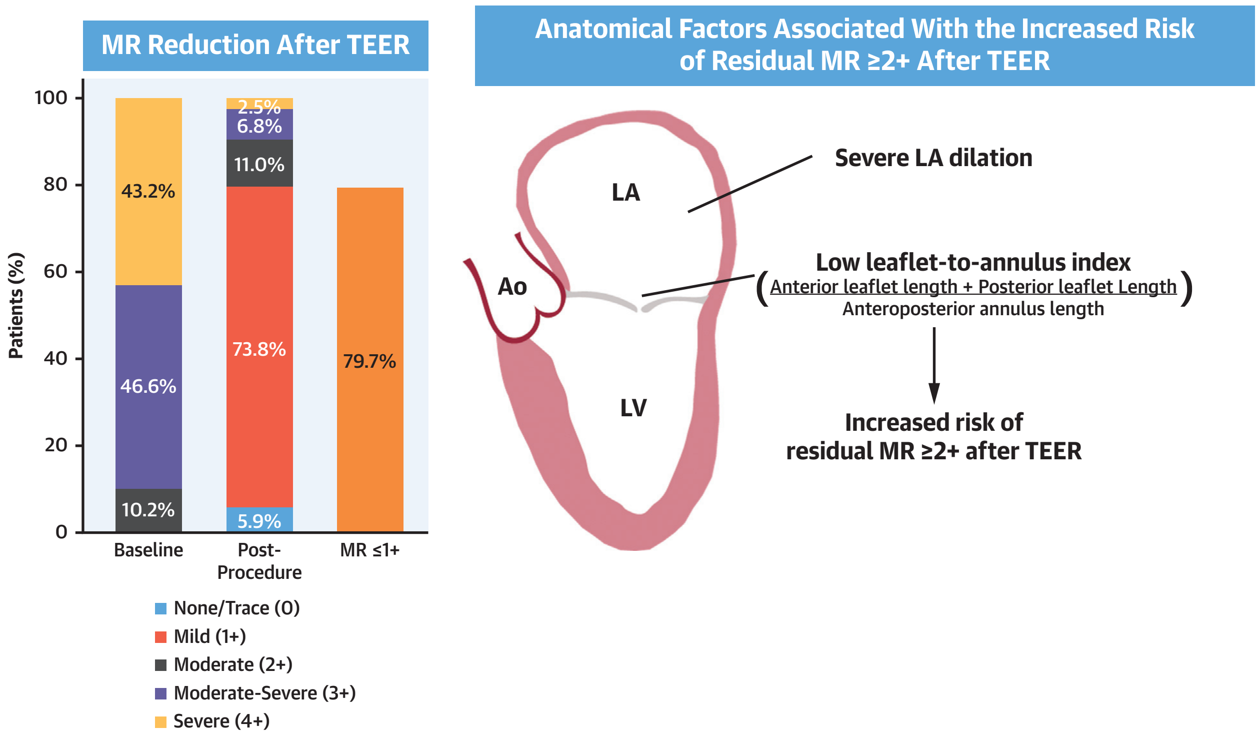
(A) In patients with atrial secondary mitral regurgitation (MR), the MR reduction persisted for 3 months and 1 year after the procedure (n = 76 and n = 51, respectively), while the MR grade was likely to increase after discharge **(B)** in patients with ventricular secondary MR (n = 163 and n = 151, respectively).

however, owing to the high burden of comorbidities, a large number of patients with ASMR have so far been conservatively treated.[4] Therefore, there is an increasing need for a less invasive therapeutic option for this population. To address this need, it is crucial to reveal the feasibility of TEER and the factors associated with procedural outcomes of TEER in patients with ASMR.

