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Prospective Study of TMVR Using Balloon-Expandable Aortic Transcatheter Valves in MAC

MITRAL Trial 1-Year Outcomes

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate 1-year outcomes of valve-in-mitral annular calcification (ViMAC) in the MITRAL (Mitral Implantation of Transcatheter Valves) trial.

BACKGROUND The MITRAL trial is the first prospective study evaluating the feasibility of ViMAC using balloon-expandable aortic transcatheter heart valves.

METHODS A multicenter prospective study was conducted, enrolling high-risk surgical patients with severe mitral annular calcification and symptomatic severe mitral valve dysfunction at 13 U.S. sites.

RESULTS Between February 2015 and December 2017, 31 patients were enrolled (median age 74.5 years [interquartile range (IQR): 71.3 to 81.0 years], 71% women, median Society of Thoracic Surgeons score 6.3% [IQR: 5.0% to 8.8%], 87.1% in New York Heart Association functional class III or IV). Access was transatrial (48.4%), transseptal (48.4%), or transapical (3.2%). Technical success was 74.2%. Left ventricular outflow tract obstruction (LVOTO) with hemodynamic compromise occurred in 3 patients (transatrial, n = 1; transseptal, n = 1; transapical, n = 1). After LVOTO occurred in the first 2 patients, pre-emptive alcohol septal ablation was implemented to decrease risk in high-risk patients. No intra-procedural deaths or conversions to open heart surgery occurred during the index procedures. All-cause mortality at 30 days was 16.7% (transatrial, 21.4%; transseptal, 6.7%; transapical, 100% [n = 1]; p = 0.33) and at 1 year was 34.5% (transatrial, 38.5%; transseptal, 26.7%; p = 0.69). At 1-year follow-up, 83.3% of patients were in New York Heart Association functional class I or II, the median mean mitral valve gradient was 6.1 mm Hg (IQR: 5.6 to 7.1 mm Hg), and all patients had ≤1+ mitral regurgitation.

CONCLUSIONS At 1 year, ViMAC was associated with symptom improvement and stable transcatheter heart valve performance. Pre-emptive alcohol septal ablation may prevent transcatheter mitral valve replacement-induced LVOTO in patients at risk. Thirty-day mortality of patients treated via transseptal access was lower than predicted by the Society of Thoracic Surgeons score. Further studies are needed to evaluate safety and efficacy of ViMAC. (J Am Coll Cardiol Intv 2021;14:830–45)

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Patients with severe mitral annular calcification (MAC) are at high risk for conventional mitral valve (MV) surgery because they often have multiple comorbid conditions, and the calcium burden makes the procedure technically challenging, precluding a successful outcome for many (1-3).

Transcatheter MV replacement (TMVR) with the off-label use of aortic balloon-expandable transcatheter heart valves (THVs) has been used as an alternative to conventional MV surgery. Data on the early experience with these procedures were collected in 2 TMVR retrospective registries, which showed 25% to 35% all-cause mortality at 30 days and 54% to 63% at 1 year (4,5). In these registries, left ventricular outflow tract obstruction (LVOTO) with hemodynamic compromise occurred in 11% to 40% of patients and was associated with poor outcomes. Alcohol septal ablation was shown to reduce TMVR-induced left ventricular outflow tract (LVOT) gradient acutely and has been a lifesaving rescue option (6). Pre-emptive use of alcohol ablation as a strategy to decrease the risk for TMVR-induced LVOTO had not been used prospectively before the clinical trial we describe herein. The MAC arm of the MITRAL (Mitral Implantation of Transcatheter Valves) trial is a prospective single-arm study, which was designed to evaluate the safety and feasibility of TMVR with a balloon-expandable THV to treat patients with severe MAC at high surgical risk. This trial allowed the pre-emptive use of alcohol ablation to decrease the risk for TMVR-induced LVOTO in patients at risk. Herein, we present 30-day and 1-year outcomes of patients in the MAC arm of the MITRAL trial.

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METHODS

This study was conducted following ethical principles according to the Declaration of Helsinki as well as U.S. Food and Drug Administration guidelines (Code of Federal Regulations Title 21, Part 812, and Good Clinical Practices recommended by the International Organization for Standardization [ISO 14155:2011]). The study was approved by the Mayo Clinic Institutional Review Board and the respective Institutional Review Boards of the participating institutions. All patients provided written informed consent.

STUDY DESIGN AND PATIENTS. The MITRAL trial early feasibility study is a physician-initiated, prospective, multicenter clinical trial (IDE G140136; NCT02370511) designed to evaluate the safety and feasibility of TMVR using the SAPIEN XT and SAPIEN 3 valves (Edwards Lifesciences, Irvine, California). The study has 3 treatment arms: 1) native MV disease with MAC, treated with valve-in-MAC (ViMAC) (n = 31); 2) failing MV annuloplasty ring, treated with mitral valve-in-ring (n = 30); and 3) failed surgical bioprostheses, treated with mitral valve-in-valve (n = 30). We report the results of the MAC arm.

Patients at high surgical risk were considered eligible for the study if they had severe MAC with severe mitral stenosis (MS) or severe mitral regurgitation (MR) with at least moderate MS and symptoms of New York Heart Association functional class II or greater. Inclusion and exclusion criteria are listed in Supplemental Appendix 1. Clinical information and cardiac imaging for study candidates were presented in a live case-review conference call to an eligibility committee.

During the course of the study, we observed that a TMVR-induced LVOT gradient could recur the day after successful alcohol septal ablation was performed to treat acute LVOTO. The suspected mechanism for recurrence was septal edema. This finding led to the hypothesis that pre-emptive alcohol septal ablation to prevent LVOTO in patients at risk could be a better strategy if performed days or weeks before TMVR to avoid the acute phase, when septal edema may occur. After this observation was made, patients who were not accepted into the study because of high risk for LVOTO were given the option of pre-emptive septal ablation with case reconsideration after follow-up computed tomographic (CT) imaging 3 to 4 weeks after alcohol ablation. The outcomes of patients undergoing septal ablation outside the trial were not collected.

ABBREVIATIONS AND ACRONYMS

CT = computed tomographic
IQR = interquartile range
LAMPOON = intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction
LVOT = left ventricular outflow tract
LVOTO = left ventricular outflow tract obstruction
MAC = mitral annular calcification
MR = mitral regurgitation
MS = mitral stenosis
MV = mitral valve
THV = transcatheter heart valve
TMVR = transcatheter mitral valve replacement
ViMAC = valve-in-mitral annular calcification

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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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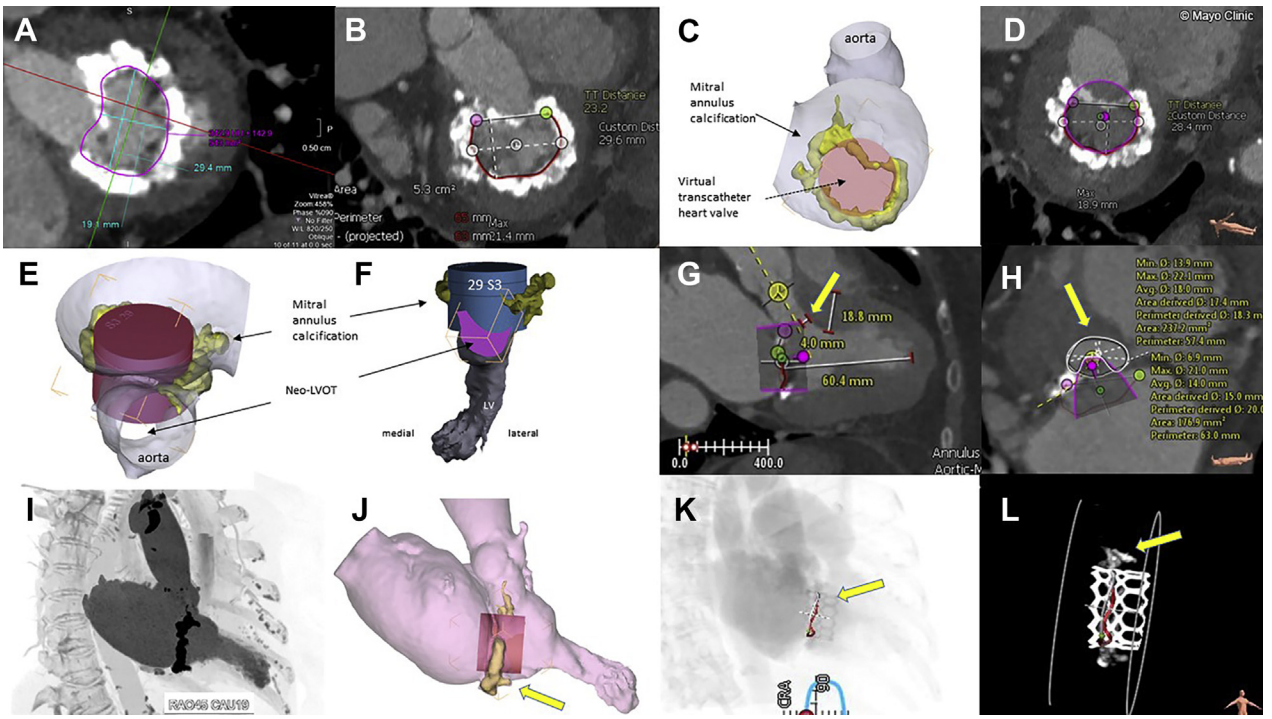
FIGURE 1 Cardiac Computed Tomographic Analysis



Measurements of a calcified mitral annulus, made with **(A)** Vitrea (Vital Images, Minnetonka, Minnesota, USA), and **(B)** 3mensio Structural Heart Workflow version 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). The mitral valve "neo-annulus" area measurement is shown from the surgeon's short-axis view during diastole (D-shape method). **(C-D)** A virtual THV is placed in the mitral annulus **(pink)**, size selected according to annulus area. **(E-F)** Neo-LVOT measurement using Mimics, Materialise, Leuven Belgium. **(G)** Virtual valve visualized in the LVOT long-axis view. The LVOT space is measured where the THV stent frame is closest to the septum **(arrow)**. **(H)** Neo-LVOT area measurement shown in short-axis view during systole. After placing the virtual valve **(pink)**, the remaining LVOT area is measured **(arrow)**. **(I)** Fluoroscopy simulation shows a coplanar view of the mitral annulus, used to determine the valve deployment angle during valve implantation. **(J)** A virtual valve is placed 80% ventricular and 20% atrial across the mitral annulus. Radiopaque landmarks such as calcium **(arrow)** are often used as surrogates to determine the landing zone of the ventricular edge of the THV stent during implantation. **(K,L)** Images after TMVR show the THV 80% ventricular and 20% atrial across the mitral annulus. CAU = caudal; CRA = cranial; RAO = right anterior oblique.

