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ORIGINAL RESEARCH

STRUCTURAL

3-Year Outcomes of Mitral Valve-in-Valve Therapy Using Balloon-Expandable Transcatheter Valves in the United States

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ABSTRACT

BACKGROUND Mitral valve-in-valve (MViV) is a safe and effective therapy for severe bioprosthetic mitral degeneration; however, longer-term outcomes are not well defined.

OBJECTIVES This study aimed to evaluate 3-year outcomes following MViV.

METHODS Outcomes of all-cause mortality, stroke, and reintervention were collected in patients undergoing transseptal MViV with the SAPIEN 3 valve family for failed surgical bioprostheses from June 2015 to March 2024 in the TVT (Transcatheter Valve Therapy) Registry, and Centers for Medicare and Medicaid Services data linkage was performed. Kaplan-Meier and Cox proportional hazards analysis was performed according to Society of Thoracic Surgeons (STS) score and procedure status.

RESULTS A total of 5,971 patients (age 72.9 ± 11.4 years, 57.9% [n = 3457 of 5,971] female) underwent MViV. Low (<4), intermediate (4-8), and high (>8) STS scores were present in 23.5% (n = 1,310 of 5,585), 35.1% (n = 1,960 of 5,585) and 41.5% (n = 2,315 of 5,585) of patients, respectively. Median follow-up duration was 377 days (Q1-Q3: 57-698 days). Mortality at 3 years was greatest in high STS score and nonelective procedures, while mortality was lowest in low STS score patients and elective procedures. Stroke rates at 3 years were comparable except between low and high STS groups. Mitral valve reintervention during 3 years of follow-up was uncommon in all groups.

CONCLUSIONS Three-year survival after MViV is highest in low STS scores and elective procedures, whereas survival was significantly lower in high STS scores and nonelective procedures. These findings emphasize the importance of early identification and treatment of patients who may benefit from MViV. Reintervention rates at 3 years are low regardless of STS score. (JACC Cardiovasc Interv. 2025;18:1454–1466) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Over the last decade, transseptal mitral valve-in-valve (MViV) has developed into a first-line therapy for patients with degenerated mitral bioprostheses as a less invasive alternative for patients at increased risk for repeat cardiac surgery.[1,2] Multiple studies have demonstrated the favorable short-term safety and efficacy of MViV, with high 30-day and 1-year survival rates.[3-5] However, only limited data are available regarding midterm outcomes of transseptal MViV.[6-8] Given the inherently smaller effective orifice resulting from the implantation of a balloon-expandable valve within a degenerated bioprosthesis with associated mildly increased mean Doppler gradients, questions have been raised regarding the long-term durability and outcomes of this groundbreaking minimally invasive therapy. These questions deepen as MViV therapy is applied to lower-surgical-risk populations who could potentially undergo either redo surgery or MViV.[2] Midterm outcome data using the newest-generation SAPIEN 3 and SAPIEN 3 Ultra balloon-expandable valves (Edwards Lifesciences) in the United States have not yet been reported but could further inform the role of MViV in the treatment of the spectrum of patients presenting with mitral bioprosthesis degeneration. To better understand midterm outcomes of this novel therapy, the goal of this study was to evaluate survival, stroke, and reintervention following MViV in a large population at 3 years of follow-up using the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) TVT (Transcatheter Valve Therapy (TVT) Registry.

METHODS

STUDY POPULATION. Patients undergoing transseptal MViV in the United States from August 2015 through March 2024 reported to the STS/ACC TVT Registry were included in this study. The TVT Registry has been approved by a central Institutional Review Board (Advarra) with a waiver of informed consent granted by the Duke University School of Medicine Institutional Review Board under the Common Rule 45 CFR 46.3. This paper conforms to the Strengthening of Reporting of Observational Studies in Epidemiology cohort guidelines.

The study inclusion criteria included patients undergoing transseptal MViV for degenerated bioprosthetic mitral valves. Patients undergoing transapical, other alternative access MViV, or mitral valve-in-ring or native mitral valve anatomy were excluded.

PROCEDURE. Transseptal MViV procedural techniques have been previously described and include transvenous access with the creation of a balloon atrial septostomy to facilitate delivery of the balloon-expandable SAPIEN 3 valve over a curved guidewire positioned in the left ventricular apex. The valve is carefully positioned under fluoroscopic and echocardiographic guidance and deployed using rapid ventricular pacing, with the failed bioprosthetic valve as an anchor. Following implantation, the delivery system is removed, and the atrial septal defect is assessed and closed with an atrial septal defect closure device if deemed necessary.

OUTCOME DEFINITIONS. The primary outcomes of interest were all-cause mortality, stroke, and repeat mitral intervention at 3 years. Secondary outcomes included NYHA functional class and quality of life defined by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year. The ratio of observed to expected mortality was reported with expected mortality defined as the STS risk score for surgical mortality.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD or median (Q1-Q3) and were compared between groups using the 2-sample *t* test or Wilcoxon rank sum test. Categorical variables were presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. The 30-day, 1-year, and 3-year adverse event rates were based on Kaplan-Meier estimates, and all comparisons were made using the log-rank test. Due to high rates of missing KCCQ Overall Summary Score data at 1 year, a sensitivity analysis using the inverse probability weighting method was used for 1-year KCCQ data.

A multivariable Cox regression model based on the lowest Akaike information criterion method was performed to identify independent predictors of 3-year mortality. Baseline characteristics that were clinically relevant were selected as candidate covariates in the model. Proportional hazards assumption was confirmed through testing based on Kolmogorov-type supremum test. Thirty-one covariates were used for adjustment: age, race, procedure status, atrial fibrillation/flutter, porcelain aorta, hostile chest, carotid stenosis, number of diseased vessels, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior myocardial infarction, previous implantable cardioverter-defibrillator, permanent pacemaker, currently on dialysis, chronic