A non-neglectable proportion of patients with significant MR are considered to have ASMR; however, the prevalence of ASMR widely varies between previous reports. Among patients undergoing mitral valve interventions, the proportion of ASMR is 7.1% to 52.8%.[14-18] In the current study, we defined ASMR as SMR with normal LV ejection fraction and LV size and the absence of wall-motion abnormality, as previously reported.[4] According to this definition, approximately a quarter of the patients with SMR were considered to have ASMR, which may be relatively higher than those in previous studies of patients undergoing TEER.[16,19] Despite the different prevalence, the patient characteristics of ASMR were consistent with the previous studies: older, more frequently women, and a higher prevalence of AF, compared with VSMR. Therefore, the variation of the proportion of ASMR between the studies might be explained by the difference in the referral rate of ASMR for mitral valve interventions. Given that patients with ASMR are rarely referred for surgical interventions,[4] there might be still sizable patients with ASMR as potential candidates for TEER.

Among patients with ASMR, the reduction of MR to ≤1+ was achieved in 80%, and the MR reduction was consistent within 1 year after TEER. These findings may suggest that TEER is a feasible and effective therapeutic option for ASMR. Furthermore, we explored the anatomical features associated with the optimal MR reduction in patients with ASMR and found that a larger LA volume index and a lower LAI were associated with a lower incidence of the reduction of MR to ≤1+. These echocardiographic characteristics are linked to the mechanisms of ASMR.[3] A larger LA volume is assumed to indicate a more advanced stage of ASMR and to pose a challenging morphology for TEER. For instance, the LA enlargement displaces the posterior mitral annulus onto the crest of the LV inlet, which restricts the motion of the posterior leaflet and further results in leaflet tethering.[20] Also, a lower LAI may be related to

CENTRAL ILLUSTRATION TEER for Atrial Secondary MR Among 118 Patients Meeting Echocardiographic Criteria



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Changes in the severity of mitral regurgitation (MR) after transcatheter edge-to-edge repair (TEER) in patients with atrial secondary MR **(left)**. Severe left atrial (LA) dilation and low leaflet-to-annulus index were associated with an increased risk of residual MR ≥2+ after TEER **(right)**. Ao = aorta; LV = left ventricle.

insufficient leaflet remodeling or excess annulus dilation. The mismatch between leaflet remodeling and annulus dilatation (ie, smaller mitral leaflets in comparison to the annulus size) leads to an insufficient leaflet coaptation and the development of ASMR.[21] The shorter leaflets in relation to the mitral annulus may limit the approximation of leaflet coaptation by an edge-to-edge procedure.[22]

The combined assessment of the LA volume index and LAI stratified the risk of residual MR after TEER. In patients with a small LA volume index and a high LAI, MR reduction to ≤1+ was achieved in 91% of cases, while this incidence decreased to 42% in patients with a large LA volume index and a low LAI. Risk stratification based on these echocardiographic parameters could assist with the patient selection for TEER and refine the procedural results of TEER in patients with ASMR.

Recently, several transcatheter annuloplasty devices have been developed. For instance, the Carillon (Cardiac Dimensions) system is a coronary sinus-based annuloplasty device and has been shown to be effective for the reduction of MR and improvement of symptoms in patients with ASMR.[18] Given the underlying mechanism of ASMR, the annuloplasty technique may be ideal as a first choice to reduce MR in patients with severely dilated annulus and short leaflets. Furthermore, a combined strategy of annuloplasty and edge-to-edge repair might provide a more favorable procedural result. Further studies are needed to explore what are the most appropriate transcatheter therapeutic strategies for ASMR, including the device selection.

The MitraClip systems have developed gradually, which allow physicians to address the various anatomical settings of MR. In the third generation