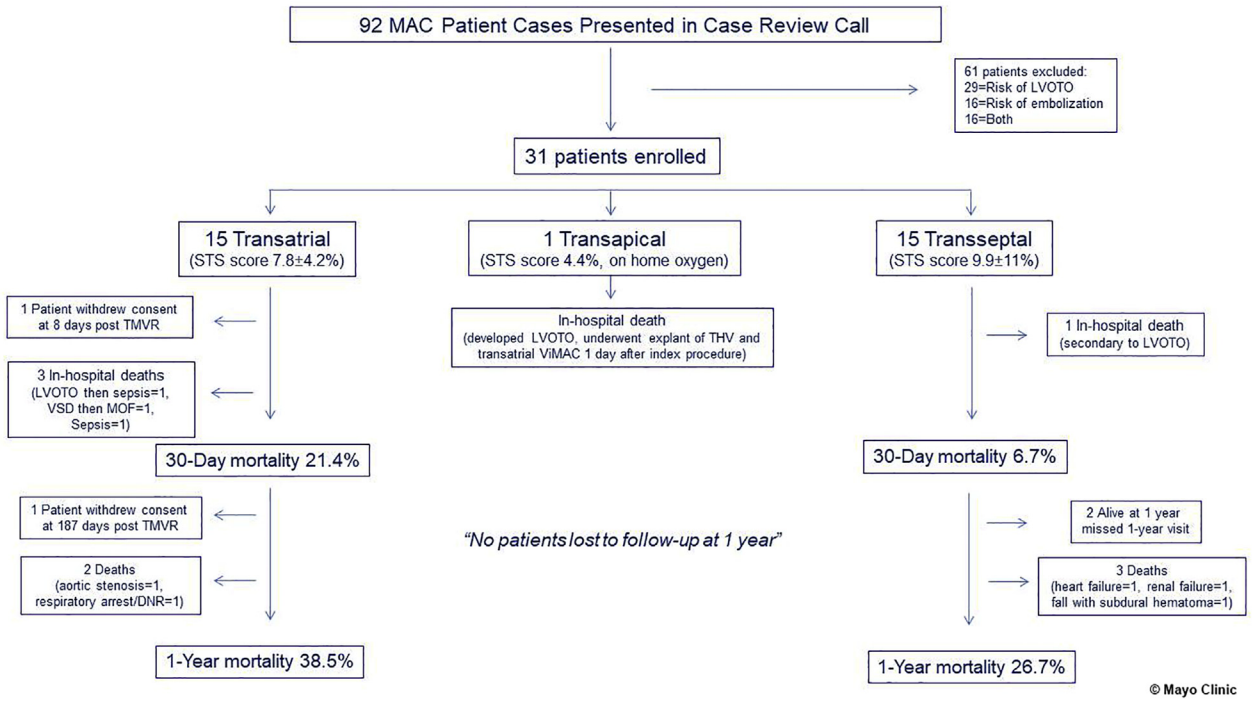
Baseline echocardiographic and CT studies were analyzed by independent core laboratories. Clinical events were adjudicated by an independent clinical events committee, and safety was monitored by a data and safety monitoring board (Supplemental Appendix 2).

PROCEDURES. Transthoracic and transesophageal echocardiography were performed according to published guidelines and analyzed at an independent core laboratory according to American Society of Echocardiography standards (7). The cardiac CT image acquisition protocol was similar to CT protocols for transcatheter aortic valve replacement (8), with adjustments for MV analysis (9), summarized in Supplemental Appendix 3 and illustrated in **Figure 1**. Transseptal, transapical, and open transatrial approaches were allowed. Access type was selected according to anatomy, with transseptal preferred for patients with favorable anatomy.

Details of the delivery access type selection and technique are provided in Supplemental Appendix 4.

OUTCOMES. The primary safety endpoint was technical success at exit from the catheterization laboratory or operating room, defined as successful delivery and retrieval of the transcatheter delivery system, deployment of a single valve in the correct position in the mitral annulus, adequate performance of the transcatheter valve including a mean MV gradient <10 mm Hg and residual MR <2+, no need for surgery or additional reintervention, and patient's departure from the procedure room alive. The primary performance endpoint was absence of MR grade

FIGURE 2 Patient Flowchart



DNR = do not resuscitate; MAC = mitral annular calcification; MOF = multiple organ failure; LVOTO = left ventricular outflow tract obstruction; STS = Society of Thoracic Surgeons; THV = transcatheter heart valve; TMVR = transcatheter mitral valve replacement; ViMAC = valve-in-mitral annular calcification; VSD = ventricular septal defect.

2+ or greater or mean MV gradient ≥10 mm Hg at 30 days and 1 year. Secondary safety endpoints included procedural success and all-cause mortality at 30 days and 1 year. Definitions and a complete list of secondary endpoints are provided in Supplemental Appendix 5.

STATISTICAL ANALYSIS. Continuous variables are summarized as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Only 1 patient was treated via transapical access. Therefore, we did not include this patient's data in the group comparison, which was between transseptal and transatrial cases. Comparisons between discrete groups were made using the Fisher exact test. Comparisons of continuous variables between groups were made using Kruskal-Wallis 1-way analysis of variance on ranks. For comparisons between time points, a Wilcoxon test was used. These comparisons included only patients with values at both time points. A Kaplan-Meier curve was generated for all-cause mortality, and treatment arms were compared using the log-rank test. All p values were 2-sided, and values <0.05 were considered to indicate statistical significance. All analyses were conducted using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between February 2015 and December 2017, 92 patients were screened and their cases presented at case-review conference calls for eligibility determination. Of these patients, 61 were excluded because of high risk for LVOTO (n = 29), embolization (n = 16), or both (n = 16). These patients were not treated with transatrial ViMAC, because they were not candidates for surgery or they refused surgery. Similarly, they were not treated with pre-emptive alcohol septal ablation, because of clinical or anatomic characteristics that made them not ideal candidates, or the local site preferred other options. A total of 31 patients were enrolled (**Figure 2**). Baseline clinical characteristics are described in **Table 1**. Briefly, the patients' median age was 74.5 years (IQR: 71.3 to 81.0 years), 71% were women, and they had multiple comorbid conditions, including 51.6% with prior aortic valve

TABLE 1 Baseline Patient Characteristics

	Total Patients* (N = 31)	Transatrial Access (n = 15)	Transseptal Access (n = 15)	p Value†
Age (yrs)	74.5 (71.3–81.0)	78.0 (73.5–81.5)	72.0 (68.5–79.5)	0.22
Female	22/31 (71.0)	12/15 (80.0)	9/15 (60.0)	0.43
Diabetes	12/31 (38.7)	7/15 (46.7)	5/15 (33.3)	0.71
Atrial fibrillation	13/31 (41.9)	7/15 (46.7)	6/15 (40.0)	1.00
Chronic kidney disease	9/31 (29.0)	3/15 (20.0)	6/15 (40.0)	0.43
Chronic obstructive pulmonary disease	15/31 (48.4)	6/15 (40.0)	8/15 (53.3)	0.72
Home oxygen therapy	7/31 (22.6)	2/15 (13.3)	4/15 (26.7)	0.65
Receiving long-term anticoagulation	9/31 (29.0)	2/15 (13.3)	7/15 (46.7)	0.11
Hospitalization for heart failure during prior 12 months	14/31 (45.2)	8/15 (53.3)	6/15 (40.0)	0.72
Prior stroke	4/31 (12.9)	3/15 (20.0)	1/15 (6.7)	0.60
Prior CABG	12/31 (38.7)	6/15 (40.0)	6/15 (40.0)	1.00
Prior AVR	16/31 (51.6)	8/15 (53.3)	8/15 (53.3)	1.00
TAVR	3/16 (18.8)	2/8 (25.0)	1/8 (12.5)	1.00
SAVR	13/16 (81.3)	6/8 (75.0)	7/8 (87.5)	1.00
Prior MV balloon valvuloplasty	4/31 (12.9)	1/15 (6.7)	3/15 (20.0)	0.60
STS score for MVR	6.3 (5.0–8.8)	6.4 (5.4–8.8)	6.2 (4.8–8.7)	0.82
NYHA functional class				0.01
I	0/31 (0.0)	0/15 (0.0)	0/15 (0.0)	
II	4/31 (12.9)	4/15 (26.7)	0/15 (0.0)	
III	22/31 (71.0)	11/15 (73.3)	11/15 (73.3)	
IV	5/31 (16.1)	0/15 (0.0)	4/15 (26.7)	