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

CMS = Centers for Medicare and Medicaid Services

KCCQ = Kansas City Cardiomyopathy Questionnaire

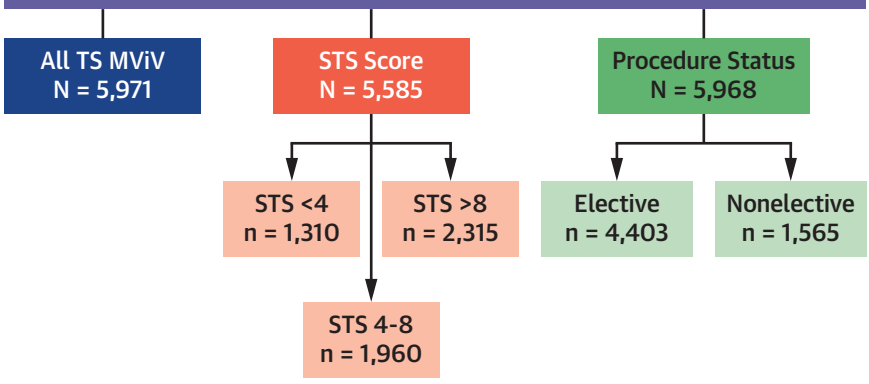
MViV = mitral valve-in-valve

STS = Society of Thoracic Surgeons

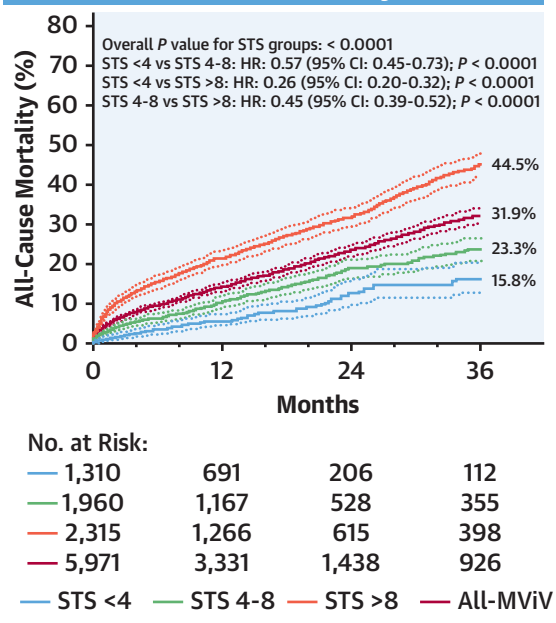
CENTRAL ILLUSTRATION MViV Outcomes From STS/ACC TVT Registry

Long-Term Outcomes of Mitral Valve-in-Valve Therapy

A Study Flow Chart



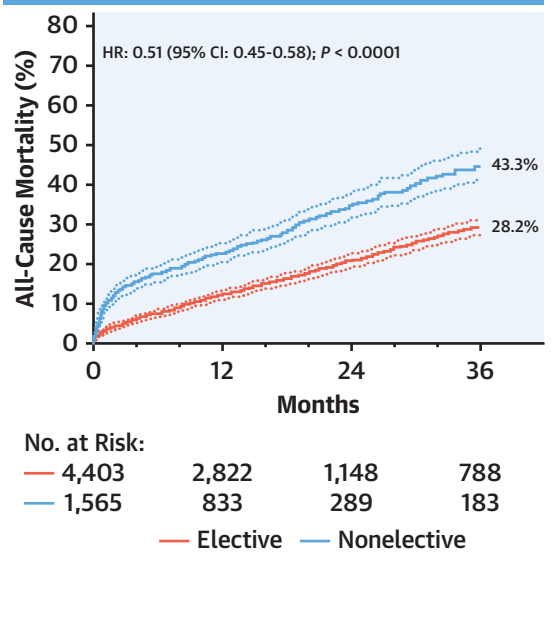
B 3-Year All-Cause Mortality for All MViV Patients and by STS Score



No. at Risk:

STS <4	1,310	691	206	112
STS 4-8	1,960	1,167	528	355
STS >8	2,315	1,266	615	398
All-MViV	5,971	3,331	1,438	926

C 3-Year All-Cause Mortality by Procedure Status



No. at Risk:

Elective	4,403	2,822	1,148	788
Nonelective	1,565	833	289	183

- 3-year survival after transseptal MViV is favorable among patients with low and intermediate STS risk scores.
- High STS risk score and nonelective procedure status are associated with higher 3-year mortality.
- MViV is an effective therapy associated with favorable mid-term outcomes in carefully selected patients.
- Strategies to treat patients before advanced comorbidities develop are needed to optimize longer-term outcomes following MViV.

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lung disease, home oxygen, hemoglobin, creatinine, glomerular filtration rate, diabetes mellitus, peripheral arterial disease, ≥ moderate aortic regurgitation, left ventricular ejection fraction <50%, cardiac index <2.2, ≥ moderate mitral regurgitation, ≥ moderate tricuspid regurgitation, immunocompromised, cardiogenic shock within 24 hours, heart failure hospitalization within past year, NYHA functional III/IV, and KCCQ Overall Summary Score.

To perform 3-year survival, stroke, and reintervention analyses, the STS/ACC TVT Registry was linked to the United States Centers for Medicare and Medicaid Services (CMS) claims data using probabilistic matching with patient birth date, gender, and transcatheter aortic valve replacement procedure date. Patients eligible for linkage were all over 65 years of age with Medicare coverage enrolled in the Medicare Parts A and B fee-for-service program. Multiple matches were removed, and only 1 unique case was used for the analysis. For non-CMS eligible patients without linked CMS claims data, TVT Registry data were used up to 1 year follow-up. In addition, we performed a landmark analysis to assess the impact of procedure status 3 months after MViV on 3-year all-cause mortality.