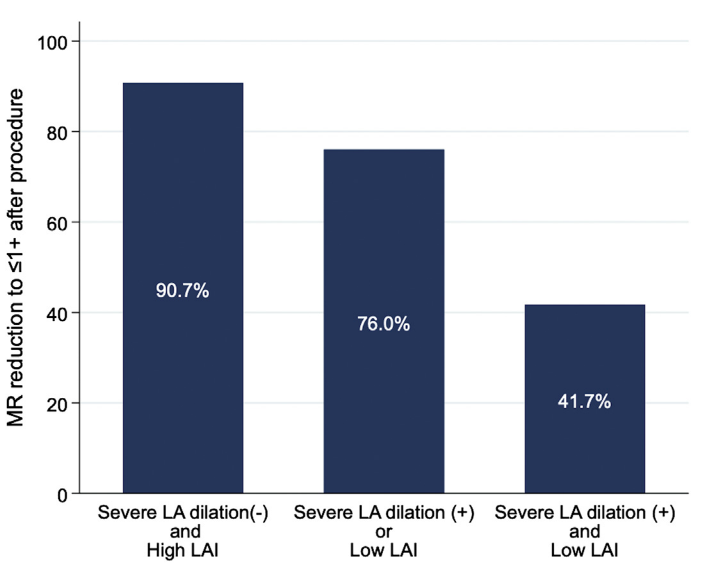
TABLE 4 Association of Echocardiographic Parameters With Postprocedural MR ≤1+ in Patients With ASMR

	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Preprocedural MR severity: 4+	0.42	0.17-1.04	0.060			
LA volume index per 1-mL/m^2 increase	0.98	0.97-0.99	0.009	0.98	0.97-0.99	0.015
Anteroposterior annulus diameter per 1-mm increase	0.96	0.88-1.05	0.393			
Anterior leaflet length per 1-mm increase	1.03	0.93-1.15	0.515			
Posterior leaflet length per 1-mm increase	1.10	0.95-1.27	0.211			
LAI per 0.1 increase	2.03	1.22-3.37	0.010	1.98	1.13-3.45	0.017
Mobile posterior leaflet length <10 mm	0.32	0.13-0.81	0.016	0.43	0.16-1.14	0.090
Coaptation length <2 mm	0.69	0.24-2.00	0.493			

Abbreviations as in Tables 1 and 2.

of the MitraClip (NTR/XTR system), 2 different sizes of clips were made available, and the delivery system was modified to improve navigation and clip positioning.[9] Furthermore, the newest generation of MitraClip (G4 system) offers 4 different clips that differ based on the clip width and arm length and the ability to independently grasp the anterior and posterior leaflets.[10] The variety of clips and improvement of the delivery system leads to a greater reduction in MR with the newer MitraClip systems.[9,10] We found that the use of the newer generations of MitraClips (NTR/XTR or G4) was associated with the optimal MR reduction in patients with ASMR, and the number of implanted clips was likely to be less in the newer generations. Notably, the independent grasping was used in more than half of the cases of MitraClip G4 system, which might imply that the independent grasping feature contributes to a greater reduction of ASMR. Thus, the new generations of the MitraClip system, which offer several size variations and an optimized independent grasping feature, may provide a more effective reduction in ASMR.

FIGURE 3 Incidence of the Reduction of MR to ≤1+ According to Echocardiographic Characteristics