Values are median (interquartile range) or n/N (%). *Includes 1 transapical case not shown in transatrial or transseptal column. †Transatrial versus transseptal.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MV = mitral valve; MVR = mitral valve replacement; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

TABLE 2 Baseline Echocardiographic Characteristics

	All Patients* (N = 31)	Transatrial Access (n = 15)	Transseptal Access (n = 15)	p Value†
Ejection fraction (%)	63.1 (55.1–66.9)	64.8 (57.6–67.1)	61.3 (52.6–66.4)	0.66
Stroke volume (ml)	59.5 (49.2–80.5)	76.1 (54.9–86.8)	55.0 (48.9–70.7)	0.16
Cardiac output (l/min)	4.6 (3.7–6.2)	4.7 (4.2–6.7)	4.2 (3.7–6.0)	0.46
Mean MVG (mm Hg)	10.0 (7.6–12.8)	8.1 (7.3–11.8)	11.1 (8.2–13.9)	0.17
MVA (cm^2)‡	2.3 (1.8–2.9)	2.4 (1.7–3.2)	2.1 (1.8–2.5)	0.55
Pulmonary artery systolic pressure (mm Hg)§	53.1 (45.0–66.0)	53.5 (51.9–72.2)	49.7 (44.7–56.2)	0.31
Peak LVOT gradient (mm Hg)	4.5 (3.1–6.9)	5.5 (2.8–7.9)	4.4 (3.6–6.8)	0.76
Mean LVOT gradient (mm Hg)	2.7 (1.7–3.9)	2.9 (1.5–4.2)	2.4 (2.0–3.7)	0.97
Mitral valve pathology				0.10
Stenosis (1 transapical)	23/31 (74.2)	9/15 (60.0)	13/15 (86.7)	
Regurgitation	3/31 (9.7)	3/15 (20.0)	0/15 (0.0)	
Both stenosis and regurgitation	5/31 (16.1)	3/15 (20.0)	2/15 (13.3)	
Severity of mitral regurgitation				0.02
None or trace (1 transapical)	6/31 (19.4)	2/15 (13.3)	3/15 (20.0)	
1 (+)	11/31 (35.5)	2/15 (13.3)	9/15 (60.0)	
2 (+)	4/31 (12.9)	3/15 (20.0)	1/15 (6.7)	
3 (+)	8/31 (25.8)	7/15 (46.7)	1/15 (6.7)	
4 (+)	2/31 (6.4)	1/15 (6.7)	1/15 (6.7)	

Values are median (interquartile range) or n/N (%). *Includes 1 transapical case not shown in the transatrial or transseptal column. †Transatrial versus transseptal. ‡Uncertain reliability; echocardiographic methods validated in rheumatic disease and not mitral annular calcification. §7 missing values.

LVOT = left ventricular outflow tract; MVA = mitral valve area; MVG = mitral valve gradient.

TABLE 3 Intraprocedural Results

	All Patients* (N = 31)	Transatrial Access (n = 15)	Transseptal Access (n = 15)	p Value†
Device				1.00
SAPIEN XT (1 transapical)	2/31 (6.5)	0/15 (0.0)	1/15 (6.7)	
SAPIEN 3	29/31 (93.5)	15/15 (100.0)	14/15 (93.3)	
Device size				0.39
23 mm	3/31 (9.7)	2/15 (13.3)	1/15 (6.7)	
26 mm (1 transapical)	9/31 (29.0)	2/15 (13.3)	6/15 (40.0)	
29 mm	19/31 (61.3)	11/15 (73.3)	8/15 (53.3)	
Access				NA
Transapical	1/31 (3.2)	0/15 (0.0)	0/15 (0.0)	
Direct open transatrial	15/31 (48.4)	15/31 (48.4)	0/15 (0.0)	
Transseptal	15/31 (48.4)	0/15 (0.0)	15/31 (48.4)	
Traditional (wire free in left ventricle)	14/15 (93.3)	0/15 (0.0)	14/15 (93.3)	
Modified (wire externalized through percutaneous sheath in left ventricle)	1/15 (6.7)	0/15 (0.0)	1/15 (6.7)	
Pre-dilation or balloon sizing	6/31 (19.4)	2/15 (13.3)	4/15 (26.7)	0.65
Additional contrast during initial deployment				1.00
No	14/31 (45.2)	7/15 (46.7)	7/15 (46.7)	
Yes (1 transapical)	17/31 (54.8)	8/15 (53.3)	8/15 (53.3)	
Additional contrast volume, ml	3.0 (0.0–4.0)	3.0 (0.0–4.0)	4.0 (2.0–6.0)	0.07
Post-dilation (none in transapical)	10/31 (32.3)	2/15 (13.3)	8/15 (53.3)	0.05
Septostomy closed in transseptal cases during index procedure‡	3/15 (20.0)	0/15 (0.0)	3/15 (20.0)	1.00
Results				
In-hospital mortality (1 transapical)	5/31 (16.1)	3/15 (20.0)	1/15 (6.7)	0.60
Cardiovascular (1 transapical)	4/31 (12.9)	2/15 (13.3)	1/15 (6.7)	1.00
Noncardiovascular	1/31 (3.2)	1/15 (6.7)	0/15 (0.0)	1.00
Technical success at exit from catheterization lab	23/31 (74.2)	11/15 (73.3)	12/15 (80.0)	1.00
LVOTO with hemodynamic compromise	3/31 (9.7)	1/15 (6.7)	1/15 (6.7)	1.00
Need for a second valve§	1/31 (3.2)	0/15 (0.0)	1/15 (6.7)	1.00
≥2 (+) residual MR (1 transapical)	4/31 (12.9)	2/15 (13.3)	1/15 (6.7)	1.00
LV perforation	1/31 (3.2)	1/15 (6.7)	0/15 (0.0)	1.00
Pericardial effusion requiring pericardiocentesis	1/31 (3.2)	0/15 (0.0)	1/15 (6.7)	1.00
Ventricular septal defect (myectomy in transatrial TMVR)	1/31 (3.2)	1/15 (6.7)	0/15 (0.0)	1.00
New pacemaker requirement (1 transapical)	5/31 (16.7)	2/15 (13.3)	2/15 (13.3)	1.00
Valve embolization	0/31 (0.0)	0/15 (0.0)	0/15 (0.0)	NA
Conversion to open heart surgery	0/31 (0.0)	0/15 (0.0)	0/15 (0.0)	NA
Paravalvular leak closure	0/31 (0.0)	0/15 (0.0)	0/15 (0.0)	NA
Myocardial infarction requiring intervention	0/31 (0.0)	0/15 (0.0)	0/15 (0.0)	NA
Major vascular complications (1 transapical)	1/31 (3.2)	0/15 (0.0)	0/15 (0.0)	NA
Echocardiographic characteristics post-TMVR				
Mean MVG (mm Hg)	2.8 (2.1–3.8)	2.8 (2.1–3.9)	2.7 (2.2–3.5)	0.61
MVA (cm^2)	3.2 (2.7–3.4)	2.7 (2.6–3.5)	3.2 (3.0–3.4)	0.21
Peak LVOT gradient (mm Hg)‡	6.3 (4.2–8.8)	6.5 (4.8–10.9)	6.3 (4.2–7.0)	0.50
Mean LVOT gradient (mm Hg)‖	3.5 (2.1–4.5)	3.0 (2.3–4.8)	3.6 (1.9–3.7)	0.82
Residual total MR				1.00
Trace or none	10/31 (32.3)	5/15 (33.3)	5/15 (33.3)	
1 (+)	17/31 (54.8)	8/15 (53.3)	9/15 (60.0)	
2 (+)	3/31 (9.7)	2/15 (13.3)	1/15 (6.7)	
≥3 (+) (1 transapical)	1/31 (3.2)	0/15 (0.0)	0/15 (0.0)	
Amount of paravalvular MR				0.89
Trace or none	14/31 (45.2)	8/15 (53.3)	6/15 (40.0)	
1 (+)	14/31 (45.2)	6/15 (40.0)	8/15 (53.3)	
2 (+)	2/31 (6.5)	1/15 (6.7)	1/15 (6.7)	
≥3 (+) (1 transapical)	1/31 (3.2)	0/15 (0.0)	0/15 (0.0)	

Values are n/N (%) or median (interquartile range). *Includes 1 transapical case not shown in transatrial or transseptal column. †Transatrial vs. transseptal. ‡1 for hypoxemia due to a right-to-left shunt and 2 for significant left-to-right shunts at the discretion of the operator. All Amplatzer Septal Occluder device. §Due to excessive atrial positioning causing mitral regurgitation. ‖10 missing values.

LV = left ventricular; LVOTO = left ventricular outflow tract obstruction; MR = mitral regurgitation; NA = not applicable; TMVR = transcatheter mitral valve replacement; other abbreviations as in Tables 1 and 2.