All P values were 2-sided, $P < 0.05$ was considered significant for all tests, and no adjustment for multiple testing was undertaken. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. A total of 5,971 patients (mean age 72.9 ± 11.4 years, 57.9% [n = 3,457 of 5,971] female, 82.5% [n = 4,924 of 5,971] Caucasian, 10.1% [n = 604 of 5,971] African American) underwent transseptal MViV and were included in the study (**Central Illustration**, **Table 1**). Baseline clinical and echocardiographic characteristics are shown in **Table 1**. Low (<4), intermediate (4-8), and high (>8) STS scores were present in 23.5% (n = 1,310 of 5,585), 35.1% (n = 1,960 of 5,585), and 41.5% (n = 2,315 of 5,585) of patients, respectively (**Central Illustration**, Supplemental Table 1). The mean STS scores in each group were as follows: 2.8 (Q1-Q3: 2.0-3.4) in the low-risk group, 5.9 (Q1-Q3: 4.9-6.9) in the intermediate-risk group, and 12.5 (Q1-Q3: 9.7-17.4) in the high-risk group. Lower-risk patients were significantly younger than intermediate-risk and high-risk patients (age 66.5 ± 12.7 years vs 73.8 ± 9.5 years vs 76.2 ± 10 years; $P < 0.0001$). In the overall population, 74.2% (n = 4,424 of 5,963) of patients had 1 prior cardiac surgery, 19.1% (n = 1,140 of 5,963) had 2 prior cardiac surgeries, and 3.5% (n = 209 of 5,963) had 3 or more. Prior stroke was present in 18.3% (n = 1,091 of 5,969) of the overall population, hypertension in 84.1% (n = 5,019 of 5,969), atrial fibrillation/flutter in 73% (n = 4,357 of 5,969), and diabetes mellitus in 27.5% (n = 1,640 of 5,965). Renal failure requiring dialysis was more common in the high-risk group, at 8.6% (n = 199 of 2,311), compared with the low-risk group, at 1.3% (n = 17 of 1,309), and intermediate-risk group, at 2.7% (n = 52 of 1,959) ($P < 0.0001$). Home oxygen use was more common in the high-risk group, at 21% (n = 486 of 2,311), compared with the low-risk group, 4.1% (n = 54 of 1,308), and intermediate-risk group, at 10.3% (n = 201 of 1,960) ($P < 0.0001$). Prior endocarditis was more common in the low-risk group. Patients in higher-risk groups were more likely to present with NYHA functional class III/IV symptoms (88.3% [n = 2,017 of 2,284] vs 72.3% [n = 931 of 1,288] in the low-risk group) and more likely to present in cardiogenic shock (present in 7% [n = 162 of 2,314] of high-risk patients at baseline compared with 1% [n = 13 of 1,309] in low-risk patients). Baseline quality of life measured by the KCCQ was worse in the higher-risk groups ($P < 0.0001$). Concomitant valvular heart disease, including aortic regurgitation, aortic stenosis, and tricuspid regurgitation, were all more common in higher-risk patients ($P < 0.05$ for all).

PROCEDURAL CHARACTERISTICS AND IN-HOSPITAL OUTCOMES. The number of MViV procedures performed each year of the study increased over time (Supplemental Figure 1). All procedures were performed by the transfemoral transseptal approach with no procedures performed via transapical or direct transatrial approaches. General anesthesia was used

CENTRAL ILLUSTRATION Continued

(A) Consecutive patients undergoing transseptal (TS) mitral valve-in-valve (MViV) from August 2015 to March 2024 that were evaluated as an overall cohort (5,971) as well as compared according to Society of Thoracic Surgeons (STS) risk score status (n = 5,585) and according to elective vs nonelective procedure status (n = 5,968). (B) Three-year all-cause mortality outcomes in the overall cohort and according to STS score. The "all MViV" group includes all TS MViV patients (n = 5,971). STS groups exclude patients with missing STS scores (n = 5,585). Higher STS score was associated with higher risk of mortality. (C) Three-year all-cause mortality outcomes by procedure status. Nonelective procedures were associated with higher risk of mortality. ACC = American College of Cardiology; TVT = Transcatheter Valve Therapy.

TABLE 1 Baseline Characteristics (n = 5,971)

Clinical characteristic	
Age, y	72.9 ± 11.4 (5,971)
Female	57.9 (3,457/5,971)
Caucasian	82.5 (4,924/5,971)
African American	10.1 (604/5,971)
STS score, %	6.9 (4.1-11.1)
BMI, kg/m^2	27.6 ± 13.3 (5,956)
Permanent pacemaker	26.4 (1,571/5,962)
Previous ICD	10.6 (632/5,960)
Prior MI	17.1 (1019/5,965)
Prior PCI	15.8 (945/5,965)
Prior CABG	29.7 (1,769/5,964)
Prior aortic valve procedure	23.9 (1,428/5,969)
Prior stroke	18.3 (1,091/5,969)
Prior TIA	9.7 (576/5,970)
Hypertension	84.1 (5,019/5,969)
Immunocompromised	7.4 (407/5,534)
Endocarditis	14.0 (835/5,966)
Diabetes mellitus	27.5 (1,640/5,965)
Peripheral arterial disease	13.9 (830/5,965)
GFR, mL/min/1.73 m^2	56.6 ± 25.0 (5,952)
Currently on dialysis	4.9 (292/5,963)
Hostile chest	12.4 (741/5,969)
Carotid stenosis	9.7 (486/5,020)
Heart failure hospitalization within past year	58.1 (2,896/4,986)
Cardiogenic shock within 24 h	4.1 (245/5,967)
Porcelain aorta	0.4 (25/5,966)
Atrial fibrillation/flutter	73.0 (4,357/5,969)
Chronic lung disease	37.6 (2,233/5,944)
Home oxygen	13.2 (788/5,964)
Positive Inotropes	9.2 (545/5,941)
BNP, pg/mL	779.3 ± 1037.7 (2,439)
NT-proBNP, pg/mL	2195.0 (967.0-5296.0)
Hemoglobin	11.6 ± 2.1 (5,952)
Operator reason for procedure	
Inoperable/extreme risk	17.2 (1,014/5,896)
High risk	61.4 (3,619/5,896)
Intermediate risk	16.0 (942/5,896)
Low risk	5.4 (321/5,896)
NYHA functional class III/IV	81.3 (4,768/5,864)
KCCQ overall summary score	33.3 (18.8-53.1)
Echocardiographic characteristic	
Left main stenosis ≥50%	4.1 (207/5,015)
Mitral annular calcification	42.4 (919/2,166)
MV area, cm^2	1.1 (0.8-1.7)
MV mean gradient, mm Hg	13.1 ± 6.2 (5,698)
LVEF, %	55.1 ± 11.7 (5,914)
≥ Moderate mitral regurgitation	53.2 (3,153/5,924)
Mitral stenosis	75.7 (4,409/5,828)
≥ Moderate aortic regurgitation	9.6 (565/5,916)
Aortic stenosis	16.7 (986/5,900)
≥ Moderate tricuspid regurgitation	57.0 (3,388/5,945)
Pulmonary capillary wedge pressure, mm Hg	26.2 ± 8.5 (2,870)
Pulmonary artery pressure, mm Hg	40.5 ± 12.3 (2,976)
Right atrial pressure/CVP, mm Hg	11.0 (7.0-16.0)
Pulmonary vascular resistance	258.1 (153.2-400.0)

Values are mean ± SD (n), % (n/N), or median (Q1-Q3).

