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Clinical Outcomes With Transcatheter Edge-to-Edge Repair in Atrial Functional MR From the EXPAND Study

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ABSTRACT

BACKGROUND Although transcatheter edge-to-edge repair (TEER) has been shown to improve clinical outcomes and improve quality of life in patients with symptomatic secondary mitral regurgitation (SMR) and left ventricular dysfunction, its effect in patients with atrial SMR (aSMR) has not been well described.

OBJECTIVES The aim of this study was to assess the safety, echocardiographic outcomes, and clinical effectiveness of TEER for aSMR.

METHODS Patients with aSMR in the prospective, observational, multicenter EXPAND (A Contemporary, Prospective, Multi-Center Study Evaluating Real-World Experience of Performance and Safety for the Next Generation of MitraClip Devices) study were identified by an echocardiography core laboratory. Follow-up occurred at discharge, 30 days, and 1 year. Key endpoints included mitral regurgitation (MR) severity, functional class, heart failure hospitalizations, mortality, and 30-day major adverse events.

RESULTS Among 1,041 patients enrolled in EXPAND, 835 patients had evaluable echocardiograms at baseline. Of these, 53 patients had aSMR and 360 had ventricular SMR (vSMR). In the aSMR cohort, TEER resulted in a significant reduction in MR through 1 year (MR grade ≤2 in 100.0%), significantly increased 1-year Kansas City Cardiomyopathy Questionnaire score (+26.6 ± 30.5 points; $P < 0.0001$), and improved functional class from baseline, similar to the effects among patients with vSMR (MR grade ≤2 in 99.5% at 1 year, 1-year increase in Kansas City Cardiomyopathy Questionnaire score 21.23 ± 24.92 points). Major adverse events at 30 days and leaflet adverse events at 1 year were infrequent in both groups.

CONCLUSIONS In a prospective, real-world, global registry, TEER for aSMR was associated with significant MR reduction and improvement in quality of life and functional class, similar to patients with vSMR. This suggests that TEER may provide clinical benefit in patients with atrial fibrillation with SMR in the setting of heart failure with preserved ejection fraction. (The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices; NCT03502811)
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Atrial functional mitral regurgitation (MR), or atrial secondary mitral regurgitation (aSMR), is a type of secondary MR associated with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) in the setting of normal leaflet function. AF can lead to atrial interstitial fibrosis, left atrial (LA) stretch, and decreased LA compliance with increased LA pressures. This LA dilation and mitral annular dilation can cause compensatory leaflet growth and remodeling to a certain point

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

aSMR = atrial secondary mitral regurgitation

ECL = echocardiography core laboratory

HFpEF = heart failure with preserved ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

NYHA = New York Heart Association

TEER = transcatheter edge-to-edge repair

vSMR = ventricular secondary mitral regurgitation

beyond which it is inadequate, as well as atriogenic leaflet tethering. Furthermore, this pathophysiology impairs mitral annular dynamics because of abnormal annular contractility and motion during systole. Specifically, 3 things occur: inadequate anteroposterior contraction; smaller annular height and flattening of the saddle shape of the annulus, which leads to increased valve stress; and decreased translational motion between the left atrium and left ventricle. All of this culminates in mitral leaflet malcoaptation, leading to aSMR.[1,2]

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional MR) trial demonstrated that in patients with moderate to severe or severe symptomatic secondary MR despite maximally tolerated guideline-directed medical therapy, transcatheter edge-to-edge repair (TEER), combined with guideline-directed medical therapy, reduces heart failure hospitalizations and mortality and improves quality of life compared with guideline-directed medical therapy alone. However, the COAPT trial excluded patients with HFpEF, and therefore there is a paucity of data regarding the potential clinical benefit of TEER in patients with symptomatic aSMR.[3] To address this evidence gap, we evaluated the echocardiographic, procedural, and clinical outcomes of patients with aSMR in the global EXPAND (A Contemporary, Prospective, Multi-Center Study Evaluating Real-World Experience of Performance and Safety for the Next Generation of MitraClip Devices) study, a prospective, observational, multicenter echocardiography core laboratory (ECL)-adjudicated study of the clinical safety and effectiveness of the MitraClip NTR/XTR system (Abbott Vascular) in a "real-world" patient population.