TABLE 4 Baseline Echocardiographic Characteristics of Patients Treated With Transseptal Access After Implementing Preemptive ASA (n = 14)

	Trans-septal		
	No ASA (n = 7)	ASA (n = 7)	p Value
Ejection fraction (%)	65.0 (57.1–69.0)	55.6 (52.6–60.0)	0.44
Stroke volume (ml)	55.6 (50.0–70.6)	55.0 (48.8–73.9)	0.92
Cardiac output (l/min)	5.7 (3.7–5.7)	4.2 (3.8–6.2)	0.47
Mean MVG (mm Hg)	12.3 (7.7–18.0)	10.6 (9.4–11.3)	0.57
MVA (cm^2)*	1.9 (1.8–2.2)	2.5 (2.0–2.8)	0.28
Pulmonary artery systolic pressure (mm Hg)†	62.0 (53.8–68.5)	44.2 (34.8–46.5)	0.01
Peak LVOT gradient (mm Hg)	4.5 (4.0–6.8)	4.6 (2.6–8.2)	0.89
Mean LVOT gradient (mm Hg)	2.7 (2.1–3.7)	2.6 (1.5–4.5)	1.00
Mitral valve pathology			0.46
Stenosis	5 (71.4)	7 (100.0)	
Regurgitation	0 (0.0)	0 (0.0)	
Both stenosis and regurgitation	2 (28.6)	0 (0.0)	
Severity of mitral regurgitation			0.27
None or trace	0 (0.0)	2 (28.6)	
1 (+)	6 (85.7)	3 (42.9)	
2 (+)	0 (0.0)	1 (14.3)	
3 (+)	0 (0.0)	1 (14.3)	
4 (+)	1 (14.3)	0 (0.0)	

Values are median (interquartile range) or n/N (%). *Uncertain reliability; echocardiographic methods validated in rheumatic disease and not mitral annular calcification. †3 missing.
ASA = alcohol septal ablation; other abbreviations as in Table 2.

replacement. The median Society of Thoracic Surgeons Predicted Risk of Mortality score was 6.3% (IQR: 5.0% to 8.8%) with a mean of 8.6 ± 8.2% (transatrial 7.8 ± 4.2%, transseptal 9.9 ± 11.0%), p = 0.50), and most patients were in New York Heart Association functional class III or IV (transatrial, 73.3%; transseptal, 100%; p = 0.01). Baseline echocardiographic characteristics are described in Table 2. Left ventricular function was normal. MS was the predominant pathology and was present in 74.2%.

Transseptal access was used for 15 patients (48.4%), transatrial for 15 patients (48.4%), and transapical for 1 patient (3.2%). Selection of transatrial access was based on the risk for embolization (n = 6), risk for LVOTO (n = 3), or both (n = 6). One patient was treated via transapical access because of challenging anatomy for transseptal access. Procedural results are shown in Table 3.

PRIMARY SAFETY ENDPOINTS AND ACUTE RESULTS. The primary safety endpoint of technical success at exit from the procedure room was 74.2% (transatrial, 73.3% [11 of 15]; transseptal, 80.0% [12 of 15]; p = 1.00). Reasons for not meeting technical success criteria in 4 transatrial cases included LVOTO, MR ≥2+, wire-induced left ventricular perforation, and ventricular septal defect due to concomitant surgical myectomy. Reasons in the 3 transseptal cases were LVOTO, MR ≥2+, and need for a second valve. There were no cases of valve embolization, need for conversion to open heart surgery, or deaths during the index procedures. The median hospital stay was 8.5 days (IQR: 4.25 to 12.75 days).

There were 5 in-hospital deaths (16.1%), which included 3 patients who were treated via transatrial access (3 of 15 [20%]). One patient who underwent transapical access died. The case was complicated by LVOTO, and the patient was treated the following day with surgical explantation of the THV and redo ViMAC with transatrial access and surgical resection of the anterior leaflet. The other remaining in-hospital death was the first patient treated in the trial. That patient underwent transseptal ViMAC (1 of 15 [6.7%]) (p = 0.60) and had LVOTO with hemodynamic compromise, as detailed later.

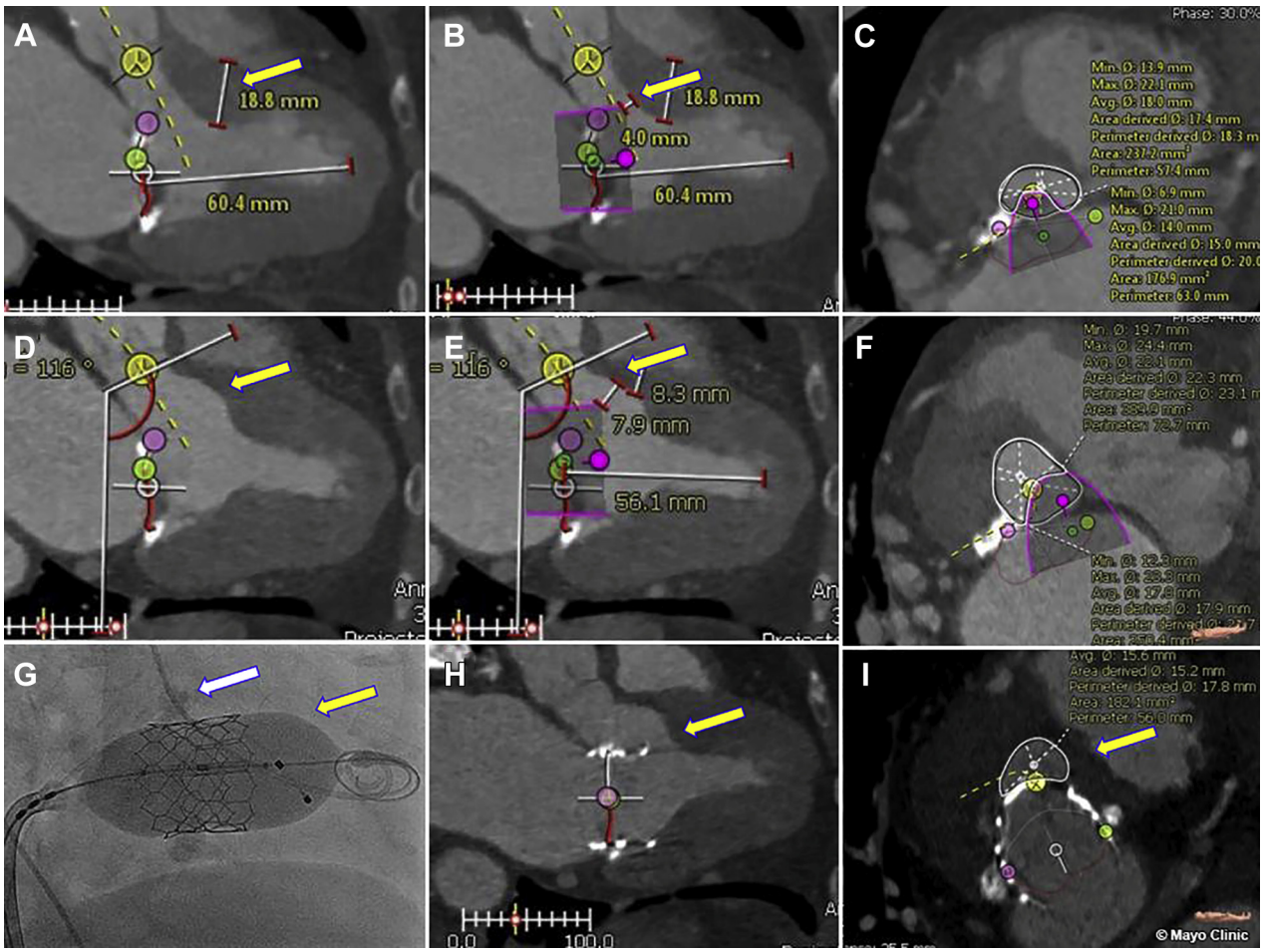
LVOTO AND PRE-EMPTIVE ALCOHOL SEPTAL ABLATION. LVOTO with hemodynamic compromise occurred in 3 patients (transseptal, n = 1; transapical, n = 1; transatrial, n = 1). Outcomes of these patients are summarized in Supplemental Appendix 6.

After the second patient was treated in this trial, we began to use pre-emptive alcohol septal ablation in patients at risk for TMVR-induced LVOTO. Seven of the remaining 14 patients treated with transseptal access were at high risk for LVOTO (median neo-LVOT area 100.0 mm^2; IQR: 87.9 to 145.0 mm^2) and underwent pre-emptive alcohol septal ablation using 1.0 ml (IQR: 0.65 to 2.0 ml) of alcohol. Baseline echocardiographic characteristics of these patients are summarized in Table 4. Repeat CT scans 45 days (IQR: 23 to 50 days) after alcohol septal ablation showed decreased risk (median neo-LVOT area 227.5 mm^2; IQR: 215.5 to 311.2 mm^2), and all underwent successful transseptal ViMAC (Figure 3). Three of the patients treated via transatrial access also underwent pre-emptive alcohol septal ablation (median 1.6 ml; IQR: 1.1 to 2.0 ml) before transatrial ViMAC (median neo-LVOT area 50.9 mm^2; IQR: 0 to 119.3 mm^2) to avoid the need for surgical myectomy during the same procedure.

ADDITIONAL ENDPOINTS. The primary performance endpoint was achieved for 88% of survivors at 30 days (22 of 25) and for 100% of patients alive who had echocardiographic data available (18 of 18) at 1 year. All-cause mortality at 30 days was 16.7% (transatrial, 21.4%; transseptal, 6.7%; p = 0.33) and at 1 year was 34.5% (transatrial, 38.5% [5 of 13]; transseptal, 26.7% [4 of 15]; p = 0.69). Kaplan-Meier survival curves are shown in the Central Illustration.

