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ORIGINAL STUDY

WILEY

Short- and mid-term outcomes in percutaneous mitral valve replacement using balloon expandable valves

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Abstract

Background: Due to elevated surgical risk, transcatheter mitral valve replacement (TMVR) is used as an alternative for treating failed bioprosthetic valves, annuloplasty repairs and mitral annular calcification (MAC). We report the procedural and longitudinal outcomes for each subtype: Mitral valve-in-valve (MVIV), mitral valve-in-ring (MViR), and valve-in-MAC (ViMAC).

Methods: Consecutive patients undergoing TMVR from October 2013 to December 2019 were assessed. Patients at high risk for left ventricular outflow tract obstruction had either alcohol septal ablation or intentional laceration of the anterior leaflet (LAMPOON).

Results: Eight-eight patients underwent TMVR; 38 MViV, 31 MViR, and 19 ViMAC procedures were performed. The median Society of Thoracic Surgery 30-day predicted risk of mortality was 8.2% (IQR 5.2, 19.9) for all. Sapien 3 (78%) and transseptal access (98%) were utilized in most cases. All-cause in-hospital mortality, technical, and procedural success were 8%, 83%, and 66% respectively. Median follow up was 1.4 years (IQR 0.5–2.9 years) and overall survival was 40% at 4 years. Differential survival rates were observed with MViV doing the best, followed by MViR and ViMAC having a <20% survival at 4 years. After adjusting for co-variates, MViV procedure was the strongest predictor of survival (HR 0.24 [95% CI 0.079–0.7]).

Conclusion: TMVR is performed in at high-risk patients with attenuated long-term survival. MViV has the best success and survival rate, but long-term survival in MViR and ViMAC is guarded.

KEYWORDS
mitral valve disease, transcatheter valve implantation, transseptal

Abbreviations: ASA, Alcohol septal ablation; CTA, Computed Tomography Angiogram; LVOT, Left Ventricular Outflow Tract; LVOTO, Left Ventricular Outflow Tract Obstruction; LAMPOON, Intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction; MVR, Mitral Valve Replacement; MVARC, Mitral Valve Academic Research Consortium; MViV, Mitral valve-in-valve; MViR, Mitral valve-in-ring; NYHA, New York Heart Association; PVL, Paravalvular Leak; THV, Transcatheter Heart Valve; TMVR, Transcatheter Mitral Valve Replacement; TEE, Trans-esophageal echocardiogram; ViMAC, Valve-in-mitral annular calcification.

1 | INTRODUCTION

In the United States, there are approximately >30,000 mitral valve repair/replacement surgeries annually.[1] While surgical mitral valve repair and replacement are gold standards for mitral valve

therapy, they have limited durability. Rates of recurrent significant mitral regurgitation (MR) with mitral valve repair can be as high as 22.5% at 5 years.[2] Primary valve failure occurs in mitral Valve Replacement (MVR) approximately 30% at 10 years and 44% at 15 years.[3] Surgery such has mitral valve reoperation and valve replacement for native mitral annular calcification considered high risk,[4-6] therefore transcatheter heart valves (THV) have been implemented as an alternative treatment.[7] These three procedural categories: Mitral valve-in-valve (MViV), mitral valve-in-ring (MViR), and valve-in-MAC (ViMAC) have scant data beyond 1 year, thus prompting Henry Ford Hospital's description of mid-term outcomes in using balloon expandable THV in failed mitral bioprotheses, annuloplasty repairs and MAC.[7,8]

2 | METHODS

2.1 | Patient population

Consecutive patients who underwent MViV, MViR, and ViMAC from August 2013 to December 2019 were assessed for technical and procedural success. Follow-up was assessed at latest clinical interaction or telephone call. A minority of patients reported in this registry have been part of other prospective studies such as the MITRAL ($n = 13$) trial (NCT02370511) and the LAMPOON ($n = 8$) study (NCT03015194).[9] The study we present was reviewed and approved by the Henry Ford Hospital Institutional Review Board.

2.2 | Patient screening

Patients underwent retrospectively gated computed tomography angiogram (CTA) to evaluate mitral annular anatomy and risk for left ventricular outflow tract obstruction (LVOTO).[10,11] Patients with predicted neo-LVOT of ≤189 mm^2 were identified as at risk for LVOT obstruction and considered for LVOT modification via either alcohol septal ablation (ASA) or intentional laceration of the anterior mitral leaflet (LAMPOON).[11-13] Some with long anterior mitral leaflets were selected for LAMPOON based prior cases of leaflet interference with the THV.[14]

2.3 | Transseptal access and THV implantation

This series includes iterative advances in TMVR at Henry Ford Hospital: (1) Development of neo-LVOT assessment[10]; (2) Early adoption of transseptal access; (3) Use of small bore apical access to provide countertraction[15]; (4) Simplification to transseptal only access; and (5) LVOT modification for preventing LVOTO.

2.3.1 | THV access

Transapical and transseptal access were performed as previously described. Transapical access was performed via lateral thoracotomy (Figure 1).[7,16] Transfemoral access required a transseptal puncture, balloon septostomy, and either creation of a transapical rail or insertion of a stiff, preformed wire into the LV for THV delivery.

Small bore percutaneous apical access management: Please see prior publications for details regarding apical access and hemostasis management (Supplemental Video 1).[15]

2.3.2 | LVOT modification

Please see published reports for ASA and LAMPOON procedures.[9,13] Repeat gated-CTA was performed to assess enlargement of the predicted neo-LVOT for TMVR at least 3 weeks post-ablation.

2.4 | Definitions

Technical success, procedural success and endpoints were assessed according to the Mitral Valve Academic Research Consortium (MVARC) definitions.[17]

2.5 | Statistical analysis

Study population was stratified into three groups (MViV, MViR, and ViMAC). Data on demographics, echocardiography, angiography and hemodynamic assessment are presented as median with the interquartile 25%–75% range (IQR) and frequencies. Events are reported in a non-hierarchical fashion. Normality of distribution was assessed using the Shapiro–Wilk statistic. Baseline continuous characteristics between the three study groups were analyzed using analysis of variance (ANOVA) test, and Pearson Chi square (χ^2) or Fisher's exact test for categorical variables, respectively. Kaplan–Meier analysis for survival of individual outcome was performed using the Cox-Mantel log-rank procedure. Cox proportional hazards models were used to calculate independent predictors of mortality. All analyses were performed using SAS version 9.4 (Cary Institute, North Carolina, USA).