BMI = body mass index; BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; cm = centimeters; CVP; central venous pressure; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MV = mitral valve; MViV = mitral valve-in-valve; NT pro-BNP = N-terminal pro-B-type natriuretic peptide; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

Continued in the next column

in 93.7% (n = 5,590 of 5,966) of procedures (Table 2). Bioprosthetic valve fracture was attempted in 8.5% (n = 260 of 3,071) of cases, and postimplantation balloon inflation was performed in 22.7% (n = 1,263 of 5,567) of cases. Successful device implantation occurred in 97.2% (n = 5,802 of 5,971) of patients in the overall group, with slightly higher success rates observed in the low-risk and intermediate-risk groups compared with the high-risk group: 97.4% (n = 1,276 of 1,310) and 98.0% (n = 1,920 of 1,960) vs 96.4% (n = 2,231 of 2,315) (P = 0.006) (Supplemental Table 2). Left ventricular outflow tract obstruction occurred in 0.5% (n = 27 of 5,971) of patients, atrial septal defect closure was performed in 8.8% (n = 528 of 5,971), and procedural mortality occurred in 0.5% (28 of 5,971) of patients (Tables 2 and 3).

In-hospital mortality occurred in 3.1% (n = 187 of 5,971) of the overall population and was more frequent in the high-risk group, at 5.3% (n = 122 of 2,315) vs 0.5% (n = 7 of 1,310) and 1.8% (n = 35 of 1,960) in the low-risk and intermediate-risk groups, respectively (Table 3, Supplemental Table 3). In-hospital stroke rates were low in all 3 groups: 0.4% (n = 5 of 1,310), 1.0% (n = 19 of 1,960), and 1.3% (n = 29 of 2,315) in low-, intermediate-, and high-risk groups, respectively (P = 0.03). Hospital length of stay was longer for higher-risk groups (P < 0.0001), and 86.8% (n = 5,185 of 5,971) of the overall group were discharged to home. Regarding medical therapy, 82.9% (n = 4,730 of 5,708) were prescribed anticoagulation, and 72.2% (n = 4,122 of 5,712) were prescribed antiplatelet therapy at hospital discharge.

1-YEAR OUTCOMES. At 1 year, NYHA functional class III/IV improved compared with baseline for the overall group, 81.3% (n = 4,768 of 5,864) to 13.7% (n = 269 of 1,968) (Tables 1 and 3). High-risk and

intermediate-risk patients were more likely to have NYHA functional class II symptoms at 1 year compared with the low-risk group, but all 3 groups similarly had a low prevalence of NYHA functional class III or IV symptoms at 1 year: for the low-risk group, 11.8% (n = 52 of 442); for the intermediate-risk group, 13.1% (n = 91 of 693); and for the high-risk group, 15.4% (n = 113 of 736) (Supplemental Table 3). The median KCCQ improvement from baseline to 1 year was 40.1 points (Q1-Q3: 19.3-60.4 points) in the overall group, and improvement was observed across all risk groups (38.6 points [Q1-Q3: 15.6-56.3 points] for low risk, 38.0 points [Q1-Q3: 19.8-57.7 points] for intermediate risk, and 42.7 points [Q1-Q3: 21.9-65.3 points] for high risk). Additional analysis using inverse probability weighting to account for high rates of incomplete 1-year KCCQ data was performed which confirmed similar findings (Supplemental Table 4). Similar proportions of patients achieved a KCCQ overall score improvement of 20 points in low, intermediate, and high STS groups: 74.3% (n = 1,317 of 1,773) in the overall group, 71.6% (n = 295 of 412) in the low-risk group, 74.4% (n = 476 of 640) in the intermediate-risk group, and 75.9% (n = 492 of 648) in the high-risk group (Supplemental Table 5).

All-cause predicted mortality at 1 year was 14.1% (95% CI: 13.1%-15.1%) in the overall group, 5.5% (95% CI: 4.3%-7.2%) in the low-risk group, 10.4% (95% CI: 9.0%-12.0%) in the intermediate-risk group, and 21.3% (95% CI: 19.6%-23.2%) in the high-risk group ($P < 0.0001$) (**Table 3**, Supplemental Table 3). At 1 year, 70.4% (n = 1,931 of 2,745) of the overall group were prescribed an anticoagulant, and 59.6% (n = 1,633 of 2,740) of patients were taking antiplatelet therapy.

Echocardiographic mean gradients were similar between groups at 1 year (7.6 ± 2.9 mm Hg for low risk, 7.6 ± 3.2 mm Hg for intermediate risk, and 7.3 ± 3.4 mm Hg for high risk; $P = 0.18$) (Supplemental Table 6). Calculated mitral valve area by echocardiogram was also similar between groups (1.6 cm^2 [Q1-Q3: 1.2-2.2 cm^2] for low risk, 1.6 cm^2 [Q1-Q3: 1.2-2.1 cm^2] for intermediate risk, and 1.7 cm^2 [Q1-Q3: 1.3-2.3 cm^2] for high risk; $P = 0.25$).

Mitral paravalvular leak was uncommon in the overall group, as 96.0% (n = 1,491 of 1,554) had no paravalvular leak, and was similar between groups (96.7% [n = 356 of 368] for low risk, 95.6% [n = 523 of 547] for intermediate risk, and 95% [n = 515 of 542] for high risk, with no paravalvular leak; $P = 0.45$) (**Table 4**, Supplemental Table 6).

TABLE 2 Procedural and In-Hospital Outcomes (N = 5,971)

Device implanted successfully	97.2 (5,802/5,971)
MVARC technical success[a]	96.9 (5,788/5,971)
Procedure status	
Elective	73.8 (4,403/5,968)
Urgent	24.2 (1,445/5,968)
Emergency	1.5 (92/5,968)
Salvage	0.5 (28/5,968)
Anesthesia type	
General anesthesia	93.7 (5,590/5,966)
Moderate sedation	6.0 (359/5,966)
Conversion to open heart surgery	0.6 (36/5,970)
Total procedure time, min	102.0 ± 55.9 (5,966)
Fluoroscopy time, min	32.5 ± 21.4 (5,377)
Contrast volume, mL	16.9 ± 39.6 (4,779)
THV type	
S3	64.9 (3,875/5,971)
S3 Ultra	23.5 (1,402/5,971)
S3 Ultra RESILIA	11.6 (694/5,971)
THV size	
20 mm	0.1 (5/5,968)
23 mm	6.6 (393/5,968)
26 mm	42.3 (2,522/5,968)
29 mm	51.1 (3,048/5,968)
Bioprosthetic valve fracture attempted	8.5 (260/3,071)
Mechanical support	3.3 (199/5,965)
Procedure aborted	0.3 (15/5,971)
Transseptal complication	0.6 (35/5,971)
Device embolization	0.2 (14/5,971)
Device migration	0.3 (16/5,971)
Procedural mortality	0.5 (28/5,971)
Length of stay, d	2.0 (1.0-4.0)
ICU length of stay, h	23.0 (0.0-37.0)
Discharged with anticoagulants	82.9 (4,730/5,708)
Discharged with antiplatelets	72.2 (4,122/5,712)
Discharged home	86.8 (5,185/5,971)

Values are % (n/N), mean ± SD (n), or median (Q1-Q3). [a]MVARC technical success was defined as the following at exit from the hybrid suite: patient is alive with successful access, delivery, and retrieval of the device delivery system and successful deployment and correct position of the first intended device, and freedom from emergency surgery or reintervention associated with the device or access procedure.