THIRTY-DAY OUTCOMES. At 30 days, 25 of 30 patients (83.3%) were alive, and 60% were in New York

FIGURE 3 Cardiac CT Findings After Pre-Emptive Alcohol Septal Ablation and Transseptal Valve-in-MAC



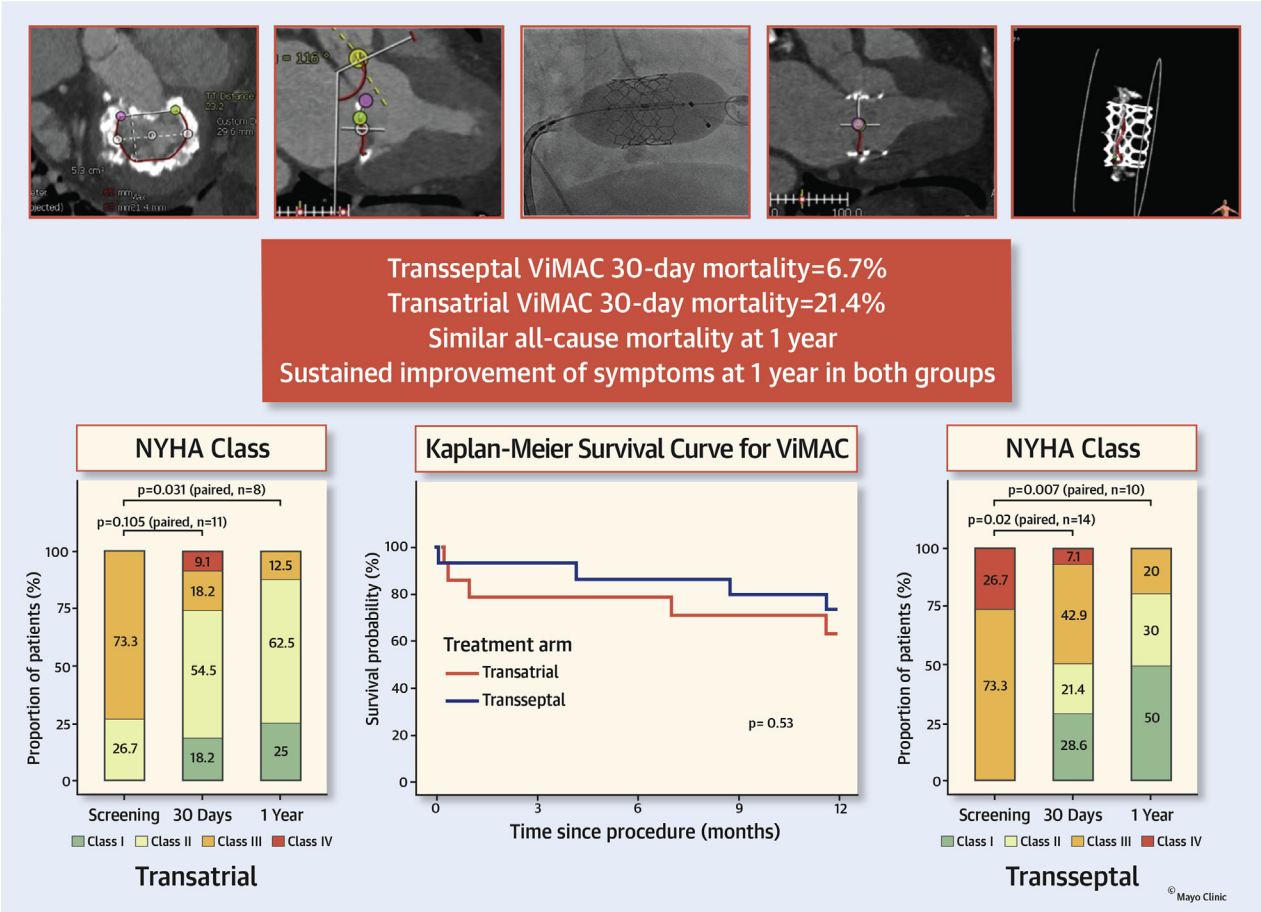
(A) Baseline cardiac computed tomographic (CT) imaging shows thick septum **(arrow)**. **(B)** After placement of a 29-mm virtual valve, the remaining space in the LVOT is reduced **(arrow)**. **(C)** Baseline neo-LVOT area during systole is 176 mm^2. CT scan obtained 4 weeks after alcohol septal ablation shows **(D)** reduced thickness of the basal septum **(arrow)**, **(E)** residual space in the LVOT larger than baseline, and **(F)** predicted neo-LVOT area during systole of 250 mm^2. **(G)** Fluoroscopy of a transseptal ViMAC implantation using a 29-mm SAPIEN 3 valve prepared with 4 ml of additional contrast to flare the ventricular edge of the THV stent **(yellow arrow)**, 80% ventricular and 20% atrial in relation to the mitral annulus **(white arrow)**. **(H)** CT image post-TMVR shows the SAPIEN 3 valve in the desired position. **(I)** Post-TMVR CT image shows the actual neo-LVOT measurement of 182 mm^2 **(arrow)**. Abbreviations as in Figure 1 and 2.

Heart Association functional class I or II. Clinical outcomes at 30 days are shown in Table 5 and echocardiographic characteristics in Table 6. New-onset acute kidney injury requiring new hemodialysis and new-onset atrial fibrillation were more frequent in transatrial cases (both 28.6% vs. 0%; p = 0.04). The need for blood transfusion in all transatrial cases was procedure related, whereas the reason for blood transfusion in the 6 transseptal cases was hemolytic anemia (n = 3) and gastrointestinal bleeding (n = 3).

1-YEAR OUTCOMES. At 1-year follow-up (median 1.0 year; IQR: 1.0 to 1.2 year), 19 of 29 eligible patients (65.5%) were alive (transatrial, 61.5%; transseptal, 73.3%; p = 0.69), and 83.3% were in New York Heart Association functional class I or II (transatrial, 87.5%; transeptal, 80%; p = 0.16).

Clinical outcomes at 1 year are summarized in Table 7 and echocardiographic characteristics in Table 8. Patients alive had significant improvements in New York Heart Association functional class (Central Illustration), distance walked in the 6-min walk test (Figure 4), and quality-of-life scores (Figure 5). THV function remained stable, with a median mean MV gradient of 6.4 mm Hg (IQR: 4.2 to 7.4 mm Hg) in transatrial cases and 6.1 mm Hg (IQR:

CENTRAL ILLUSTRATION **30-Day and 1-Year Outcomes of Valve-in-Mitral Annular Calcification in the Mitral Implantation of Transcatheter Valves Trial**



Guerrero, M. et al. J Am Coll Cardiol Intv. 2021;14(8):830–45.

Early and late outcomes for functional capacity (New York Heart [NYHA] Association functional class) in the transatrial group **(left)** and transseptal group **(right)** and for survival **(middle)**. ViMAC = valve-in-mitral annular calcification.

5.7 to 6.8 mm Hg) in transeptal cases (p = 0.93) (Figure 6), and all patients had 1+ or less total MR.

Five patients developed hemolytic anemia by 1 year (transatrial, 7.7% [1 of 13]; transseptal, 26.7% [4 of 15]; p = 0.33). Three patients with trace paravalvular leak developed hemolysis within 30 days. One of these patients was treated with mitral valve-in-valve. The paravalvular leak spontaneously resolved in 2 patients, but they required transfusion. Of the 2 additional patients who developed hemolysis after 30 days, 1 was treated by paravalvular leak closure, and 1 was treated conservatively.

The anticoagulation regimens and valve thrombosis summaries are described in Supplemental Appendix 7. There were no late device embolization or migration events or endocarditis.

DISCUSSION

This is the first prospective, multicenter, early feasibility clinical trial with independent imaging core laboratories and independent clinical events adjudication to evaluate the safety and feasibility of ViMAC using balloon-expandable aortic THVs. The following were the main findings: 1) transseptal ViMAC in carefully selected patients was associated with 30-day mortality lower than predicted by the Society of Thoracic Surgeons score; 2) pre-emptive alcohol