3 | RESULTS

From August 2013 to December 2019, a total of 88 cases of TMVR were performed at Henry Ford Hospital. A total of 38, 31, and 19 patients were treated with MViV, MViR, and ViMAC, respectively (Table 1). The patients in each group were elderly and at high risk for surgery. The MVIR group was unique from MViV and ViMAC groups due to having fewer women but a higher proportion of coronary artery disease, prior bypass surgery and 3–4+ mitral regurgitation (Table 1). Additionally, atrial fibrillation rates across the three cohorts were uneven, the MViV (82%) group had the highest proportion. Otherwise, overall TMVR population was significant for chronic kidney disease (1.4 ± 0.9) and an elevated mitral mean gradient (5.9 ± 2.5 mmHg). All but two cases had pre-procedural cardiac CT scans.

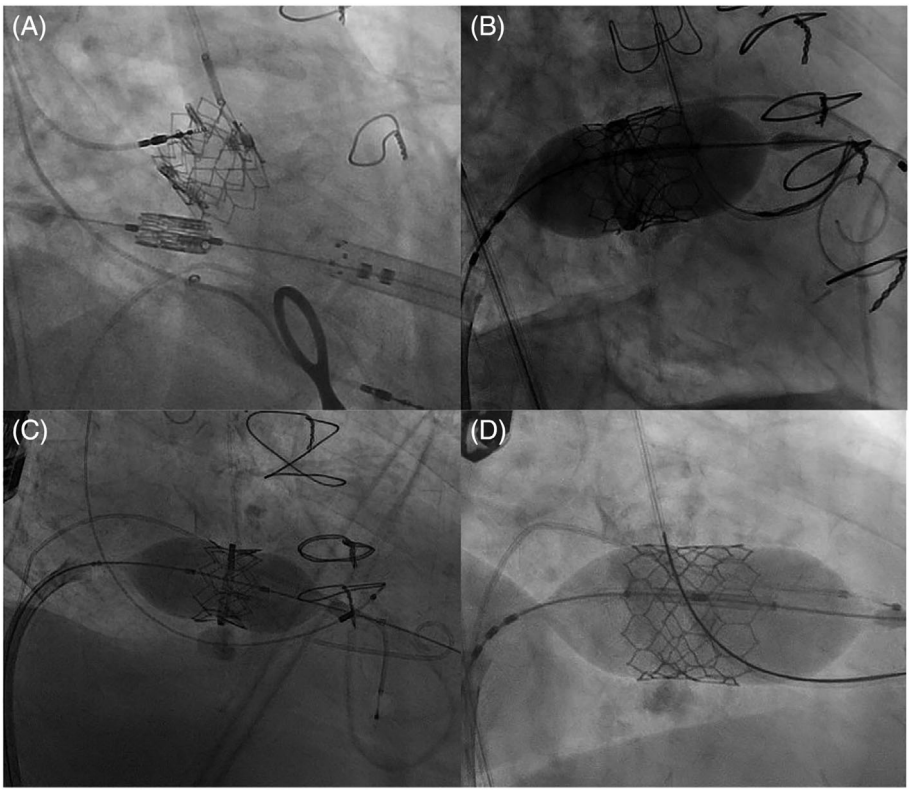


FIGURE 1 Various iterations of transcatheter mitral valve replacement. (A) Transapical implantation of a 23 mm Sapien XT (Edwards Lifesciences, Irvine, CA) valve. (B) Implantation of 26 mm Sapien 3 (Edwards Lifesciences, Irvine, CA) via transseptal approach. (C) Transseptal implantation of a 26 mm Sapien XT valve inside a Carpentier 28 mm annuloplasty ring (Edwards Lifesciences, Irvine, CA). (D) Transseptal implantation of a 29 mm Sapien-3 valve in heavy mitral annular calcification (MAC)

Median overall predicted neo-LVOT was 297 mm^2 (IQR 172, 524mm^2) with a notably median smaller predicted neo-LVOTs for the ViMAC cohort (Table 1).

3.1 | Procedural technique

The TMVR experience at Henry Ford Hospital experienced a series of iterative changes (Table 2). Two cases (2.2%) were performed with large bore transapical access, the remainder ($n = 86$) utilized transfemoral, transseptal access. An apical rail was used in 21% of transseptal cases. Patients high-risk for LVOTO were relatively common as alcohol septal ablation (ASA) or intentional laceration of the anterior mitral leaflet (LAMPOON) were performed in 11% and 25% of patients respectively. Distribution of LAMPOON and ASA amongst the three groups was uneven (Table 2). Most of valves utilized were either 26 or 29 mm valves, a minority of cases used 23 mm prostheses (16%).

3.2 | Procedure results

Overall procedural success was 60%, individualized cohort procedural success was 79%, 58%, and 26% for MViV, MViR, and ViMAC, respectively ($p = 0.048$) (Table 3). Overall technical success was 83% with individual cohort technical success of 97%, 77%, and 63% for MViV, MViR, and ViMAC, respectively ($p < 0.001$). All-cause in-hospital mortality for each group was 5%, 7%, and 37% for MViV, MViR, and ViMAC, respectively (p-value 0.001). There were 2 (2.2%) valve embolizations, both early in the ViMAC experience ultimately resulting in death (Supplemental Video 2). One ventricular perforation occurred from the delivery wire. Second valves were required in 0%, 19%, and 11% of the MViV. MViR and ViMAC cohorts, respectively ($p = 0.02$). THV post-dilation was common and occurred in the ViMAC arm the most (MViV 29%, MViR 58%, and ViMAC 74%, $p = 0.002$). As a reference, details of the anatomic dimensions, prosthesis manufacturer for MViV and MViR, THV utilized and each case type (Supplemental Tables 1–3). No direct correlation with ring type or sizes were associated with PVL or second valves. Likewise for ViMAC cases, there was no direct correlation with anatomy and PVL or second valve implantation.

Paravalvular leak impacted success, 3–4+ PVL occurred in 18% of cases (Table 3). ViMAC had the highest proportion (MViV 3%, MViR 29%, ViMAC 32%, $p = 0.04$). Of the 3–4+ PVL cases, one valve embolized. In the ViMAC patients, two required second valves while another underwent percutaneous PVL repair, and the remainder of the leaks were not addressed. Two of the ViR cases suffered PVL due to surgical ring dehiscence. The ViR cases with leaks between the ring and THV had successful percutaneous PVL repairs (Supplemental Video 3). The lone ViV PVL pre-existed prior to the TMVR and was not elucidated until after valve implantation.