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METHODS

The trial was approved by the institutional review committee at each site, and all subjects provided written informed consent and were eligible to receive the MitraClip per the currently approved indications for use in their respective geographies.

STUDY DESIGN. EXPAND was a prospective, multicenter, single-arm, international, postmarket study of patients undergoing commercial implantation of the MitraClip NTR/XTR system. A total of 1,041 consecutive subjects were enrolled at 57 sites in North America, Europe, and the Middle East. Study physicians at each site recorded clinical and demographic data on prespecified case report forms. Patients underwent TEER per local standard of care. Clinical and ECL-adjudicated follow-up occurred at baseline, discharge, 30 days, and 12 months. The primary endpoint was MR severity ≤2+ at 30-day follow-up. MR severity was assessed per American Society of Echocardiography guidelines, consistent with the methodology of prior MitraClip trials.[4] Other key outcome measures collected include 30-day and 1-year MR severity, New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, heart failure hospitalization, all-cause mortality, 30-day major adverse events, and 1-year leaflet adverse events. Major adverse events (all-cause mortality, myocardial infarction, stroke, and nonelective cardiovascular surgery because of device-related complications) through 30 days were adjudicated by a clinical adjudication committee. Acute device success was defined as the successful implantation of the MitraClip device without the occurrence of device-related complications through discharge. Acute procedural success was defined as successful implantation of the MitraClip device with a resulting MR severity of 2+ or less on discharge echocardiography. Adverse events through 1 year were site reported. An independent ECL (MedStar Health Research Institute) adjudicated echocardiographic outcomes, including MR etiology (primary [ie, degenerative]), secondary [ie, functional], or mixed), MR severity, baseline mitral valve anatomical characterization, and left ventricular (LV) dimensional measurements. An independent physician committee, which included the director of the ECL, reviewed and adjudicated single-leaflet device attachment and leaflet damage events.[5,6] All available data at the different time points were used for echocardiographic and quality-of-life outcomes.

DEFINITION OF aSMR. aSMR was defined as the presence of LV ejection fraction (LVEF) ≥45% with no regional wall motion abnormalities, no structural evidence of mitral valve morphologic abnormalities, and a history of AF with any 1 of the following echocardiographic parameters indicating LA or mitral annular enlargement: LA volume index >34 mL/m^2, LA diameter >4.0 cm in men or >3.8 cm in women, LA diameter index >2.3 cm/m^2, LA area index >10.4 cm^2/m^2 in men or >11 cm^2/m^2 in women, or mitral annular systolic anteroposterior diameter ≥35 mm. LA and mitral annular echocardiographic parameters were based on the 2015 American Society of

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Echocardiography chamber quantification guidelines.[7] The presence of any 1 criterion was sufficient for inclusion. This definition highlights the 3 key concepts of aSMR: 1) normal LV size and function; 2) abnormal LA size and function; and 3) lack of other reasons for MR (ie, Carpentier type 1).