TABLE 5 30-Day Clinical Outcomes

	All Patients* (N = 30)	Transatrial Access† (n = 14)	Transseptal Access (n = 15)	p Value‡
All-cause mortality (1 transapical)	5/30 (16.7)	3/14 (21.4)	1/15 (6.7)	0.33
Cardiovascular (1 transapical)	4/30 (13.3)	2/14 (14.3)	1/15 (6.7)	0.60
Noncardiovascular	1/30 (3.3)	1/14 (7.1)	0/15 (0.0)	0.48
Device success	17/30 (56.7)	9/14 (64.3)	8/15 (53.3)	0.71
Procedural success	16/30 (53.3)	9/14 (64.3)	7/15 (46.7)	0.46
Primary performance endpoint in survivors at 30 days§	22/25 (88.0)	10/11 (90.9)	12/14 (85.7)	1.00
Stroke‖ (1 transapical)	2/30 (6.7)	1/14 (7.1)	0/15 (0.0)	0.48
Ischemic (1 transapical)	2/30 (6.7)	1/14 (7.1)	0/15 (0.0)	0.48
Hemorrhagic	0/30 (0.0)	0/14 (0.0)	0/15 (0.0)	NA
Myocardial infarction requiring revascularization	0/30 (0.0)	0/14 (0.0)	0/15 (0.0)	NA
Mitral valve reintervention after index procedure (MViV)¶ (1 transapical)	2/30 (6.7)	0/14 (0.0)	1/15 (6.7)	1.00
Septostomy closed in transseptal cases (3 during index procedure, 1 after index procedure)	4/15 (26.7)	NA	4/15 (26.7)	NA
Acute kidney injury requiring hemodialysis (1 transapical)	5/30 (16.7)	4/14 (28.6)	0/15 (0.0)	0.04
Blood transfusion (1 transapical)	16/30 (53.3)	9/14 (64.3)	6/15 (40.0)	0.27
Major vascular complication (1 transapical)	1/30 (3.3)	0/14 (0.0)	0/15 (0.0)	NA
New permanent pacemaker requirement (1 transapical)	5/30 (16.7)	2/14 (14.3)	2/15 (13.3)	1.00
New-onset atrial fibrillation (1 transapical)	5/30 (16.7)	4/14 (28.6)	0/15 (0.0)	0.04
New rehospitalization for heart failure	4/30 (13.3)	1/14 (7.1)	3/15 (20.0)	0.60
Device embolization or migration	0/30 (0.0)	0/14 (0.0)	0/15 (0.0)	
Hemolytic anemia#	3/30 (10.0)	0/14 (0.0)	3/15 (20.0)	0.22
Valve thrombosis	0/30 (0.0)	0/14 (0.0)	0/15 (0.0)	NA
Endocarditis	0/30 (0.0)	0/14 (0.0)	0/15 (0.0)	NA
New York Heart Association functional class				0.33
I	6/25 (24.0)	2/11 (18.2)	4/14 (28.6)	
II	9/25 (36.0)	6/11 (54.5)	3/14 (21.4)	
III	8/25 (32.0)	2/11 (18.2)	6/14 (42.9)	
IV	2/25 (8.0)	1/11 (9.1)	1/14 (7.1)	

Values are n/N (%). *Includes 1 transapical case not shown in the transatrial or transseptal column. †1 withdrew consent at 8 days post-TMVR before discharge to physical therapy center. ‡Transatrial vs. transseptal. §Reason for not meeting performance endpoint was mean mitral valve gradient of 10.2 mm Hg in a transatrial case as well as MR 2 (+) and 3 (+) in 2 transseptal cases. ‖All during index hospitalization. ¶1 transseptal MViV for hemolytic anemia in a transseptal case and 1 transatrial valve-in-MAC for left ventricular outflow tract obstruction and paravalvular leakage in the transapical case. #1 treated with MViV and 2 spontaneously resolved, but all required transfusion.

MAC = mitral annular calcification; MViV = mitral valve-in-valve; NA = not applicable.

septal ablation preformed 3 to 4 weeks before ViMAC can prevent LVOTO during transseptal ViMAC in patients at high risk; 3) THVs performed adequately in most patients, and these outcomes were maintained at 1 year; and 4) ViMAC was associated with significantly diminished symptoms, improved 6-min walk distance, and improved quality-of-life scores.

Our results differ from those of prior retrospective studies that showed ViMAC to be feasible but associated with procedural complications and high 30-day and 1-year mortality (4,5). Outcomes for our patients improved significantly with careful patient selection and strategies to decrease risk for TMVR-induced LVOTO, such as pre-emptive alcohol septal ablation performed weeks before transseptal ViMAC or surgical resection of the anterior leaflet during transatrial ViMAC.

MORTALITY. At 1 year, all-cause mortality in the entire cohort was 34.5%, lower than that reported in prior registries (4,5). For patients treated via transseptal access, 1-year all-cause mortality was 26.7%. This is a remarkable improvement from the 51.1% mortality rate for transseptal cases in the TMVR in MAC Global Registry (4) and is similar to 1-year mortality for transcatheter MV edge-to-edge repair procedures with the MitraClip (Abbott Vascular, Santa Clara, California) reported for the United States (10).

Compared with the outcomes of TMVR studies evaluating THVs designed for the MV, the 30-day (6.7%) and 1-year (26.7%) all-cause mortality rates of transseptal ViMAC cases in this study were identical to the 30-day (6%) and 1-year (26%) mortality rates reported for the initial feasibility study of the

TABLE 6 Echocardiographic Characteristics at 30 Days

	All Patients* (N = 25)	Transatrial Access (n = 11)	Transseptal Access (n = 14)	p Value†
Ejection fraction (%)	55.5 (50.7-66.2)	55.0 (48.9-65.3)	56.0 (51.5-66.2)	0.49
Stroke volume (ml)	65.3 (46.3-76.2)	76.4 (46.3-85.9)	62.3 (48.7-70.6)	0.14
Cardiac output (l/min)	5.1 (3.8-6.0)	5.6 (4.9-7.0)	4.9 (3.4-5.4)	0.11
Mean MVG (mm Hg)	6.0 (5.2-7.8)	7.4 (5.0-8.6)	5.9 (5.3-7.1)	0.44
MVA (cm^2)‡	2.9 (2.5-3.3)	2.9 (2.6-3.1)	2.9 (2.5-3.4)	0.89
Pulmonary artery systolic pressure (mmHg)§	50.5 (41.6-69.9)	42.0 (38.9-64.0)	54.2 (47.9-70.3)	0.425
Peak LVOT gradient	7.2 (4.8-11.6)	7.2 (5.9-11.7)	6.8 (4.5-11.0)	0.41
Mean LVOT gradient	3.5 (2.7-6.1)	3.2 (3.1-6.8)	3.7 (2.6-6.0)	0.83
Severity of total mitral regurgitation				1.00
None to trace	17/25 (68.0)	8/11 (72.7)	9/14 (64.3)	
1 (+)	6/25 (24.0)	3/11 (27.3)	3/14 (21.4)	
2 (+)	1/25 (4.0)	0/11 (0.0)	1/14 (7.1)	
≥3 (+)	1/25 (4.0)	0/11 (0.0)	1/14 (7.1)	
Severity of paravalvular mitral regurgitation				0.15
None to trace	20/25 (80.0)	11/11 (100.0)	9/14 (64.3)	
1 (+)	3/25 (12.0)	0/11 (0.0)	3/14 (21.4)	
2 (+)	1/25 (4.0)	0/11 (0.0)	1/14 (7.1)	
≥3 (+)	1/25 (4.0)	0/11 (0.0)	1/14 (7.1)	

Values are median (interquartile range) or n/N (%). *At 30 days, 25 echocardiographic studies were available (5 patients died and 1 withdrew consent 8 days after valve-in-MAC). †Transatrial vs. transseptal. ‡Uncertain reliability; standard echocardiographic methods are validated in rheumatic disease and not MAC or after TMVR. §8 missing values.
Abbreviations as in Tables 2, 3, and 5.

Tendyne transcatheter valve system (Abbott Structural Heart, Santa Clara, California) (11) and similar to or lower than the initial experience with the Intrepid TMVR system (Medtronic, Redwood City, California), which reported 30-day mortality of 14% and 1-year mortality of 23.8% (12). However, these early feasibility studies involved different patient populations with mostly functional MR in noncalcified MVs. Taking into consideration that the MITRAL trial is an early experience with a small number of patients, achieving 1-year mortality similar to that shown for a well-established and safe procedure such as transcatheter edge-to-edge MV repair or early experience with TMVR is encouraging and demonstrates this to be a treatment option for at least some patients in a group that is otherwise difficult to treat.

LVOTO AND THE ROLE OF PRE-EMPTIVE ALCOHOL SEPTAL ABLATION. The new concept of performing pre-emptive alcohol septal ablation before TMVR was instituted in this trial. We had previously described the role of emergency percutaneous alcohol septal ablation for acutely reducing TMVR-induced LVOTO, which can be a lifesaving strategy (6). After implementing pre-emptive alcohol septal ablation to decrease the risk for LVOTO in patients at risk (after the first 2 patients enrolled), 7 of the remaining 14 patients treated via transseptal access were considered to have a high risk for LVOTO and underwent pre-emptive alcohol septal ablation 3 to 4 weeks before TMVR. All of these patients underwent successful transseptal ViMAC and were alive at 30 days.

The LAMPOON procedure (intentional laceration of the anterior mitral leaflet to prevent LVOTO) was developed after the MITRAL trial started and was not used in this study. The 30-day mortality of patients who had transseptal access in our study was lower than the 13.3% mortality of transseptal ViMAC reported in the LAMPOON (Intentional Laceration of the Anterior Mitral Leaflet to Prevent Left Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Implantation) trial (13). The number of patients in these studies is small, therefore, meaningful comparisons cannot be made.