As a cohort there was a 5% and 7% rate of major/extensive and life-threatening bleeding, respectively (Table 3). Two of the major bleeds were related to serial catheter exchanges, while an extensive bleed occurred from post-procedural abdominal hematoma related to heparin infusion. One patient experienced major blood loss due to

TABLE 1 Baseline characteristics

	Overall $N = 88$	MViV $N = 38$	MViR $N = 31$	ViMAC $N = 19$	*p*-value
Female gender (%)	51 (57)	26 (68)	11 (34)	14 (74)	0.0065
Age (years)	76 (65, 83)	76 (65, 84)	77 (64, 83)	77 [70, 88]	0.794
CAD (%)	43 (49)	13 (34)	21 (68)	9 (47)	0.0212
Prior MI (%)	16 (18)	6 (16)	9 (28)	1 (5)	0.0939
PAD (%)	11 (12)	3 (8)	5 (16)	3 (16)	0.5225
Prior CABG (%)	32 (36)	10 (26)	17 (53)	5 (26)	0.0293
≥1 sternotomy (%)	74 (84)	38 (100)	30 (97)	6 (32)	0.0001
DM (%)	23 (26)	6 (16)	10 (31)	7 (37)	0.1468
LVEF (%)	55 (45, 63)	58 (52, 64)	50 (35, 55)	62 (55, 68)	0.001
NYHA Class III/IV (%)	84 (96)	37 (97)	29 (94)	18 (95)	0.7397
HTN (%)	67 (76)	28 (74)	24 (77)	15 (79)	0.8885
MR ≥3+ (%)	42 (47)	17 (45)	22 (69)	3 (17)	0.0006
Baseline Cr (g/dl)	1.2 (1.0, 1.5)	1.2 (1.0, 1.4)	1.2 (1.0, 1.6)	1.1 (1.0, 1.4)	0.682
Hemodialysis (%)	4 (5)	2 (6)	1 (3)	1 (6)	0.9048
COPD (%)	37 (42)	15 (40)	11 (34)	11 (58)	0.2712
Severe PH (%)	29 (34)	14 (38)	9 (30)	6 (32)	0.4421
Mitral gradient (mmHg)	10.3 (6.7, 12.5)	11.1 (9.1, 14.2)	7.0 (5.2, 10.5)	11 (7.1, 12.8)	0.013
Atrial fibrillation (%)	56 (63)	31 (82)	21 (66)	4 (21)	0.0001
Prior stroke (%)	19 (21)	8 (21)	6 (19)	5 (26)	0.8400
PPM (%)	30 (34)	14 (37)	12 (38)	4 (21)	0.3946
STS PROM score	8.2 (5.2, 14.9)	9.0 (6.2, 14.9)	6.1 (4.3, 11.8)	11.3 (4.7, 21.3)	0.331
Projected neo-LVOT	297 (172, 524)	310 (227, 568)	416 (226, 573)	125 (60, 201)	0.011

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; DM, diabetes mellitus; HTN, hypertension; LVOT, left ventricular outflow tract; MI, myocardial infarction; MViV, mitral valve-in-valve; MViR, mitral valve-in-ring; MR, mitral regurgitation; NYHA, New York Heart Association; PAD, peripheral arterial disease; PH, pulmonary hypertension; PPM, permanent pacemaker; SD, standard deviation; STS PROM, Society of Thoracic Surgeon Predicted Risk of Mortality; ViMAC, valve in mitral annular calcification.

TABLE 2 Procedural characteristics

	Overall $N = 88$	MViV $N = 38$	MViR $N = 31$	ViMAC $N = 19$	*p*-value
Procedural characteristics					
Sapien TFX	3 (3)	0 (0)	1 (3)	2 (11)	0.12
Sapien XT	16 (18)	10 (26)	3 (10)	3 (16)	0.195
Sapien 3	69 (78)	28 (74)	27 (87)	14(74)	0.344
Valve >23 mm (%)	74 (84)	33 (87)	24 (77)	17 (90)	0.4365
Large bore Transseptal access (%)	86 (98)	37 (97)	31 (100)	18 (95)	0.470
Small bore apical access (%)	18 (21)	8 (21)	7 (23)	3 (16)	0.8400
LVOT modified (%)	31 (35)	5 (13)	13 (42)	13 (68)	0.0001
Alcohol septal ablation (%)	10 (11)	4 (11)	1 (3)	5 (26)	0.0432
LAMPOON (%)	21 (25)	1(3)	12 (39)	8 (42)	0.0002
Post dilation (%)	43 (49)	11 (29)	18 (58)	14 (74)	0.002
ASD closure (%)	48 (55)	25 (66)	16 (52)	7 (37)	0.1082

Abbreviations: ASD, atrial septal defect; LAMPOON, Intentional laceration of the anterior mitral valve leaflet to prevent LVOT obstruction; LVOT, left ventricular outflow tract; MViV, mitral valve-in-valve; MViR, mitral valve-in-ring; ViMAC, valve-in-mitral annular calcification.

hemolysis and required transfusion of 3 units of packed cells. Of the life-threatening bleeds, 5/6 were related to the procedure. Three were related to apical access resulting in two hemothorax and one pericardial effusion. One retroperitoneal bleed occurred from inferior epigastric artery laceration. The remaining two bleeds were non-access site related and occurred in the hospitalization after the procedure.

TABLE 3 In-hospital and late outcomes

In-hospital					
	Overall $N = 88$	**MViV $N = 38$**	**MViR $N = 31$**	**ViMAC $N = 19$**	***p*-value**
Procedural success (MVARC) (%)	53 (60)	30 (79)	18 (58)	5 (26)	0.001
Technical success (MVARC) (%)	73 (83)	37 (97)	24 (77)	12(63)	<0.001
Moderate–severe PVL	16 (18)	1 (3)	9 (29)	6 (32)	0.04
PVL closure	7 (8)	1 (3)	5(16)	1 (5)	0.106
Repeat TMVR	8 (9)	0	6 (19)	2 (11)	0.020
LVOT obstruction	11 (13)	0	2 (7)	9 (47)	0.0001
Valve embolization	2 (2)	0	0	2 (11)	0.0243
Minor VC	3 (3)	1 (3)	1 (3)	1 (5)	0.8732
Major VC	3 (3)	3 (8)	0	0	0.1296
Major bleeding	4 (5)	1 (3)	2 (7)	1 (5)	0.740
Life threatening bleeding inpatient	6 (7)	3 (8)	1 (3)	2 (11)	0.5740
Late major/life-threatening bleeding	4 (4)	2 (5)	1 (3)	1 (5)	0.908
Stroke	2 (2)	1 (3)	1 (3)	0	0.7443
AKI (RIFLE stage 1–3)	11 (13)	3 (8)	5 (16)	3 (16)	0.5225
Hemolysis	4 (5)	1 (3)	2 (7)	1 (5)	0.7397
In-patient death	11 (13)	2 (5)	2 (7)	7 (37)	0.001
Late outcomes					
Valve thrombosis	6 (7)	3 (8)	2 (7)	1 (6)	0.9423
Death	38 (43)	9 (24)	16 (52)	13 (68)	0.003