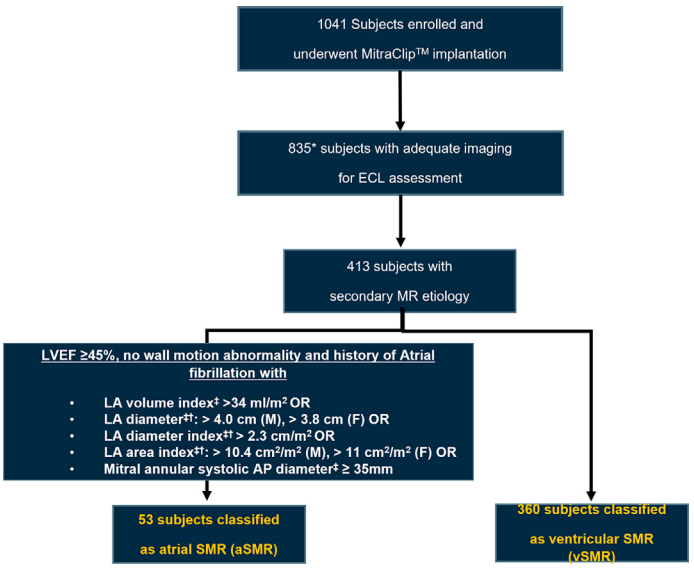
STATISTICAL ANALYSIS. Categorical variables are reported as count (percentage) and continuous variables as mean ± SD or median (IQR) as appropriate. Categorical variables were compared using the Fisher exact test, and the Bowker test was used for paired nominal data. Continuous variables were compared using Student's *t*-tests unless the data were not normally distributed, in which case the Wilcoxon rank sum test was used. Changes in MR severity, NYHA functional class, and KCCQ score from baseline to later intervals were assessed using an analysis of covariance, adjusting for baseline differences on paired data. All analyses were by intention-to-treat. A 2-sided *P* value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION. From April 5, 2018, through March 29, 2019, the EXPAND study enrolled 1,041 subjects, of whom 835 had adequate imaging for echocardiographic assessment. Of these, 413 (49.5%) had secondary MR etiology. A total of 53 patients were classified as having aSMR (12.8%) and 360 as having ventricular secondary mitral regurgitation (vSMR) (87.2%) (**Figure 1**). At 1-year follow-up, there were 34 patients with evaluable, paired echocardiograms in the aSMR cohort and 192 patients in the vSMR cohort. The median follow-up duration was 12.0 months (IQR: 11.0-12.8 months).

BASELINE CHARACTERISTICS. The baseline demographic, clinical, and echocardiographic characteristics of the study population are shown in **Table 1**. Patients with aSMR were older than those with vSMR (79.4 ± 6.9 years vs 74.7 ± 10.0 years; $P < 0.0001$), were more frequently women (61.1% vs 39.6%; $P = 0.0003$), and had a similar Society of Thoracic Surgeons Predicted Risk of Mortality for surgical mitral valve repair or replacement. Patients with aSMR had similar MR severity, significantly higher LVEFs, and significantly smaller LV dimensions. The mitral annular systolic anteroposterior diameter was smaller in patients with aSMR compared with those with vSMR (28.3 ± 4.4 mm vs 31.1 ± 4.0 mm; $P < 0.01$). Both groups had abnormal LA measurements, with patients with aSMR having numerically higher indexed metrics, such as LA volume index, although these did not reach statistical significance.

FIGURE 1 Study Population



117 subjects without baseline images from sites and 89 subjects not evaluable by ECL
Lang et al, ASE 2015 Chamber Quantification Guidelines, Cut-off value based on 1 SD above the population mean in Supplemental Table 9. AP = anteroposterior; ECL = echocardiography core laboratory; F = female; LA = left atrial; M = male; MR = mitral regurgitation; SMR = secondary mitral regurgitation.

ECHOCARDIOGRAPHIC OUTCOMES. TEER resulted in significant reductions in MR at 30 days and 1 year compared with baseline (**Central Illustration**) in both groups. Among those with aSMR, 97.9% of patients had ≤2+ MR and 89.4% had ≤1+ MR at 30 days of follow-up ($P < 0.0001$ compared with baseline). At 1 year, 100% of patients had ≤2+ MR, and 94.1% had ≤1+ MR ($P < 0.001$ compared with baseline). Among patients with vSMR, 98.6% had ≤2+ MR and 90.3% had ≤1+ MR at 30 days ($P < 0.0001$). At 1 year, 99.5% of patients had ≤2+ MR, and 92.8% of patients had ≤1+ MR ($P < 0.0001$). The degree of MR reduction after TEER did not differ significantly between the aSMR and vSMR groups at 30 days ($P = 0.53$) and 1 year ($P = 0.99$). Similar findings were observed among the patients with ECL-adjudicated 3+ or 4+ MR at baseline (Supplemental Figure 1).