ICU = intensive care unit; MVARC = Mitral Valve Academic Research Consortium; S3 = SAPIEN 3; THV = transcatheter heart valve.

3-YEAR CLINICAL OUTCOMES. Median follow-up duration for the overall group was 377 days (Q1-Q3: 57-698 days) (Supplemental Table 7). In this analysis, there were 3,663 Medicare-eligible patients (≥65 years of age and enrolled between October 1, 2015, to December 31, 2022), of which 80.5% (n = 2,948 of

TABLE 3 In-Hospital, 30-Day, and 1-Year Outcomes

	MViV (n = 5,971)	95% CI
In-hospital outcome		
All-cause mortality	3.1 (187/5,971)	2.7-3.6
Cardiac death	1.8 (110/5,971)	1.5-2.2
Mitral valve re-intervention	0.4 (22/5,971)	0.2-0.5
Major vascular complication	1.3 (76/5,971)	1.0-1.6
Life-threatening bleeding	1.3 (78/5,971)	1.0-1.6
New requirement for dialysis	1.0 (59/5,971)	0.7-1.2
Myocardial infarction	0.1 (8/5,971)	0.0-0.2
New pacemaker without baseline pacemaker	1.2 (51/4,400)	0.8-1.5
New onset atrial fibrillation	1.4 (49/3,563)	1.0-1.8
Stroke	1.0 (61/5,971)	0.8-1.3
TIA	0.1 (5/5,971)	0.0-0.2
LVOT obstruction	0.5 (27/5,971)	0.3-0.6
Device thrombosis	0.2 (11/5,971)	0.1-0.3
Cardiac perforation	0.9 (56/5,971)	0.7-1.2
ASD closure	8.8 (528/5,971)	8.1-9.6
Any readmission	0.2 (14/5,971)	0.1-0.4
Cardiac readmission	0.1 (7/5,971)	0.0-0.2
Heart failure readmission	0.0 (2/5,971)	0.0-0.1
30-d outcome		
All-cause mortality	4.2 (244)	3.7-4.7
Observed-to-expected mortality ratio	0.47	NA
Cardiac death	2.2 (126)	1.8-2.6
Mitral valve re-intervention	0.5 (30)	0.4-0.8
Major vascular complication	1.5 (85)	1.2-1.8
Life-threatening bleeding	1.4 (78)	1.1-1.7
New requirement for dialysis	1.2 (66)	0.9-1.5
Myocardial infarction	0.3 (16)	0.2-0.5
New pacemaker without baseline pacemaker	1.5 (61)	1.1-1.9
New-onset atrial fibrillation	1.7 (57)	1.3-2.1
Stroke	1.6 (96)	1.4-2.0
TIA	0.2 (10)	0.1-0.3
LVOT obstruction	0.5 (27)	0.3-0.7
Device thrombosis	0.2 (13)	0.1-0.4
ASD closure	9.0 (533)	8.3-9.7
Any readmission	9.1 (501)	8.3-9.9
Cardiac readmission	1.7 (95)	1.4-2.1
Heart failure readmission	2.2 (122)	1.9-2.6
NYHA functional class		
I	45.3 (1,727/3,812)	43.7-46.9
II	39.9 (1,519/3,812)	38.3-41.4
III	13.2 (502/3,812)	12.1-14.3
IV	1.7 (64/3,812)	1.3-2.1
KCCQ overall summary score: change from baseline to 30 d	35.9 (14.6-56.3)	34.4-36.3
1-y outcome		
All-cause mortality	14.1 (690)	13.1-15.1
Cardiac death	5.1 (232)	4.4-5.7
Mitral valve re-intervention	1.6 (77)	1.3-2.1
Major vascular complication	1.7 (95)	1.4-2.1
Life threatening bleeding	2.6 (124)	2.2-3.1
New requirement for dialysis	1.8 (88)	1.4-2.2
Myocardial infarction	0.8 (34)	0.6-1.1
New pacemaker without baseline pacemaker	3.0 (103)	2.5-3.7
New onset atrial fibrillation	3.1 (90)	2.5-3.8
Stroke	3.9 (190)	3.4-4.5
TIA	0.6 (24)	0.4-0.9
LVOT obstruction	0.5 (27)	0.3-0.7
Device thrombosis	0.5 (23)	0.3-0.8
ASD closure	9.8 (564)	9.1-10.6
Anticoagulant use	70.4 (1,931/2,745)	68.6-72.1
Antiplatelet use	59.6 (1,633/2,740)	57.7-61.4
Any readmission	32.3 (1,372)	30.9-33.8
Cardiac readmission	8.7 (345)	7.8-9.6
Heart failure readmission	10.5 (434)	9.6-11.5

Continued on the next page

3,663) were matched with CMS database for long-term follow-up evaluation. In the overall group, 3-year mortality was 31.9%, stroke was 9.9%, and reintervention was 3.2% (**Central Illustration**, **Figures 1A and 1B**). Mortality at 3 years increased with higher STS score groups at 15.8%, 23.3%, and 44.5%, respectively ($P < 0.0001$ for all comparisons) (**Central Illustration**). Stroke rates at 3 years were comparable except between low and high STS groups (7.6% vs 11.4%; $P = 0.002$) (**Figure 1A**). Mitral valve reintervention during 3 years of follow-up was similarly uncommon in all groups, at 3.8%, 3.0%, and 2.8% ($P = 0.71$), respectively (**Figure 1C**).