Abbreviations: AKI, acute kidney injury; LVOT, left ventricular outflow tract; MVARC, Mitral Valve Research Consortium; MViV, mitral valve-in-valve; MViR, mitral valve-in-ring; PVL, paravalvular leak; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; TMVR, transcatheter mitral valve replacement; VC, vascular complication; ViMAC, valve-in-mitral annular calcification.

Acute kidney injury (AKI) RIFLE stages 1–3 occurred in 13% of the overall cases (Table 3). A slight minority of cases (5/11) were AKI Stage 1, were periprocedural and ultimately their renal function returned to baseline. Of the remaining cases, all were Stage 3 (6/11), four patients required dialysis. Most cases were suspected to be due to CIN but hypoperfusion from cardiac arrest and hemolysis were each blamed for one case of Stage 3 AKI.

3.3 | Late outcomes

Median follow up time was 1.4 years (IQR 0.5–2.9 years). One-year clinical follow-up was 66%, 74%, and 42% for MViV, MViR, and ViMAC, respectively. Overall survival at 2 years was 60% and approximately 40% surviving at 4 years (Figure 2). When examining the population in its distinct procedure types (MViV, MViR, ViMAC), a hierarchy of survival was observed with MViV performing the best and ViMAC performing the worst (Figure 3, log-rank $p = 0.0002$). Four-year survival for MViV was 77% while MViR and ViMAC patients tended to have limited long-term survival (MViR <20%, MViMAC <20% $p = 0.0002$), particularly ViMAC as only 42% survival was observed at 1 year. When adjusting for co-variates, the strongest predictor of survival was a MViV procedure (HR 0.24 [95% CI 0.079–0.7]) (Table 4). Small valve sizes (<26 mm), LVOTO and moderate/severe PVL were suggestive as predictors of mortality but were not statistically significant (Table 4).

Risk for LVOTO was prevalent in our series and LVOTO attenuated survival (Figure 4). Median predicted baseline predicted neo-LVOT in 32 patients with LVOT modification was 169 mm^2 (IQR 78, 231). About 1/3rd (35%) of cases utilized LVOT modification in the form of either ASA or LAMPOON and 13% (11/88) of patients did have LVOTO. LAMPOON was performed in 4/25 (16%) excessively long anterior mitral leaflets. Three patients suffered LVOTO without antecedent LVOT modification (Supplemental Video 4). Median predicted neo-LVOT of patients with LVOTO was 68 mm^2 (IQR 58, 103 mm^2) and median gradient post-implantation was 36.7 mmHg (IQR 31.95, 59.1 mmHg). Four patients died prior to discharge. Two rescue alcohol septal ablations were performed, one in a patient without pre-emptive LVOT modification and another with LVOTO despite LAMPOON. The majority of ViMAC patients (68%) required LVOT modification. All MViV cases with LVOT modification did not obstruct, while 7% (2/31) and 47% (9/19) MViR and ViMAC cases suffered LVOTO, respectively (*p*-value <0.001). The overall success rate of LVOT modification was 100%, 84.6%, and 30.7% in MViV, MViR, and ViMAC, respectively ($p = 0.003$). Long term survival of LVOTO cases was attenuated compared to the remaining TMVR patients (log-rank $p = 0.0074$) (Figure 4).

Valve thrombosis occurred in 7% (6/88) of cases. The median time to the diagnosis of thrombosis was 96 days (IQR 66, 112 days).

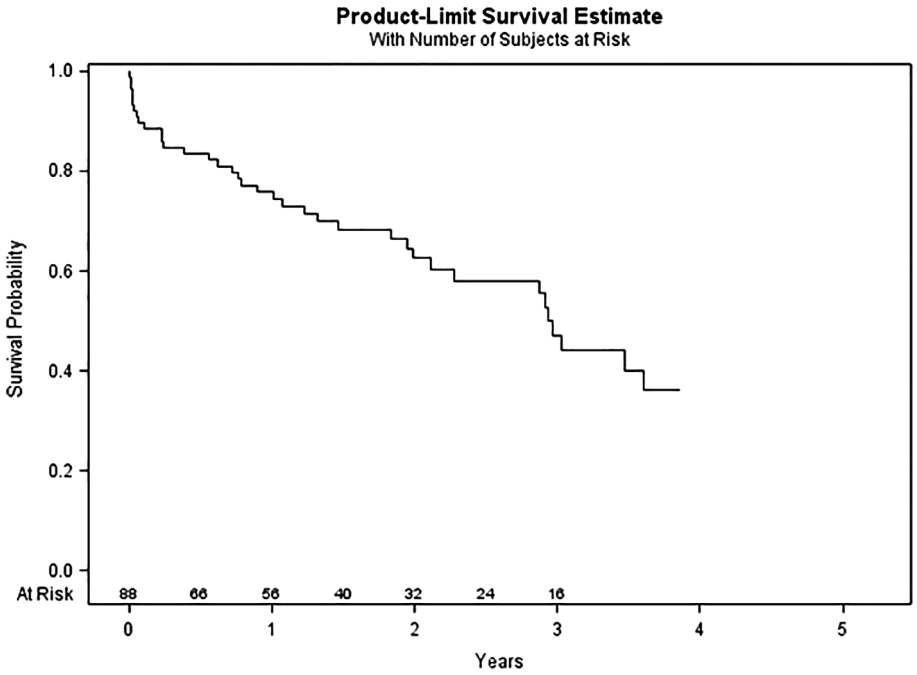


FIGURE 2 Kaplan–Meier estimate of overall cohort survival for transcatheter mitral valve replacement (TMVR)