PROCEDURAL OUTCOMES. The median procedure time was 80.0 minutes (IQR: 56.0-123.0 minutes) among patients with aSMR and 79.0 minutes (IQR: 55.0-108.5 minutes) among those with vSMR. A mean

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TABLE 1 Baseline Characteristics

	aSMR (n = 53)	vSMR (n = 360)	*P* Value
Age, y	79.4 ± 6.9 (53)	74.7 ± 10.0 (360)	<0.0001
Male	39.6 (21/53)	61.1 (220/360)	0.003
STS-PROM, MVR	9.3 ± 5.2 (37)	8.7 ± 7.8 (261/360)	0.57
STS-PROM, MV repair	6.8 ± 4.7 (39)	7.3 ± 7.7 (244)	0.60
Atrial fibrillation	100.0 (53)	77.0 (194/252)	<0.0001
Diabetes	26.4 (14/53)	29.9 (106/354)	0.60
Renal failure	39.6 (21/53)	48.2 (171/355)	0.24
COPD	17.0 (9/53)	19.8 (68/344)	0.71
Pacemaker implantation	23.1 (12/52)	20.4 (73/358)	0.65
NYHA functional class ≥III	84.9 (45/53)	82.8 (298/360)	0.70
KCCQ score	40.7 ± 25.6 (51)	44.1 ± 23.4 (338)	0.37
MR grade ≥3+	58.5 (31/53)	51.1 (182/356)	0.39
Severe TR	23.5 (12/51)	13.2 (44/334)	0.05
LV ejection fraction, %	60.06 ± 5.85 (53)	35.99 ± 11.23 (324)	<0.001
LVEDD, cm	5.3 ± 0.6 (52)	6.19 ± 0.92 (344)	<0.001
LVESD, cm	3.8 ± 0.6 (52)	5.17 ± 1.08 (341)	<0.001
LVEDV, mL	116.9 ± 41.2 (53)	191.70 ± 80.40 (324)	<0.001
LVESV, mL	46.6 ± 17.9 (53)	126.86 ± 67.66 (325)	<0.001
LA volume index, mL/m^2	70.2 ± 49.2 (49)	58.5 ± 30.1 (317)	0.11
LA diameter, cm			
Male	5.1 ± 1.2 (20)	5.2 ± 0.8 (189)	0.92
Female	4.7 ± 0.8 (30)	4.7 ± 0.8 (120)	0.76
LA diameter index, cm/m^2	2.8 ± 0.6 (50)	2.7 ± 0.5 (308)	0.38
LA area index, cm^2/m^2			
Male	18.7 ± 7.9 (19)	15.8 ± 4.6 (188)	0.14
Female	17.3 ± 6.5 (30)	15.9 ± 5.5 (129)	0.27
Mitral annular systolic anteroposterior diameter, mm	29.3 ± 4.4 (53)	31.1 ± 4.8 (342)	<0.01
Mitral annular calcification	7.5 (4/53)	9.4 (32/339)	0.80
Mitral leaflet calcification	1.9 (1/53)	3.9 (13/337)	0.70
Significant cleft/scallop	2.0 (1/51)	3.8 (13/338)	0.99
Significant secondary jet	5.7 (3/53)	5.0 (17/339)	0.74
Primary jet outside A2P2	3.8 (2/53)	3.8 (13/339)	0.99
Presence of a wide jet	9.4 (5/53)	11.5 (39/339)	0.66

Values are mean ± SD (n) or % (n/N).

aSMR = atrial secondary mitral regurgitation; COPD = chronic obstructive pulmonary disease; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MV = mitral valve; MVR = mitral valve replacement; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgery Predicted Risk of Mortality; TR = tricuspid regurgitation; vSMR =ventricular secondary mitral regurgitation.

of 1.4 ± 0.6 clips per case were used in the cohort of patients with aSMR. XTR clips were used alone in 30.8% (16 of 52), NTR clips alone in 55.8% (29 of 52), and a combination in 13.5% (7 of 52). In comparison, a mean of 1.5 ± 0.6 clips per case were used in patients with vSMR, with XTR clips alone in 42.7% (153 of 358), NTR clips alone in 42.5% (152 of 358), and a combination in 14.8% (53 of 358). The rate of device success in patients with aSMR was 94.3% (50 of 53) and in those with vSMR was 98.6% (355 of 360) ($P = 0.07$), and acute procedural success was 94.3% (50 of 53) vs 95.0% (341 of 359) ($P = 0.74$).