OUTCOMES ACCORDING TO PROCEDURE STATUS. Characteristics according to procedural status are detailed in Supplemental Tables 8 to 11. Elective procedures were associated with lower 3-year mortality compared with nonelective procedures (28.2% vs 43.3%) (HR: 0.51; 95% CI: 0.45-0.58; $P < 0.0001$) (**Central Illustration**). Following landmark analysis excluding the first 3 months following the procedure, elective procedure status remained a predictor of lower 3-year mortality (HR: 0.69; 95% CI: 0.58-0.82; $P < 0.0001$) (Supplemental Figure 2). Stroke and reintervention rates were similar between elective and nonelective procedure status at 3 years (**Figures 2A and 2B**).

PREDICTORS OF MORTALITY. On multivariable analysis, several predictors of 3-year mortality were identified (**Figure 3**). The strongest predictors of 3-year mortality included current hemodialysis, cardiogenic shock on presentation, and immunocompromised state. Additional significant predictors of 3-year mortality included ejection fraction <50%, heart failure hospitalization within the past year, and home oxygen use.

DISCUSSION

This large multicenter study is the first to present 3-year clinical outcomes of patients undergoing transseptal MViV in the U.S. TVT Registry. Major findings from this analysis include: 1) 3-year mortality rates were lowest in patients with low and intermediate STS scores (15.8% and 23.3%, respectively); 2) 3-year mortality and stroke rates were higher in patients with high vs low STS scores (44.5% vs 15.8% and 11.4% vs 7.6%, respectively); 3) elective procedure status was associated with lower 3-year mortality and similar stroke rates compared with nonelective procedure status; and 4) mitral valve reintervention rates at 3 years were similarly low (<4%) in all groups. These findings highlight the growing role of MViV in

the longitudinal treatment of patients with mitral valve disease who require mitral valve replacement. In this study, durability of MViV was good at 3 years in all patient groups, with low rates of reintervention.

3-YEAR SURVIVAL IN HIGH-RISK PATIENTS. Mortality rates during the first 3 years after transseptal MViV varied significantly depending on the severity of patient comorbidities. In patients with STS scores >8, the mortality rate increased sharply to over 10% in the first 3 months despite a low procedural mortality rate of 0.6%, high device implant success rates, and low rates of procedural complications. Given the consistency of procedural results despite the risk profile, it is likely that the higher mortality rate was driven by a higher frequency of comorbidities, including more advanced age, kidney and lung disease, and more advanced heart failure with concomitant valvular heart disease. For example, high-risk patients had a 5-fold higher rate of home oxygen use, 7-fold higher rate of cardiogenic shock, and 7-fold higher rate of renal failure requiring dialysis at the time of presentation, all of which were previously shown to be associated with increased mortality at 1 year of follow-up.[2] These important signs of advanced multiorgan dysfunction, which are more frequent in the high STS risk group, likely underly the contrasting survival following transseptal MViV. Of note, the mean STS predicted mortality in this group was 15.5%, which further conveys the true risk beyond the definition of ">8%." Despite this higher mortality, the symptomatic response and quality-of-life improvements in patients who reached 1 year of follow-up were comparable to low- and intermediate-risk groups, highlighting the fact that a large subset of high STS risk patients benefit greatly from this intervention. Similar findings have been demonstrated in transcatheter mitral valve replacement trials of high STS risk patients, in which despite high 1-year mortality, large quality-of-life improvements were observed.[6,7]

3-YEAR OUTCOMES IN LOW- AND INTERMEDIATE-RISK PATIENTS. Patients in the low- and intermediate-risk groups experienced high procedural success rates and favorable rates of stroke and reintervention at 3 years of follow-up after transseptal MViV in the U.S. TVT Registry. Although the echocardiographic mean mitral prosthetic gradient was elevated post-procedure, it remained stable at 1 year, and rates of repeat intervention were low, suggesting that the

TABLE 3 Continued

	MViV (n = 5,971)	95% CI
NYHA functional class		
I	48.7 (959/1,968)	46.5-51.0
II	37.6 (740/1,968)	35.5-39.8
III	12.3 (241/1,968)	10.8-13.8
IV	1.4 (28/1,968)	1.0-2.1
KCCQ overall summary score: change from baseline to 1 y	40.1 (19.3-60.4)	38.0-40.6

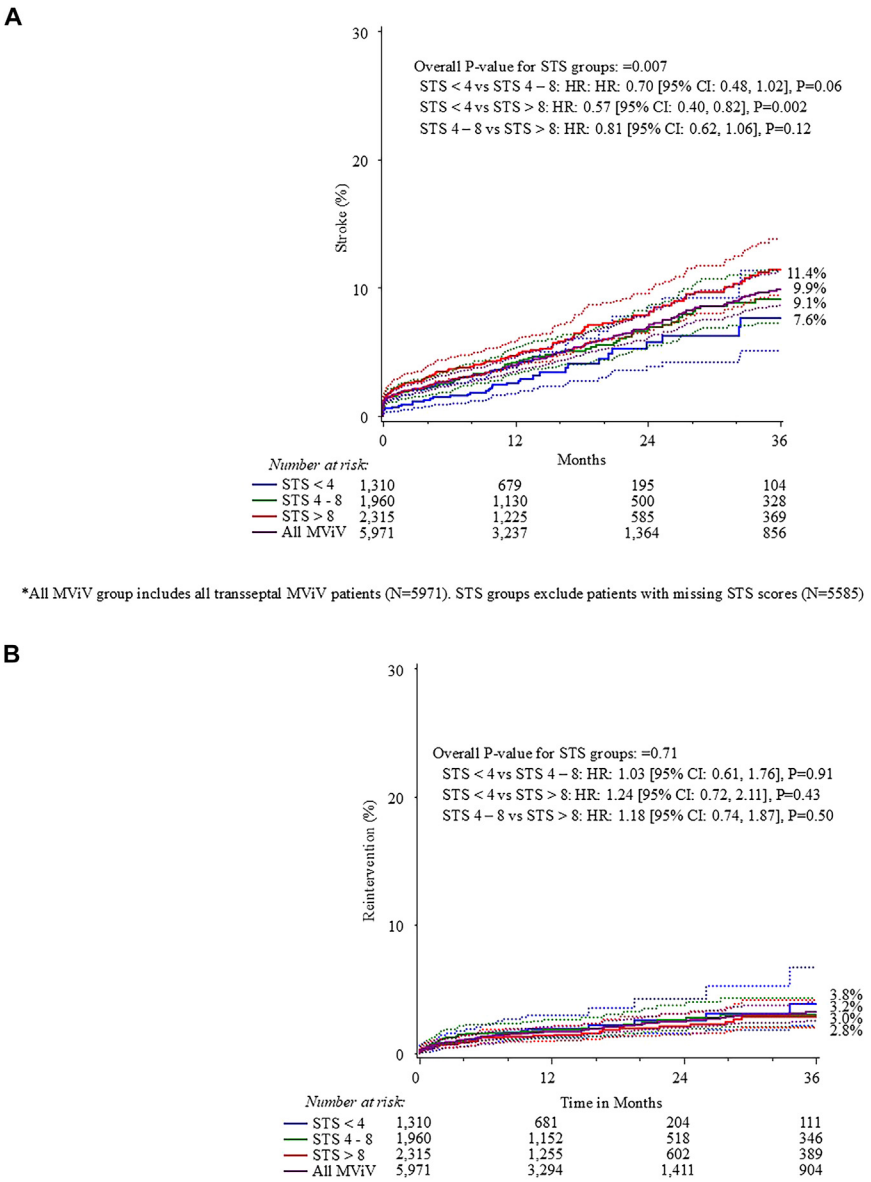
Values are % (n/N), Kaplan-Meier estimate % (n), or median (Q1-Q3).
ASD = atrial septal defect; LVOT = left ventricular outflow tract; MViV, mitral valve-in-valve; other abbreviations as in Table 1.