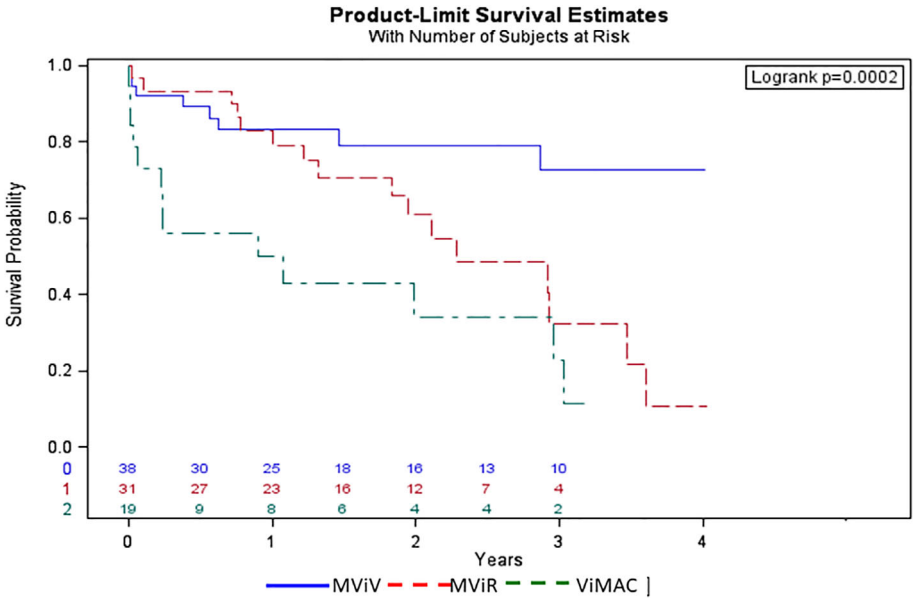


FIGURE 3 Kaplan–Meier estimate of survival when transcatheter mitral valve replacement (TMVR) is individualized to procedure type. Survival for mitral valve-in-valve (MViV) (Blue), mitral valve-in-ring (MViR) (dashed red), and valve-in-MAC (ViMAC) (dashed green) demonstrate significantly impaired survival for ViMAC and attenuated long-term survival for MViR compared to MViV [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Multivariate analysis for predictors of death

	Hazard ratio	95% confidence interval
Degenerated bioprosthesis versus severe MAC	0.235	0.079–0.700
Failed annuloplasty ring versus severe MAC	0.596	0.235–1.514
Mean gradient >10 mmHg	0.705	0.142–3.508
LVOT obstruction	1.694	0.568–5.048
Valve size <26 mm	2.249	0.833–6.704
Moderate–severe PVL	1.411	0.486–4.093
GI bleed	0.984	0.509–1.904

Abbreviations: GI, gastrointestinal; LVOT, left ventricular outflow tract; PVL, paravalvular leak; MAC, mitral annular calcification.

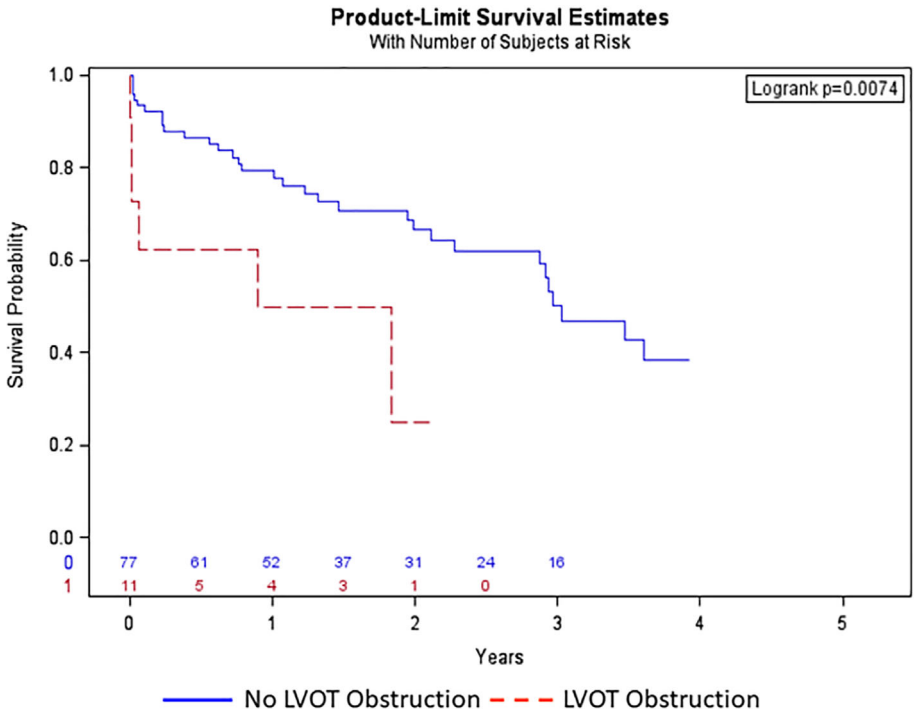


FIGURE 4 Kaplan–Meier estimate of survival comparing patients with (blue) and without (dashed red) left ventricular outflow tract (LVOT) obstruction [Color figure can be viewed at wileyonlinelibrary.com]