CLINICAL OUTCOMES. In patients with aSMR, clinical follow-up was available at 30 days in 53 of 53 (100%) and at 1 year in 46 of 53 (86.8%). Similarly, in patients with vSMR, clinical follow-up was available at 30 days in 336 of 360 (93.3%) and at 1 year in 311 of 360 (86.4%).

At 1 year, all-cause mortality was 14.1% in patients with aSMR, compared with 18.2% in those with vSMR ($P = 0.41$) (Central Illustration). Heart failure hospitalization occurred in 18.1% of patients with aSMR compared with 27.2% of those with vSMR at 1 year ($P = 0.16$) (Central Illustration).

TEER resulted in a marked improvement in quality-of-life measures (Central Illustration). The paired, adjusted KCCQ overall summary score improved at 1 year by 26.6 ± 30.5 points in the aSMR group ($P < 0.0001$) and by 21.23 ± 24.92 points in the vSMR group ($P < 0.0001$). There was no significant difference in the change in KCCQ overall score between the aSMR and vSMR groups at 1 year ($P = 0.96$). In the aSMR group, 52.8% of patients were alive, with a ≥5-point increase in KCCQ overall score at 1 year, compared with 42.8% of patients in the vSMR group ($P = 0.17$).

TEER resulted in a significant reduction in heart failure symptoms among patients with aSMR (Central Illustration). At baseline, 85% of patients were in NYHA functional class III or IV, compared with 23% at 30 days ($P < 0.001$) and 21% at 1 year ($P < 0.0001$). This was similar to the functional improvement in the vSMR group, in which 83% of patients were in NYHA functional class III or IV at baseline, compared with 21% of patients at 30 days ($P < 0.001$) and 19% at 1 year postprocedure ($P < 0.0001$).

Adjudicated 30-day major adverse events are listed in Table 2. All-cause death occurred in 2 patients (3.8%) with aSMR and in 9 patients (2.5%) with vSMR ($P = 0.64$). None of the patients with aSMR (0%) and 4 of the patients (1.1%) with vSMR required nonelective cardiovascular surgery for device-related complications. Overall, the rate of 30-day major adverse events was 3.8% in patients with aSMR and 3.6% in those with vSMR. At 1 year, single-leaflet device attachment had occurred in 1 patient with aSMR (1.9%) and 7 with vSMR (1.9%). No patient with aSMR (0%) and 2 with vSMR (0.6%) had leaflet injury.