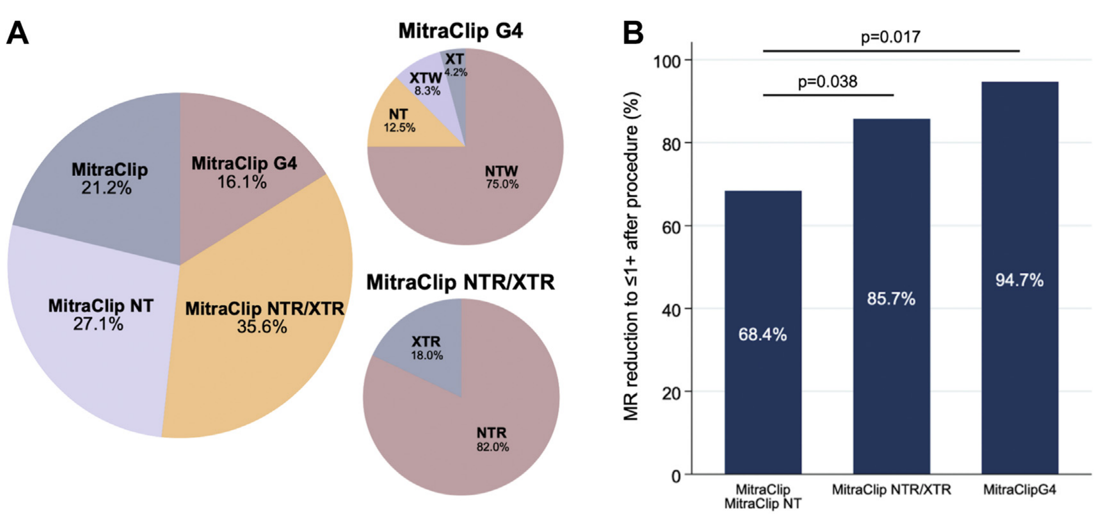


In patients with atrial secondary mitral regurgitation (MR), the combined assessment of left atrial (LA) dilation (cutoff of LA volume index: 85 mL/m^2) and leaflet-to-annulus index (LAI) (cutoff: 1.10) stratified the incidence of the MR reduction to ≤1+.

It still remains unclear whether the reduction of MR produced by TEER improves clinical outcomes in patients with ASMR. No previous studies have addressed the prognostic impact of MR reduction in patients with ASMR. In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, patients with a history of AF had larger LA volumes, smaller LV volumes, and larger mitral annuli than those without AF,[23] which corresponded to the features of ASMR. In this subgroup, TEER reduced adverse events compared with conservative therapy. These data may indicate that MR reduction by TEER can improve clinical outcomes in patients with ASMR, although the study population of the COAPT trial was composed of SMR patients with LV systolic dysfunction. Nevertheless, further clinical studies are needed to investigate the prognostic benefits of TEER in patients with ASMR.

STUDY LIMITATIONS. First, because this was a retrospective study from a single center, the present analyses might be subject to a selection bias of the study population. Nevertheless, this is the first study to explore the predictive factors of optimal MR reduction by TEER in patients with ASMR. Moreover, no previous study has shown the effectiveness of the newer MitraClip systems for ASMR, which are now mainly used devices in the clinical setting. Second, our assessment of the etiology of MR was not adjudicated by a core laboratory. Because the definition of ASMR has still not been established, we used a definition of ASMR that was shown in a previous study,[5] and conventional echocardiographic assessments, including the classification of primary or secondary MR and the assessments of the LV geometry and function, were

FIGURE 4 Different Incidence of the Reduction of MR to ≤1+ Between the Generations of MitraClip Systems



(A) The distribution of MitraClip generations and clip sizes. **(B)** Incidence of the reduction of mitral regurgitation (MR) according to the generations of MitraClip system.

performed based on the current guidelines. The clinical and echocardiographic characteristics of ASMR in the present study were comparable to those in the previous studies. Therefore, the selection bias owing to our classification may be limited. Third, we evaluated follow-up echocardiographic assessments at 3 months and 1 year after TEER, but the follow-up rate was relatively low. Therefore, further investigations are needed to validate our preliminary findings.

CONCLUSIONS

TEER with the MitraClip system achieved a high rate of MR reduction to ≤1+ in patients with ASMR, which was comparable to VSMR patients. Among the echocardiographic parameters, a large LA volume index and a low LAI were associated with insufficient MR reduction by TEER. Although our findings suggest that TEER with the MitraClip system is a safe and feasible approach in patients with ASMR, the risk score that we obtained might be useful to refine the device selection for transcatheter mitral valve treatment in this subgroup of SMR patients.

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PERSPECTIVES

WHAT IS KNOWN? ASMR is a subtype of SMR that has a poor prognosis.

WHAT IS NEW? TEER achieved a high rate of MR reduction to ≤1+ in patients with ASMR. Severe left atrial dilation and a low LAI were associated with a low incidence of the MR reduction to ≤1+ after TEER. Our findings highlight that TEER is a safe and feasible option for patients with ASMR and may refine device selection for transcatheter mitral valve treatments in this subgroup of SMR patients.

WHAT IS NEXT? A further investigation is needed to assess that the MR reduction by TEER can improve clinical outcomes in patients with ASMR.

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KEY WORDS atrial secondary mitral regurgitation, MitraClip, transcatheter edge-to-edge repair

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