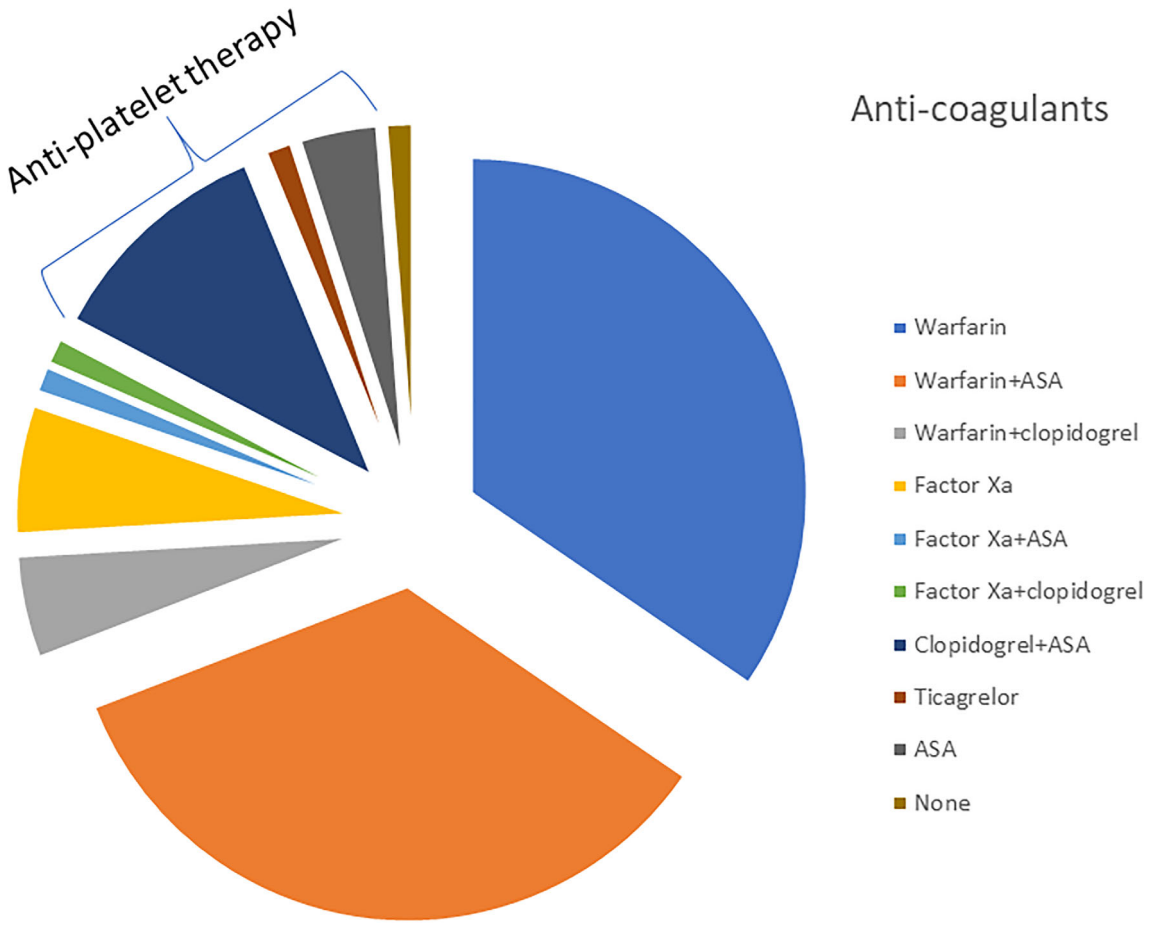
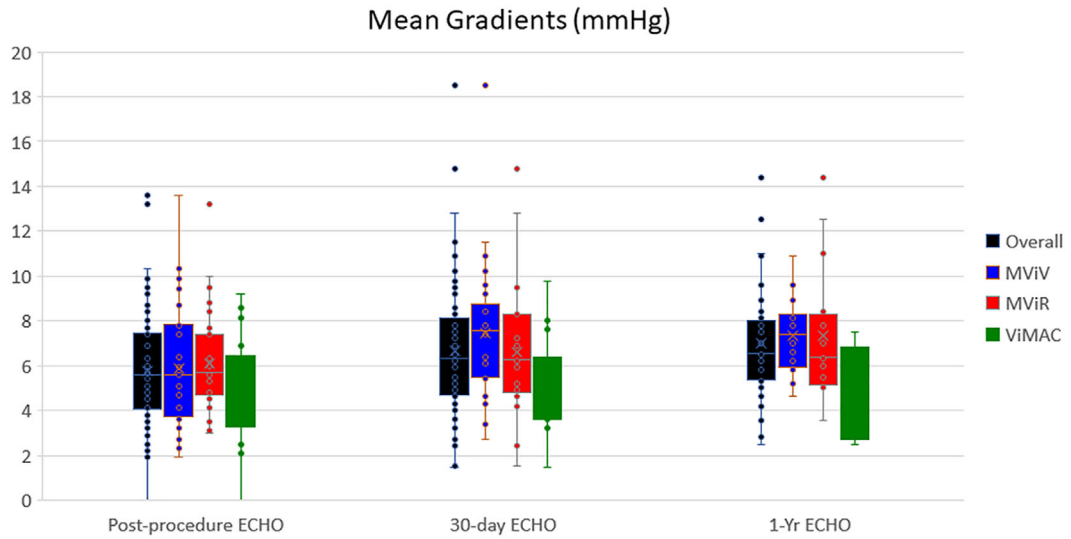


FIGURE 5 Discharge medications of the overall cohort. The majority (76%) of the patients were discharged with either warfarin or a factor Xa inhibitor [Color figure can be viewed at wileyonlinelibrary.com]



	Post-Procedure (n)	30-Day (n)	1-Year (n)	P-value
Overall (88)	5.8 ±2.4 (85)	6.6±2.9 (73)	7±2.4 (37)	0.038
MViV (38)	5.9±2.7 (37)	7.5±3.1 (30)	7.3±1.8 (15)	0.039
MViR (31)	6.1±2.3 (31)	6.6±2.7 (30)	7.4±2.9 (15)	0.26
ViMAC (19)	5.3±2.1 (17)	5±2.3 (13)	5±2.1 (7)	0.92

FIGURE 6 Mean gradients of the overall cohort (black), mitral valve-in-valve (MViV) (blue), mitral valve-in-ring (MViR) (red), and valve-in-MAC (ViMAC) (green) from immediately post-implantation to 1 year [Color figure can be viewed at wileyonlinelibrary.com]

Of the 81 patients surviving to discharge, 82.7% were prescribed oral anticoagulation on discharge. The remainder took antiplatelet therapy in some fashion (Figure 5). Valve thrombosis developed in 3% (2/67) and 28.6% (4/14) of patients with and without oral anticoagulation, respectively ($p = 0.001$).