TABLE 4 Discharge, 30-Day, and 1-Year Echocardiographic Outcomes (N = 5,971)

Discharge	
MV area, cm^2	1.8 (1.4-2.5)
MV mean gradient, mm Hg	6.5 ± 2.8 (5,401)
Mitral paravalvular leak	
None	96.1 (4,466/4,647)
Mild	3.6 (169/4,647)
Moderate	0.2 (8/4,647)
Severe	0.1 (4/4,647)
≥Moderate mitral regurgitation	0.6 (35/5,496)
≥Moderate tricuspid regurgitation	37.7 (1,154/3,061)
30 d	
MV area, cm^2	1.7 (1.3-2.2)
MV mean gradient, mm Hg	7.5 ± 3.0 (4,028)
LVEF, %	54.0 ± 11.4 (4,106)
Mitral paravalvular leak	
None	96.5 (3,286/3,405)
Mild	3.3 (112/3,405)
Moderate	0.2 (7/3,405)
Severe	0.0 (0/3,405)
≥Moderate mitral regurgitation	0.7 (29/4,096)
≥Moderate tricuspid regurgitation	38.9 (1,583/4,065)
1 y	
MV area, cm^2	1.6 (1.2-2.2)
MV mean gradient, mm Hg	7.5 ± 3.2 (1,906)
LVEF, %	54.1 ± 11.3 (1,995)
Mitral paravalvular leak	
None	96.0 (1,491/1,554)
Mild	3.7 (57/1,554)
Moderate	0.1 (2/1,554)
Severe	0.3 (4/1,554)
≥Moderate mitral regurgitation	0.9 (17/1,950)
≥Moderate tricuspid regurgitation	33.8 (661/1,957)

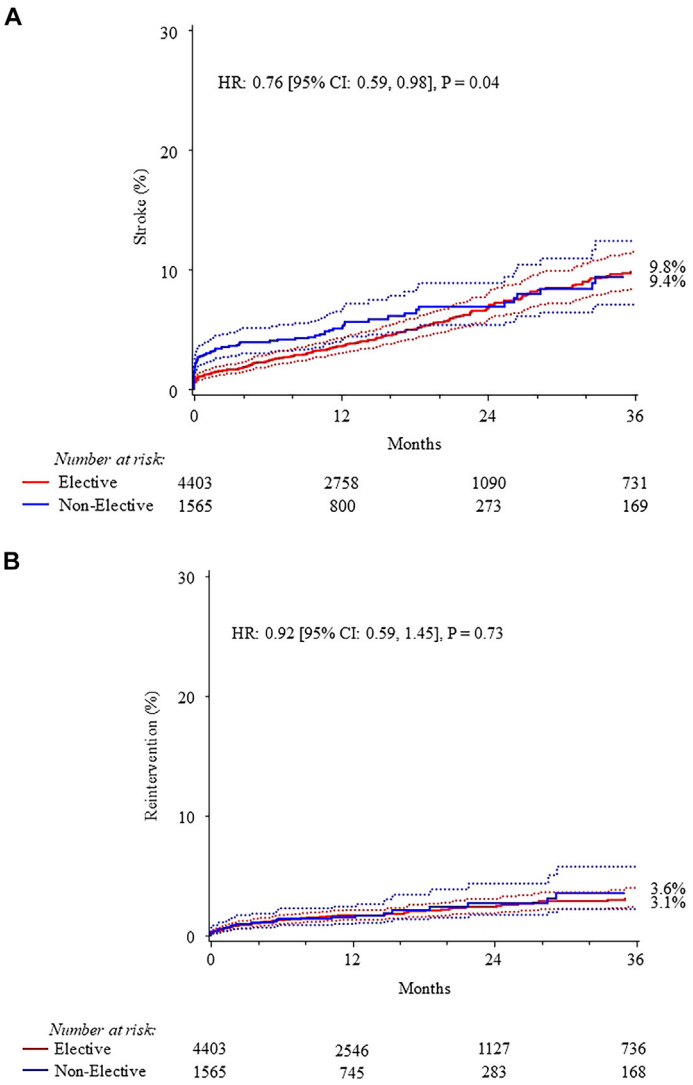
Values are median (Q1-Q3), mean ± SD (n), or % (n/N).
Abbreviations as in Table 1.

FIGURE 1 3-Year Outcomes



(A) Three-year stroke outcomes in the overall cohort and according to Society of Thoracic Surgeons (STS) score. The "all mitral valve-in-valve (MViV)" group includes all transseptal MViV patients (n = 5,971). STS groups exclude patients with missing STS scores (n = 5,585). Higher STS score was associated with higher risk of stroke. (B) Three-year reintervention outcomes in the overall cohort and according to STS score. The "all MViV" group includes all transseptal MViV patients (n = 5,971). STS groups exclude patients with missing STS scores (n = 5,585). Higher STS score was associated with similar rates of reintervention.