ACCESS TYPE SELECTION PROCESS. Transseptal access was preferred in patients with favorable anatomy who were considered to have low risk for valve embolization and LVOTO. Risk for valve embolization was assessed by analysis of calcium amount and distribution on cardiac CT imaging. This assessment was initially descriptive. During the course of our study and using data from the TMVR in MAC registry for validation, a cardiac CT score was developed to categorize MAC severity and predict valve embolization. A MAC score of 6 or less was associated with a very high (60%) risk for valve embolization or migration (14). A MAC score of 7 or greater and a

TABLE 7 1-Year Clinical Outcomes

	All Patients* (N = 29)	Transatrial Access† (n = 13)	Transseptal Access (n = 15)	p Value‡
All-cause mortality (1 transapical)	10/29 (34.5)	5/13 (38.5)	4/15 (26.7)	0.69
Cardiovascular (1 transapical)	6/29 (20.7)	3/13 (23.1)	2/15 (13.35)	1.00
Noncardiovascular	4/29 (13.8)	2/13 (15.4)	2/15 (13.35)	0.58
Primary performance endpoint in survivors at 1 yr (1 missed echocardiography study)	18/18 (100)	8/8 (100)	10/10 (100)	1.00
Stroke§ (1 transapical)	2/29 (6.9)	1/13 (7.7)	0/15 (0.0)	0.46
Ischemic (1 transapical)	2/29 (6.9)	1/13 (7.7)	0/15 (0.0)	0.46
Hemorrhagic	0/29 (0.0)	0/13 (0.0)	0/15 (0.0)	NA
Myocardial infarction requiring revascularization	0/29 (0.0)	0/13 (0.0)	0/15 (0.0)	NA
Mitral valve reintervention after index procedure (1 transapical)‖	4/29 (13.8)	1/13 (7.7)	2/15 (13.3)	1.00
Septostomy closed in transseptal cases (3 during index procedure, 2 after index procedure)	5/15 (33.3)	NA	5/15 (33.3)	NA
Acute kidney injury requiring hemodialysis (1 transapical)	5/29 (17.2)	4/13 (30.8)	0/15 (0.0)	0.01
Blood transfusion (1 transapical)	17/29 (62.1)	9/13 (76.9)	7/15 (46.7)	0.14
Major vascular complication (1 transapical)	1/29 (3.4)	0/13 (0.0)	0/15 (0.0)	NA
New permanent pacemaker requirement (1 transapical)	5/29 (17.2)	2/13 (15.3)	2/15 (13.3)	1.00
New-onset atrial fibrillation (1 transapical)	5/29 (17.2)	4/13 (30.7)	0/15 (0.0)	0.07
New rehospitalization for heart failure¶	11/29 (37.9)	4/13 (30.8)	7/15 (46.7)	0.46
Device embolization or migration	0/29 (0)	0/13 (0.0)	0/15 (0.0)	NA
Hemolytic anemia#	5/29 (17.2)	1/13 (7.7)	4/15 (26.7)	0.33
Valve thrombosis	1/29 (3.4)	0/13 (0.0)	1/15 (6.7)	1.00
Endocarditis	0/29 (0.0)	0/13 (0.0)	0/15 (0.0)	NA
New York Heart Association functional class**				0.16
I	7/18 (38.9)	2/8 (25.0)	5/10 (50.0)	
II	8/18 (44.4)	5/8 (62.5)	3/10 (30.0)	
III	3/18 (16.7)	1/8 (12.5)	2/10 (20.0)	
IV	0/18 (0.0)	0/8 (0.0)	0/10 (0.0)	

Values are n/N (%). *Includes 1 transapical case not shown in the transatrial or transseptal column. †1 withdrew consent at 8 days after transatrial ViMAC before discharge to a physical therapy center, and 1 withdrew consent at day 187 after transatrial ViMAC. ‡Transatrial vs. transseptal. §All during index hospitalization. ||2 within 30 days: 1 transseptal MViV for hemolysis and 1 transatrial valve-in-MAC for left ventricular outflow tract obstruction and paravalvular leakage after transapical ViMAC. 2 after 30 days: both paravalvular leak closures (1 transatrial and 1 transseptal case). ¶The reason for heart failure was identified as volume overload in patients with pre-existing systolic dysfunction in 1 and diastolic dysfunction in 3 of the transatrial cases. The reason in transseptal cases was diastolic heart failure in 3, aortic stenosis in 1, and mild paravalvular leak in 1. It was thought to be attributable to persistent septostomy in 2 patients who underwent closure of an atrial septal defect during that admission. #3 cases at 30 days: 1 patient was treated with MViV, and 2 patients had spontaneous resolution, but all required transfusion. There were 2 additional cases of hemolytic anemia after 30 days: 1 was treated with paravalvular closure and 1 conservatively. **1 missing value (1 patient alive at 1 year did not have a 1-year follow-up visit).

ViMAC = valve-in-MAC; other abbreviations as in Tables 3 and 5.

neo-LVOT >190 mm^2 were the main criteria for selecting transseptal access in our study.

OTHER INTRAPROCEDURAL CHALLENGES. In contrast to results from prior registries, no cases of valve embolization occurred in this trial. In a registry report by Yoon et al. (5), the valve embolization rate was 6.9%, and in the TMVR in MAC Global Registry, it was 4.3% (4). We attribute the absence of valve embolization in our study to careful cardiac CT analysis and use of the CT MAC score to help predict valve anchoring (14). At 30 days, hemolytic anemia was present in 20% of transseptal cases (3 of 15) but no transatrial cases. There was no correlation with large paravalvular leak; these 3 patients with hemolytic anemia had trace paravalvular leak at 30 days and had none at 1 year. We suspect the higher flow velocity in small paravalvular leak jets contributed to hemolysis events in these patients. This hemolysis rate is higher than the 3.8% rate reported in the TMVR in MAC Global Registry, and it was not reported by Yoon et al. (5). However, those were both retrospective studies, and they may not have actively screened for and captured hemolysis data, as was done in our study. Possibly the newer design of the SAPIEN 3 Ultra may help address this limitation.

THV PERFORMANCE ENDPOINT. The primary performance endpoint of absence of MR grade 2+ or greater or mean MV gradient ≥10 mm Hg was achieved in all patients alive with echocardiographic data available at 1 year. We do not suspect that this is due to survivorship bias. There were 5 deaths after 30 days. Three of those subjects met THV

TABLE 8 Echocardiographic Characteristics at 1 Year

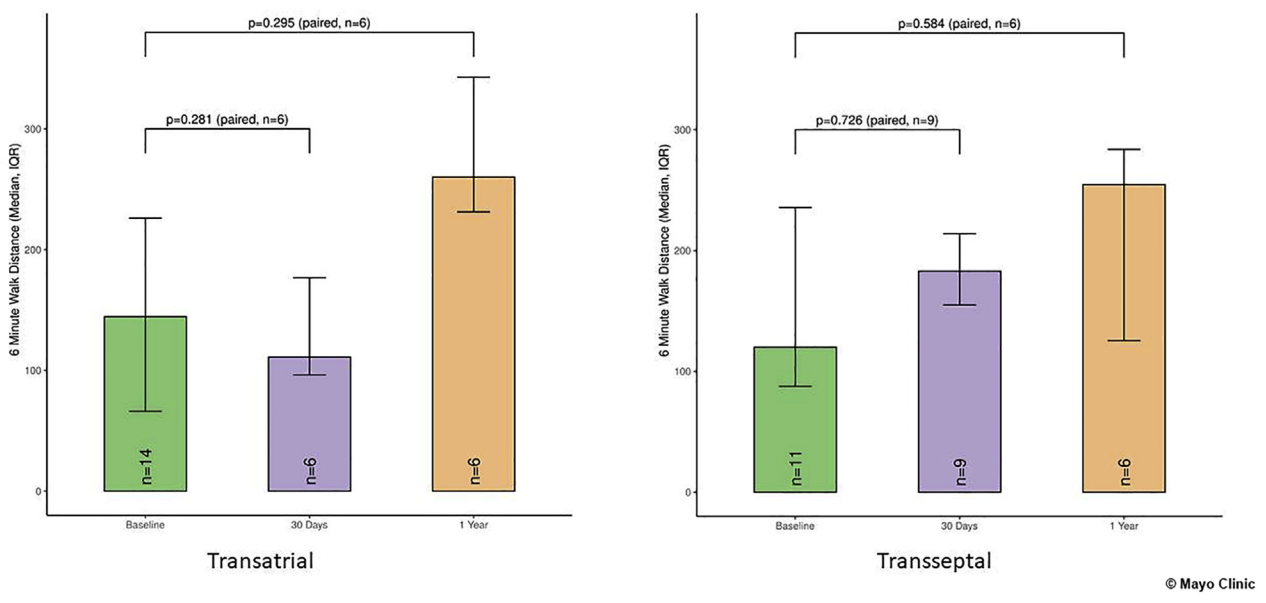
	All Patients* (N = 18)	Transatrial Access (n = 8)	Transseptal Access (n = 10)	p Value†
Ejection fraction (%)	65.3 (60.8-69.9)	68.4 (64.4-71.3)	64.5 (60.4-65.5)	0.18
Stroke volume (ml)	89.2 (62.8-94.5)	89.2 (69.9-94.2)	77.7 (60.9-98.9)	1.00
Cardiac output (l/min)	5.1 (4.5-7.4)	5.1 (4.7-6.8)	5.9 (4.4-7.7)	1.00
Mean MVG (mm Hg)	6.1 (5.6-7.1)	6.4 (4.2-7.4)	6.1 (5.7-6.8)	0.93
MVA (cm^2)‡	3.1 (2.6-3.9)	2.6 (2.3-3.0)	3.8 (3.0-4.1)	0.05
Pulmonary artery systolic pressure (mm Hg)§	39.3 (35.0-48.3)	37.7 (26.7-48.3)	40.0 (36.8-52.1)	0.46
Peak LVOT gradient	5.3 (3.5-8.4)	6.8 (5.1-9.0)	4.2 (3.5-6.4)	0.27
Mean LVOT gradient	3.1 (2.2-4.9)	3.9 (2.8-5.1)	2.4 (2.2-4.1)	0.48
Severity of total mitral regurgitation				0.66
None to trace	10/18 (55.6)	5/8 (62.5)	5/10 (50.0)	
1 (+)	8/18 (44.4)	3/8 (37.5)	5/10 (50.0)	
2 (+)	0/18 (0)	0/8 (0)	0/10 (0)	
≥3 (+)	0/18 (0)	0/8 (0)	0/10 (0)	
Severity of paravalvular mitral regurgitation				0.48
None to trace	16/18 (88.9)	8/8 (100.0)	8/10 (80.0)	
1 (+)	2/18 (11.1)	0/8 (0.0)	2/10 (20.0)	
2 (+)	0/18 (0)	0/8 (0)	0/10 (0)	
≥3 (+)	0/18 (0)	0/8 (0)	0/10 (0)	

Values are median (interquartile range) or n/N (%). *At 1 yr, 18 echocardiographic studies were available: 10 patients died, 1 withdrew consent 8 days after transatrial TMVR, 1 withdrew consent 187 days after transatrial TMVR, and 1 patient alive at 1 yr did not have a 1-yr follow-up visit. †Transatrial vs. transseptal. ‡Uncertain reliability; standard echocardiographic methods are validated in rheumatic disease and not for MAC or after TMVR. §5 missing values.