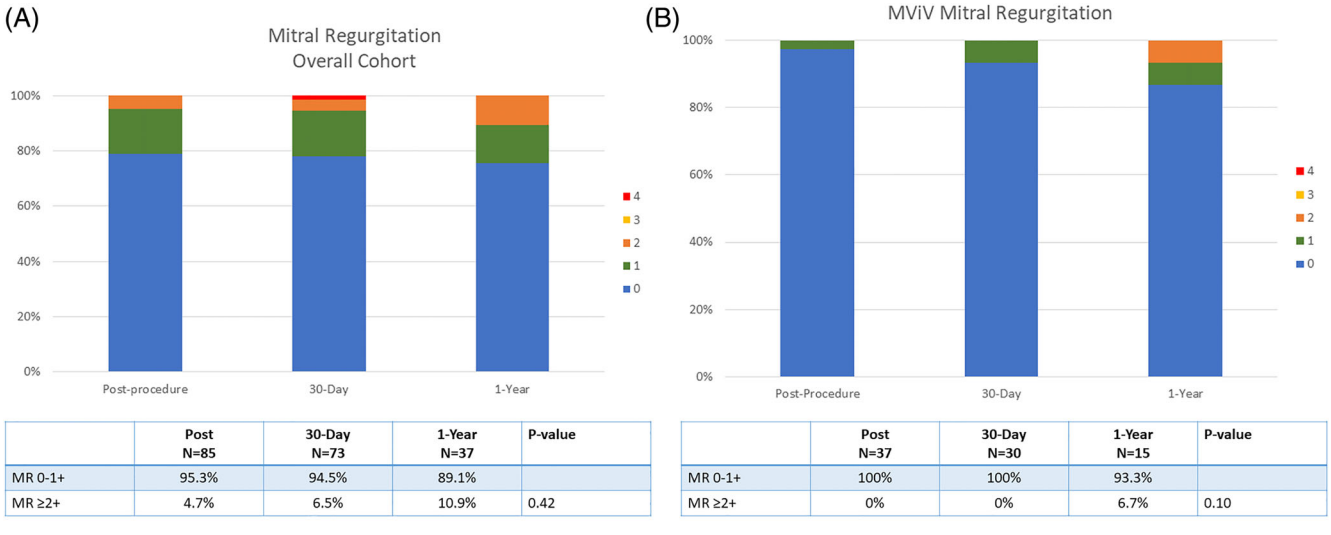
3.4 | Echocardiography

Mid-term echocardiographic outcomes show that the gradients increase slightly over time. Echocardiographic 1-year follow-up was available for 39%, 48%, and 37% of MViV, MViR, and ViMAC, respectively. Mean gradient post-TMVR was 5.8 ± 2.4 mmHg, 6.6 ± 2.9 mmHg at 30 days, and 7 ± 2.4 mmHg at 1 year ($p = 0.03$) (Figure 6). The differences in gradients from baseline to 1 year appear to mostly driven by the MViV cohort while the MViR and ViMAC groups did not have significantly different gradients during follow up (Figure 6). Rates of ≥2+ mitral regurgitation (MR) was low initially (4.7%), but despite the increased proportion of ≥2 + MR (10.8%) at 1 year it was not statistically significant ($p = 0.42$) (Figure 7). No significant changes in the rates of ≥2+ MR in each of the subgroups were observed over the course of a year (Figure 7).

4 | DISCUSSION

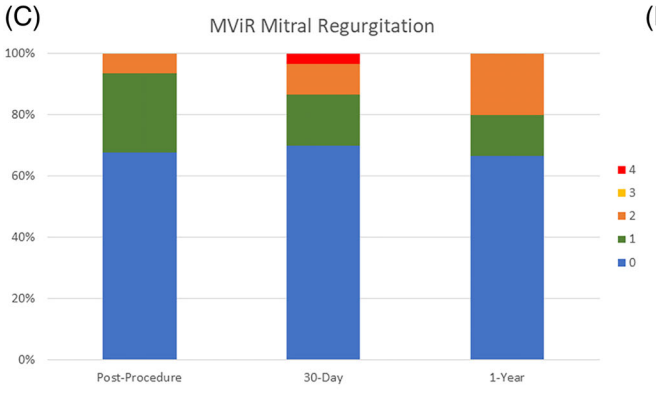
Conclusions drawn from this registry include: (1) MViV procedures are safe and have the best long-term survival; (2) MViR procedures are feasible but do carry risks such as paravalvular leak and higher likelihood for requiring a second valve; (3) ViMAC procedures are challenging due to high rates of LVOTO, paravalvular leak and potential for valve embolization; (4) Valve thrombosis is a long-term concern and further investigation is required to delineate the appropriate duration of anticoagulation; (5) Threat of LVOTO is common with 35% of the entire population undergoing some type of modification and in spite of modification, LVOTO occurred in 13% of cases; and (6) MViR and ViMAC have poor long-term prognosis.

Previously, the longest follow up was a series of 23 transcatheter mitral valve replacements performed via apical access for MViV cases.[16] Median follow up was 2 years (IQR 1.03–3.06 years) and at the time of the latest assessment, the median survival was 90.4%. One patient suffered from LVOT obstruction post-TMVR but this patient had pre-existing hypertrophic obstructive cardiomyopathy. Despite the early experience, the excellent 2-year survival reinforces the fact that MViV cases have the best outcomes. Otherwise, the next longest follow up published is a 7-year French experience with TMVR that mirrors our experience.[18] In this study, 91 patients with even distribution between MViV, MViR, and ViMAC underwent TMVR. One-year and 2-year mortality rates were 21% (95% CI 9.9–38.8) and 35.7% (95% CI 19.2–56.5) respectively. In the largest series to date, a multicenter registry of 521 TMVR were able to show a 23.5% 1-year mortality rate.[7] Both the French and large multicenter registry showed that MViV procedures have best immediate and intermediate-term survival while MViR and especially ViMAC patients have higher rates of procedural complications, post-TMVR perivalvular leak and mortality.[7,18]

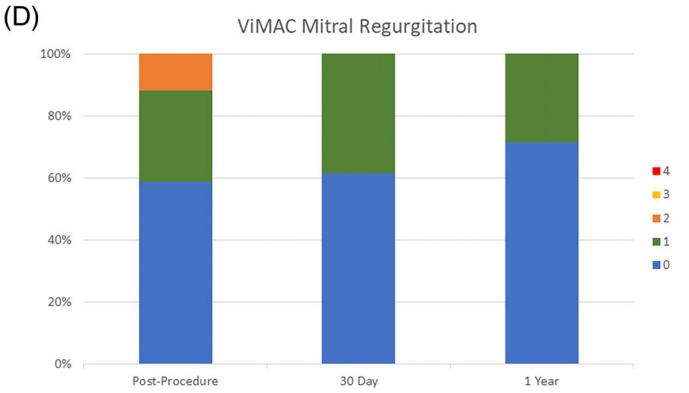


	Post N=85	30-Day N=73	1-Year N=37	P-value
MR 0-1+	95.3%	94.5%	89.1%	
MR ≥2+	4.7%	6.5%	10.9%	0.42