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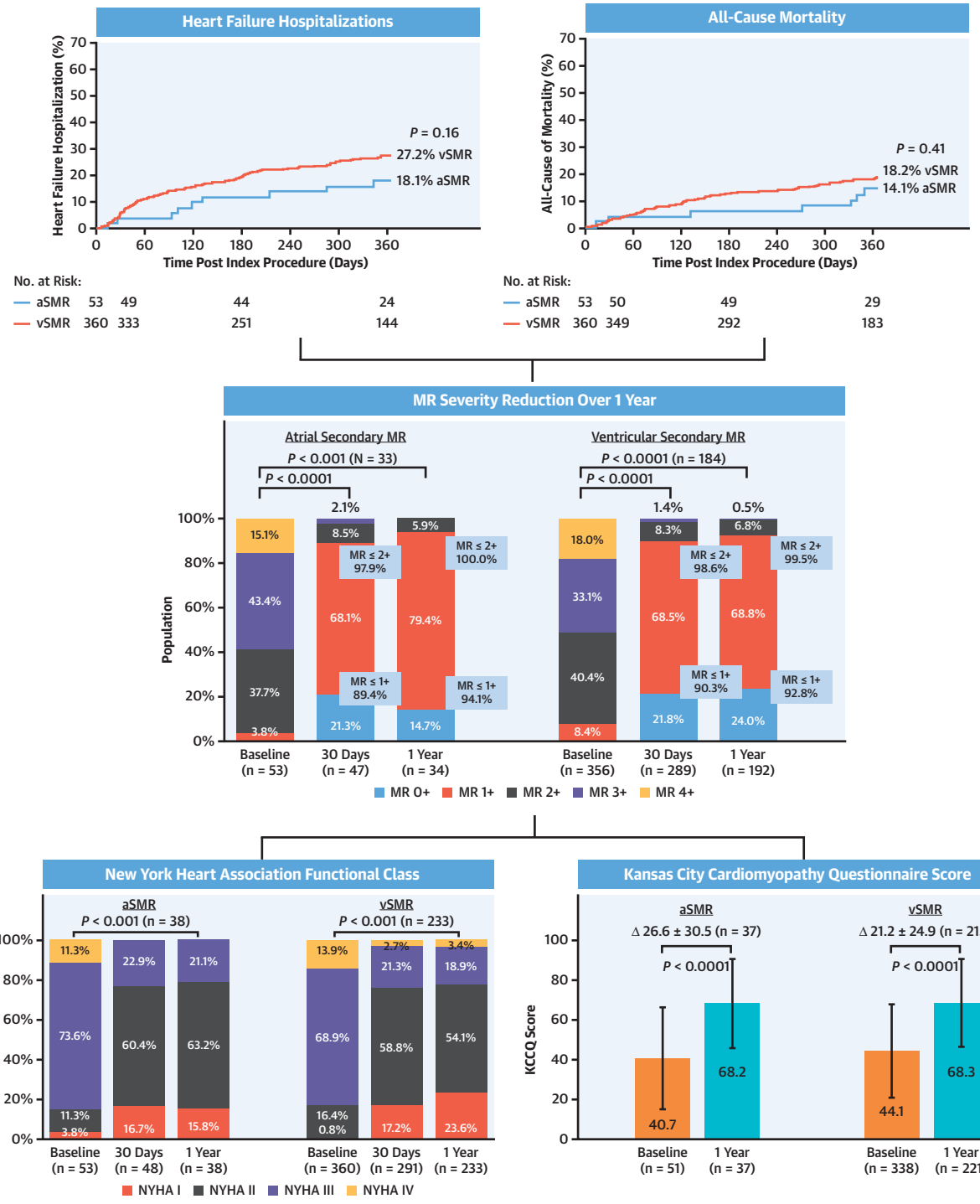
CENTRAL ILLUSTRATION **Clinical Outcomes in Subjects With Atrial vs Ventricular Secondary Mitral Regurgitation**



Sodhi N, et al. J Am Coll Cardiol Intv. 2022;15(17):1723–1730.

Mitral regurgitation severity before and after transcatheter edge-to-edge repair among patients with atrial (aSMR) and ventricular (vSMR) secondary mitral regurgitation (SMR) (*P* values reflect comparisons of paired data), heart failure hospitalization after transcatheter edge-to-edge repair among patients with atrial and ventricular SMR (*P* values reflect comparisons of paired data), all-cause mortality after transcatheter edge-to-edge repair among patients with atrial and ventricular SMR (*P* values reflect comparisons of paired data), New York Heart Association (NYHA) functional class before and after transcatheter edge-to-edge repair among patients with atrial and ventricular SMR (*P* values reflect a comparison of paired data), and change in quality of life after transcatheter edge-to-edge repair among patients with atrial and ventricular SMR (*P* values reflect comparisons of paired data). The Kansas City Cardiomyopathy Questionnaire score is represented as mean ± SD.