Abbreviations as in Tables 2, 3, and 5.

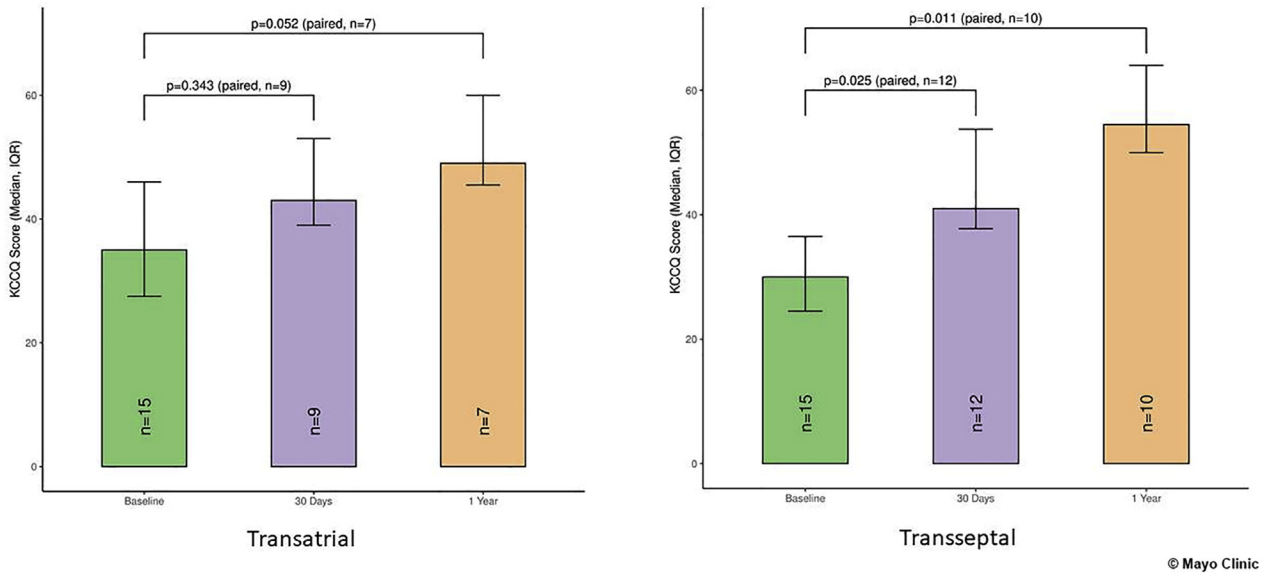
performance endpoint at 30 days and 2 did not because of MR grade 2+. These 2 subjects died of noncardiovascular causes, subdural hematoma after head trauma subsequent to a fall, and end-stage renal disease on day 355 post-ViMAC. The latter underwent 1-year follow-up transthoracic echocardiography prior to his death, which showed a mean MV gradient of 5.8 mm Hg and 1+ MR, meeting the performance

FIGURE 4 6-Min Walk Test



IQR = interquartile range.

FIGURE 5 Quality-of-Life Score



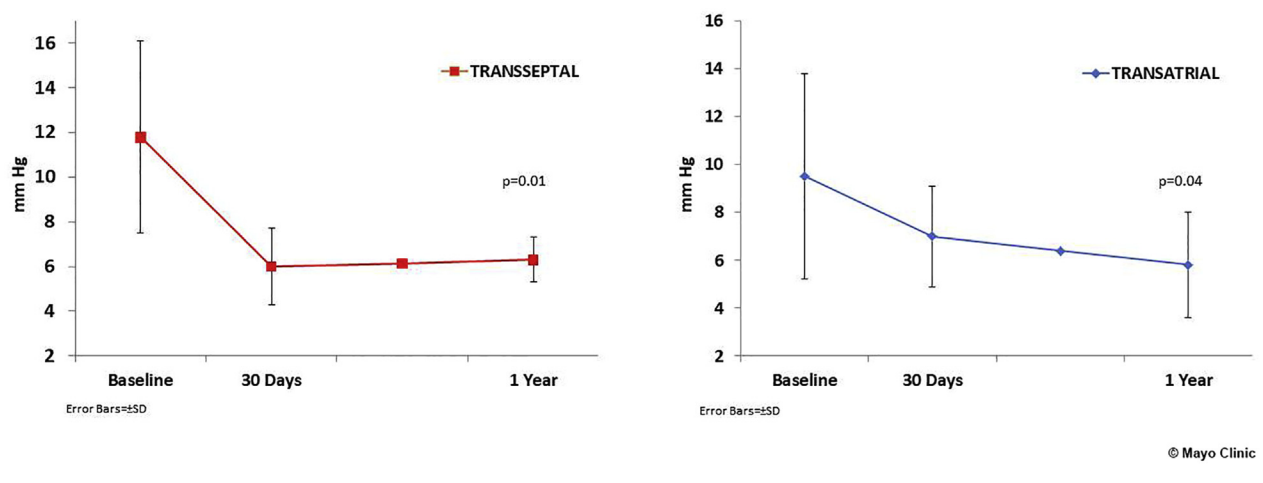
IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire.

endpoint. These results are encouraging considering the round shape of the aortic THV and the oval saddle shape of the native MV, which could result in more residual paravalvular leak. Although the mean MV gradient was higher than reported in THV designed for the mitral position (6.1 ± 1.6 mm Hg vs. 3.0 ± 1.1 mm Hg), the amount of residual MR was similar (11).

FEMALE SEX. Most of the patients included in this study were women (71%), unlike in many other research trials, but the mostly female population is similar to that of other prior MAC registry studies (4,5). The reasons for this may be multifactorial, including a higher prevalence of MAC in women and higher surgical risk, resulting in women's being referred more often for TMVR.

STUDY LIMITATIONS. First, this was an early feasibility study with a small number of patients enrolled. Because it was not randomized and controlled, the results cannot provide evidence that MV intervention

FIGURE 6 Mean Mitral Valve Gradient



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in patients with advanced MV dysfunction attributable to MAC is associated with decreased mortality. Similarly, assignment to access type was not randomized; therefore, difference in outcomes among access types can only generate hypotheses. In addition, outcomes of patients who were not accepted in the trial were not collected. Therefore, data on the natural history of these patients is unknown.

Second, the outcomes of septal ablation procedures performed outside the trial in preparation for possible patient enrollment were not collected. Patients may have undergone alcohol septal ablation that resulted in poor outcomes, and their cases were never presented for enrollment in this study. Alcohol septal ablation was the only LVOTO risk reduction strategy used in transseptal cases. Percutaneous laceration of the anterior leaflet with the LAMPOON procedure was developed after the MITRAL trial was initiated and not used in this study. Therefore, safety of these 2 important strategies was not compared.

Finally, the patient population in our study was highly selected, with the initial screen failure rate at 2 to 1. Therefore, our results cannot be applied to the general population.

NEXT STEPS. Further studies are needed to refine the patient selection process and standardize the transseptal ViMAC technique. The MITRAL II pivotal trial will evaluate the safety and effectiveness of transseptal ViMAC with the SAPIEN 3 Ultra THV (NCT04408430) in patients at high surgical risk.

CONCLUSIONS

ViMAC was associated with significant alleviation of symptoms and improvement in quality of life as well as stable THV performance at 1 year. TMVR-induced LVOTO can be prevented with pre-emptive alcohol septal ablation in patients at risk. In patients treated with transseptal access, 30-day mortality was lower than predicted by the Society of Thoracic Surgeons score, and 1-year mortality was similar to that reported for transcatheter MV repair and replacement populations. Further studies are needed to evaluate the safety and efficacy of ViMAC.

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PERSPECTIVES

WHAT IS KNOWN? Patients with severe MAC often have high surgical risk. TMVR is emerging as an alternative for these patients.

WHAT IS NEW? High-risk patients with severe MAC and MV dysfunction who were treated with a ViMAC procedure had significant reduction of symptoms and improvement in quality of life, as well as stable THV performance at 1 year. Alcohol septal ablation performed 3 to 4 weeks before TMVR can decrease the risk for TMVR-induced LVOTO and facilitate safe transseptal ViMAC in patients who were previously ineligible because of this risk.

WHAT IS NEXT? Further studies are needed to confirm the safety and efficacy of ViMAC, refine patient selection to improve technical success, and evaluate longer term outcomes.

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KEY WORDS mitral annular calcification, mitral valve disease, mitral valve replacement, transcatheter mitral valve replacement

APPENDIX For inclusion and exclusion criteria, trial operations, supplemental methods, study endpoints, outcomes, and supplemental references, please see the online version of this paper.