	Post N=37	30-Day N=30	1-Year N=15	P-value
MR 0-1+	100%	100%	93.3%	
MR ≥2+	0%	0%	6.7%	0.10



	Post N=31	30-Day N=30	1-Year N=15	P-value
MR 0-1+	93.6%	92.7%	73.3%	
MR ≥2+	6.4%	13.3%	26.7%	0.164



	Post N=17	30-Day N=13	1-Year N=7	P-value
MR 0-1+	88.3%	100%	100%	
MR ≥2+	11.7%	0%	0%	0.288

FIGURE 7 Mitral regurgitation over time for the (A) Overall cohort; (B) mitral valve-in-valve (MViV); (C) mitral valve-in-ring (MViR); (D) valve-in-MAC (ViMAC). Transcatheter mitral valve replacement (TMVR) largely abolished mitral regurgitation and no progression in mitral regurgitation (MR) was seen over time [Color figure can be viewed at wileyonlinelibrary.com]

ViMAC deserves particular attention given the outcomes. The only two valve embolizations occurred in ViMAC, and a significant proportion required LVOT modification. Even with 68% of the ViMAC cohort undergoing LVOT modification, 47% still met the MVARC definition of LVOT obstruction. High rates of severe paravalvular leak (32%) were present, giving the ViMAC the lowest procedural success rate. Other large multicenter series mirror the Henry Ford Hospital experience with high rates of severe PVL and device reintervention. The first registry, a 116 patient study demonstrated a 11.2% rate of hemodynamically significant LVOT obstruction despite 19.8% of patients undergoing open transatrial implantation with anterior leaflet resection.[19] At 1 year, the overall survival was 47.3%. Similarly, the multicenter French study showed a high rate of LVOT obstruction (39.7%) and 12.1% of patients requiring alcohol septal ablation.[7]

MViR cases have lower long-term survival and a higher rate of procedural complications compared to MViV. The first observation is that a considerable number of cases (16%) required second valves. One limiting factor is that the landing zone for the THV is short and valve implantation precarious. If the delivery system is not coaxial, and the THV is short (i.e., 23 mm), landing the THV in the ring can be difficult. One unexpected complication was annuloplasty dehiscence ($n = 2$). A report from a multicenter registry reflected similar experience with 12.1% of patients requiring second valves and 17.7% requiring re-intervention, frequently for PVL closure.[7] Moderate or greater mitral regurgitation at 30 days was seen in 13.3% and 12.6% of Henry Ford Hospital and Yoon et al.'s multicenter registry, respectively.[7]

A unique feature of our dataset is the high proportion pre-emptive LVOT modification (35%). Despite the use ASA or LAMPOON, 13% still experienced LVOTO. Of note, most of the LVOTO cases occurred in the ViMAC cohort, due to small ventricular size. LAMPOON was intended to prevent catastrophic obstruction during TMVR, therefore the parameters for "optimal" and "acceptable" LVOT gradients were <30 mmHg and <50 mmHg, respectively, against a background of

predicted mean 81 ± 51 mm^2 neo-LVOT.[9] The prospective study showed that LAMPOON achieved a 97% rate of optimal LVOT gradient and 100% rate of acceptable LVOT gradient. Alternatively, in a retrospective analysis of a multicenter registry, median increase in neo-LVOT post ASA was 111.2 mm^2 (IQR 71.4–193.1 mm^2) and 4/28 (14%) patients did not achieve sufficient predicted neo-LVOT despite ASA, ultimately receiving transatrial TMVR, LAMPOON or deferral of the procedure.[13] The advantage of LAMPOON is that it obviates procedure delay ASA requires. However, LAMPOON is technically challenging, while ASA is simpler. It is likely that neither technique can resolve LVOTO completely therefore they should be considered complementary rather than competitive procedures.

Valve thrombosis occurred in 7% of the overall cohort with a median time of 96 days (range 34–674 days). This suggests the late development of valvular thrombosis remains an issue bearing implications for the duration of anticoagulation.[20] A single center Israeli surgical valve registry documented that 9/45 cases of biprosthetic MVR with native leaflet preservation suffered thrombosis at a mean follow up of 11.9 months.[21] It is unclear when patients may stop anticoagulation and this subject requires further investigation.

4.1 | Limitations

This is a retrospective analysis and the conclusions drawn are hypothesis generating. The sample size of the separate groups is too small for meaningful subgroup analysis, especially if exploring differences in outcomes of LVOT modification or other procedural techniques. The high proportion of LVOT modification in this series may not be generalizable. Several cases in this registry do reflect the early experience of the procedure, a time when CT case planning and techniques of LVOT modification were immature. Of course, confounding from unmeasured variables such as frailty or baseline anemia may have impacted procedural and short-term mortality and biased results. Additionally, an imaging core lab was not used to adjudicate post-procedural echocardiograms.

5 | CONCLUSIONS

MViV is associated with favorable short- and long-term outcomes. Lower rates of technical success and more complications were observed with MViR. ViMAC interventions fraught with hazard and due to LVOTO, PVL and challenging THV anchoring. Long-term survival in MViR and ViMAC was poor in this series. These results warrant further investigation in identifying patient factors and anatomy conducive to long-term success in TMVR.

5.1 | Impact on daily practice

This series demonstrated a technical success rate of 97%, 77%, and 63% for MViV, MViR, and ViMAC cases, respectively. Survival at 4 years was found to be the best in MViV patients (77%) while MViR and ViMAC long-term survival was <20%. MViR and ViMAC procedures bear more complexity and caution should be exercised when performing these procedures.

CONFLICT OF INTEREST

Marvin H. Eng, MD and Tiberio Frisoli are clinical proctors for Edwards Lifesciences and Medtronic. Dee Dee Wang, MD has received research grant support from Boston Scientific; and is a consultant for Edwards Lifesciences, Boston Scientific, and Materialise. Adam B. Greenbaum is a proctor for Edwards Lifesciences, Medtronic and Abbott Vascular; holds equity in Transmural Systems; and receives research support to his employer from Edwards Lifesciences, Abbott Vascular, Medtronic, and Boston Scientific. Mayra Guerrero has received research support from and has been a proctor/consultant to Edwards Lifesciences. Faraj Kargoli, MD, Hasan Nemeh MD, James C. Lee MD, Brian P. O'Neill, Pedro S. Villablanca and Janet Wyman NP have no conflicts to declare. Dr William W. O'Neill has received grant support from Edwards Lifesciences and Abiomed.

DATA AVAILABILITY STATEMENT

The data is available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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