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TABLE 2 Adverse Events

	aSMR (n = 53)	vSMR (n = 360)	*P* Value
30-d major adverse events[a]	3.8 (2/53)	3.6 (13/359)	0.99
All-cause death	3.8 (2/53)	2.5 (9/359)	0.64
CV death	3.8 (2/53)	2.5 (9/359)	0.64
Stroke	0.0 (0/53)	0.3 (1/359)	0.99
Nonelective CV surgery for device-related complications	0.0 (0/53)	1.1 (4/359)	0.99
SLDA	0.0 (0/53)	0.3 (1/359)	0.99
Iatrogenic atrial septal defect requiring intervention	0.0 (0/53)	0.6 (2/359)	0.99
Need for mitral valve replacement instead of repair at least in part because of the MitraClip procedure or the presence of MitraClip device	0.0 (0/53)	1.1 (4/359)	0.99
Leaflet adverse event[b]			
SLDA	1.9 (1/53)	1.9 (7/360)	0.99
Leaflet injury	0.0 (0/53)	0.6 (2/360)	0.99

Values are % (n/N). [a]30-day major adverse events adjudicated by clinical events committee. [b]SLDA and leaflet injury adjudicated by an independent physician committee on the basis of procedural and follow-up images and clinical and surgical reports up to 1 year.

CV = cardiovascular; SLDA = single-leaflet device attachment; other abbreviations as in Table 1.

DISCUSSION

aSMR is an increasingly recognized entity with unique pathophysiology culminating from atrial dilation and annular remodeling that is associated with MR in the presence of normal LV function and AF.[1] The safety and efficacy of TEER in this population were not evaluated in the COAPT study and are not addressed in current society guidelines, which provide recommendations for TEER in patients with symptomatic, severe secondary MR in the presence of LV dysfunction and severe, primary MR in patients at high or prohibitive surgical risk.[7] We analyzed the prospective, global EXPAND study to determine the incidence, procedural results, and outcomes of TEER for aSMR in real-world clinical practice. We found that TEER led to a significant reduction in MR severity and improvements in functional class and quality-of-life measures similar to those among patients with vSMR. The rates of heart failure hospitalization and survival at 1 year and the rate of major adverse events at 30 days were also comparable. These findings suggest that TEER may be a therapeutic option for patients with clinically significant aSMR. In our cohort of patients undergoing commercial mitral TEER, a central ECL classified approximately 12% of secondary MR cases as atrial in nature. This prevalence is similar to the 14% reported in a consecutive series of patients undergoing transesophageal echocardiography[8] but is higher than the 4.5% and 7.5% of patients with secondary MR reported in Spanish and Italian registries of patients undergoing TEER for aSMR, respectively.[9,10] The difference in prevalence between our study and prior experiences may be due to the definitions of aSMR used and interobserver variability with respect to echocardiographic analysis. We used an independent ECL to classify the mechanism of MR using a consistent set of definitions on the basis of criteria established by the American Society of Echocardiography. Particularly in this area, where there is no consistent definition of aSMR, the use of an ECL is a distinguishing feature of this study not only to identify aSMR but also to quantify MR severity, rather than site-reported data or definitions that are not uniformly applied, which may result in inconsistent and less reliable data. aSMR appears to represent the MR mechanism of a significant fraction of patients undergoing TEER in current clinical practice. The proportion of patients presenting with symptomatic aSMR is likely to grow even further with the increasing incidence of AF and HFpEF.[1]

There is a paucity of prospective, adjudicated data regarding the safety and efficacy of TEER for the treatment of symptomatic aSMR. In the COAPT study, patients with AF had higher ejection fractions and LA volumes than those without AF, suggesting an atrial component to their secondary MR, and TEER had a similar treatment effect irrespective of the presence of AF.[11] However, that analysis does not address the role of TEER in patients with AF with normal ejection fractions and significant MR. In the EXPAND study, patients with aSMR had numerically larger indexes of atrial volume and significantly smaller LV dimensions than patients with vSMR, with a mean LVEF of 60%. Patients with aSMR and those with vSMR undergoing TEER had similar rates of device success and acute procedural success, and therefore any potential differences between the 2 MR mechanisms with respect to the extent of leaflet coaptation, tenting height, and leaflet tension did not appear to influence acute procedural outcomes. TEER for aSMR led to high rates of MR reduction (≤1+ in 89% and ≤2+ in 98% at 30 days), marked improvement in functional status (NYHA functional class III or IV from 84.9% to 22.9%), and a clinically large improvement in quality of life (mean KCCQ overall summary score increase of 27 points at 1 year), which were not statistically different from that observed among patients with vSMR. Our findings are consistent with those of 2 prior studies that also evaluated the outcomes of TEER for aSMR, which also demonstrated excellent MR reduction and reduced symptoms. Our global study expands upon those findings with prospectively collected case report forms, an ECL that applied the aSMR definition consistently across all patients and evaluated all