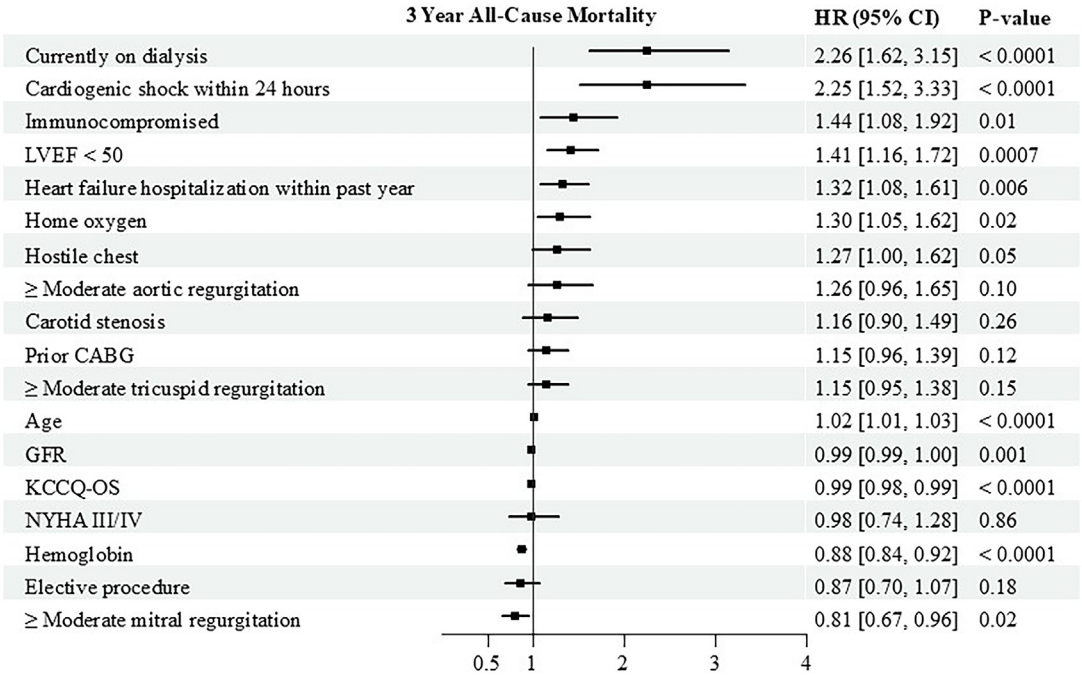
FIGURE 2 3-Year Outcomes According to Procedure Status



(A) Nonelective procedures were associated with higher risk of stroke. (B) Nonelective procedures were associated with similar rates of reintervention.

elevated gradient was not deemed to be of clinical significance. It is plausible that some of these patients would be candidates for redo cardiac surgery based on their STS risk scores if their MViV procedural result was unsatisfactory. Of note, mortality rates at 3 years were higher than expected (15.8% and 23.3% mortality at 3 years), accounting for the mean age of patients, with mean age 66.5 ± 12.7 years in the low-risk group and 73.8 ± 9.5 years in the intermediate-risk group. In a recent analysis of the intermediate-risk patients enrolled in the PARTNER (Placement of Aortic Transcatheter Valves) 3 MViV registry, there were no mortalities observed at 1 year of follow-up in 50 carefully selected patients, illustrating the minimally invasive and successful nature of the MViV procedure when applied to patients without severe

FIGURE 3 Predictors of 3-Year All-Cause Mortality



Forest plot depicting selected covariates for prediction of all-cause mortality using the lowest Akaike information criterion multivariable Cox regression model. CABG = coronary artery bypass grafting; GFR = glomerular filtration rate; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction.

comorbidities.[9] Importantly, even patients with a low STS risk score can be deemed "high risk" for repeat cardiac surgery after heart team evaluation, often based on important variables including functional/ambulatory status and technical impediments such as porcelain aorta or hostile chest, among others. In the present study, 47.5% of low STS risk and 57.4% of intermediate STS risk score group patients were deemed high risk for cardiac surgery based on the site determination. It is likely that other comorbidities not captured in the STS score contributed to the 3-year mortality rates observed in these groups.

Medical management following successful MViV is an important aspect of longitudinal care. Prosthetic valve thrombosis is an important complication in MViV to be aware of, occurring in approximately 6% of patients during the first year.[9] When detected early, prosthetic valve thrombosis can be treated successfully with anticoagulation therapy. To avoid prosthetic valve thrombosis, most patients undergoing MViV are treated with anticoagulation therapy. This was the case in the current overall study population, in which 82.9% were prescribed anticoagulation at hospital discharge and 70.4% continued this therapy at 1-year follow-up.

IMPORTANCE OF SURVEILLANCE AND TIMELY TREATMENT. Several findings of the present study emphasize the importance of early identification of candidates for MViV to allow for prompt treatment. Patients with heart failure hospitalizations within the last year had higher 3-year mortality, suggesting that earlier identification and treatment may have an impact on prognosis. Patients undergoing urgent nonelective procedures had a nearly 2-fold higher mortality at 3 years, further supporting this concept. Indeed, signs of advanced presentation, such as cardiogenic shock on presentation and current

hemodialysis use, were some of the strongest independent predictors of 3-year mortality. Careful surveillance of patients with senescent mitral bioprostheses by a cardiovascular specialist with annual echocardiography is essential to identify prosthetic valve dysfunction promptly, which may lead to improved outcomes.

STUDY LIMITATIONS. Study limitations include the observational design and the use of self-reported site data in the TVT Registry. Regular audits of the data are performed by the STS/ACC to maintain data accuracy. Although the majority of MViV procedures performed in the United States are captured in this registry, a minority of centers do not participate in the TVT Registry, and their data are not included. Echocardiographic data beyond 1 year is not reported in the TVT Registry and thus is unavailable for this dataset. Finally, the use of CMS data linkage to obtain long-term outcomes beyond 1 year may introduce bias given different comorbidities present in CMS vs non-CMS eligible patients.

CONCLUSIONS

Three-year survival after MViV is highest in low STS score populations and significantly lower in high STS score patients treated in the United States. Nonelective procedures and patients with advanced heart failure presentation and multiorgan dysfunction had the highest 3-year mortality, emphasizing the importance of early identification and treatment of patients who may benefit from MViV. Reintervention rates at 3 years are low regardless of STS score.

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PERSPECTIVES

WHAT IS KNOWN? Short-term outcomes after transseptal MViV are favorable, with high procedural success rates.

WHAT IS NEW? Three-year survival after transseptal MViV is lowest in patients with low STS risk scores. High STS risk score and nonelective procedure status are associated with higher 3-year mortality. Reintervention rates after MViV are low at 3 years regardless of STS score.

WHAT IS NEXT? Strategies to treat patients before advanced comorbidities develop are needed to optimize longer-term outcomes following MViV.

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