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echocardiograms at baseline and follow-up, a clinical events committee that adjudicated all clinical events, and an independent physician committee that adjudicated all potential single-leaflet device attachment and leaflet injury events. Furthermore, TEER was performed with the third-generation MitraClip device, which is more reflective of current technical approaches than the prior studies that predominantly included patients with earlier generation devices.

Our findings underscore the substantial morbidity and mortality associated with patients with symptomatic aSMR referred for intervention and the possible therapeutic utility of TEER. Patients with aSMR within the EXPAND study had similar baseline functional class and quality-of-life scores as patients with vSMR, and the rates of survival and heart failure hospitalization at 1 year were comparable. Although guideline-directed medical therapy and cardiac resynchronization therapy targeting the failing left ventricle improve outcomes in vSMR, therapies that provide clinical benefit for patients with HFpEF are lacking, other than sodium-glucose cotransporter-2 inhibition.[12] Furthermore, aSMR might also be successfully treated with arrhythmia control.[13] Our analysis supports the utility of TEER in patients with symptomatic HFpEF and aSMR on the basis of specific criteria (ie, the presence of AF, normal LV size and function, abnormal LA size and function, and normal leaflets).

STUDY LIMITATIONS. The definition of aSMR varies substantially across studies, and a particular definition will affect the observed prevalence, characteristics, and clinical outcomes of the identified patients. We based our definition upon the guidelines of the American Society of Echocardiography. As the COAPT trial enrolled patients with LVEFs $< 50\%$, there may be an overlap in patient characteristics between the present study and that trial, although the mean LVEF in COAPT was 31%, and only 4 of the 53 patients with aSMR in the present study had LVEFs between 45% and 50%. Baseline and paired echocardiograms were unavailable or uninterpretable in 19.8% of patients, which may have influenced the reported prevalence of aSMR and the rates of echocardiographic outcomes. This analysis was post hoc and not prespecified in the study protocol. The relatively small number of patients with aSMR limits the ability to detect statistically significant differences in clinical outcomes compared with vSMR. This study did not include a control group that did not undergo TEER, so this analysis cannot address the clinical benefit of TEER in aSMR compared with medical therapy alone for AF (eg, enhanced rate control or restoration of normal rhythm) or HFpEF; however, medical therapies for HFpEF are limited. Finally, the fourth-generation MitraClip system, which may improve MR reduction through wider clip arms and independent leaflet capture (controlled gripper actuation), was not used in this study. The safety and effectiveness of this system are currently being studied in the EXPAND G4 registry (NCT04177394).

CONCLUSIONS

In a prospective, real-world, global registry, TEER for aSMR was associated with high rates of MR reduction and significant improvement in quality of life and functional class. These effects appeared similar to those observed in patients with vSMR. This suggests that TEER may provide clinical benefit in patients with AF with SMR in the setting of HFpEF.

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PERSPECTIVES

WHAT IS KNOWN? There is a paucity of data regarding the potential clinical benefit of TEER in patients with symptomatic aSMR.

WHAT IS NEW? Using data from the real-world, prospective EXPAND registry, this study demonstrates that compared to patients with ventricular secondary MR, patients with aSMR had similar MR reduction, improvement in NYHA functional class and KCCQ score, and comparable heart failure hospitalizations and survival at 1 year.

WHAT IS NEXT? Future study on remodeling capacity after TEER in such patients is needed.

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KEY WORDS atrial secondary MR, mitral regurgitation, mitral valve repair

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

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