4-26-2021

Prospective Evaluation of Transseptal TMVR for Failed Surgical Bioprostheses: MITRAL Trial Valve-in-Valve Arm 1-Year Outcomes

Mayra Guerrero

Amit Pursnani

Akhil Narang

Michael Salinger

Dee Dee Wang

See next page for additional authors

Authors

Mayra Guerrero, Amit Pursnani, Akhil Narang, Michael Salinger, Dee Dee Wang, Mackram Eleid, Susheel K. Kodali, Isaac George, Lowell Satler, Ron Waksman, Christopher U. Meduri, Vivek Rajagopal, Ignacio Inglessis, Igor Palacios, Mark Reisman, Marvin H. Eng, Hyde M. Russell, Ashish Pershad, Kenith Fang, Saibal Kar, Rajj Makkar, Jorge Saucedo, Paul Pearson, Ujala Bokhary, Tatiana Kaptzan, Brad Lewis, Carl Tommaso, Philip Krause, Jeremy Thaden, Jae Oh, Roberto M. Lang, Rebecca T. Hahn, Martin B. Leon, William W. O'Neill, Ted Feldman, and Charanjit Rihal

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 14, NO. 8, 2021

PUBLISHED BY ELSEVIER

Prospective Evaluation of Transseptal TMVR for Failed Surgical Bioprostheses

MITRAL Trial Valve-in-Valve Arm 1-Year Outcomes

Mayra Guerrero, MD,[a] Amit Pursnani, MD,[b] Akhil Narang, MD,[c] Michael Salinger, MD,[d] Dee Dee Wang, MD,[e] Mackram Eleid, MD,[a] Susheel K. Kodali, MD,[f] Isaac George, MD,[g] Lowell Satler, MD,[h] Ron Waksman, MD,[h] Christopher U. Meduri, MD,[i] Vivek Rajagopal, MD,[i] Ignacio Inglessis, MD,[j] Igor Palacios, MD,[j] Mark Reisman, MD,[k,*] Marvin H. Eng, MD,[e] Hyde M. Russell, MD,[l] Ashish Pershad, MD,[m,†] Kenith Fang, MD,[m] Saibal Kar, MD,[n] Rajj Makkar, MD,[o] Jorge Saucedo, MD,[d] Paul Pearson, MD,[p] Ujala Bokhary, MD,[b] Tatiana Kaptzan, PHD,[q] Brad Lewis, MS,[r] Carl Tommaso, MD,[b] Philip Krause, MD,[b] Jeremy Thaden, MD,[a] Jae Oh, MD,[a] Roberto M. Lang, MD,[s] Rebecca T. Hahn, MD,[f] Martin B. Leon, MD,[f] William W. O'Neill, MD,[e] Ted Feldman, MD,[t] Charanjit Rihal, MD[a]

ABSTRACT

OBJECTIVES The aim of this study was to assess 1-year clinical outcomes among high-risk patients with failed surgical mitral bioprostheses who underwent transseptal mitral valve-in-valve (MViV) with the SAPIEN 3 aortic transcatheter heart valve (THV) in the MITRAL (Mitral Implantation of Transcatheter Valves) trial.

BACKGROUND The MITRAL trial is the first prospective study evaluating transseptal MViV with the SAPIEN 3 aortic THV in high-risk patients with failed surgical mitral bioprostheses.

METHODS High-risk patients with symptomatic moderate to severe or severe mitral regurgitation (MR) or severe mitral stenosis due to failed surgical mitral bioprostheses were prospectively enrolled. The primary safety endpoint was technical success. The primary THV performance endpoint was absence of MR grade ≥2+ or mean mitral valve gradient ≥10 mm Hg (30 days and 1 year). Secondary endpoints included procedural success and all-cause mortality (30 days and 1 year).

RESULTS Thirty patients were enrolled between July 2016 and October 2017 (median age 77.5 years [interquartile range (IQR): 70.3 to 82.8 years], 63.3% women, median Society of Thoracic Surgeons score 9.4% [IQR: 5.8% to 12.0%], 80% in New York Heart Association functional class III or IV). The technical success rate was 100%. The primary performance endpoint in survivors was achieved in 96.6% (28 of 29) at 30 days and 82.8% (24 of 29) at 1 year. Thirty-day all-cause mortality was 3.3% and was unchanged at 1 year. The only death was due to airway obstruction after swallowing several pills simultaneously 29 days post-MViV. At 1-year follow-up, 89.3% of patients were in New York Heart Association functional class I or II, the median mean mitral valve gradient was 6.6 mm Hg (interquartile range: 5.5 to 8.9 mm Hg), and all patients had MR grade ≤1+.

CONCLUSIONS Transseptal MViV in high-risk patients was associated with 100% technical success, low procedural complication rates, and very low mortality at 1 year. The vast majority of patients experienced significant symptom alleviation, and THV performance remained stable at 1 year. (J Am Coll Cardiol Intv 2021;14:859–72)

From the [a]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; [b]Division of Cardiology, NorthShore University HealthSystem, Evanston, Illinois, USA; [c]Division of Cardiology, Northwestern Memorial Hospital, Chicago, Illinois, USA; [d]Division of Cardiology, Froedtert Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [e]Center for Structural Heart Disease, Henry Ford Hospital, Detroit, Michigan, USA; [f]Division of Cardiology, Columbia University Medical Center, New York, New York, USA; [g]Department of Surgery, Columbia University Medical Center, New York, New York, USA; [h]Division of Cardiology, Medstar Washington Hospital Center, Washington, DC, USA; [i]Division of Cardiology, Piedmont Hospital, Atlanta, Georgia, USA; [j]Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA; [k]Division of Cardiology, University of Washington Medical Center, Seattle, Washington, USA; [l]Division of Cardiovascular Surgery, NorthShore University HealthSystem, Evanston, Illinois, USA: [m]Division of Cardiology, Banner University Medical Center, Phoenix, Arizona, USA; [n]Division of Cardiology, Los Robles Regional Medical Center, Thousand Oaks, California, USA; [o]Department of Cardiology, Cedars-Sinai Heart Institute, Los Angeles, California, USA; [p]Division of Cardiovascular Surgery, Froedtert Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [q]Cardiovascular Research Unit, Mayo Clinic, Rochester, Minnesota, USA; [r]Division of Biostatistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA; [s]Division of Cardiology, University of Chicago Medical Center, Chicago, Illinois, USA; and [t]Edwards Lifesciences, Irvine, California, USA. *Dr. Reisman is currently affiliated with the Weill Medical Center, New York, New York, USA. †Dr. Pershad is currently affiliated with the Division of Cardiology, Chandler Regional and Mercy Gilbert Medical Center, Gilbert, Arizona, USA.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2021.02.027

ABBREVIATIONS AND ACRONYMS

CT = computed tomographic

IQR = interquartile range

LVOT = left ventricular outflow tract

MAC = mitral annular calcification

MR = mitral regurgitation

MV = mitral valve

MVG = mitral valve gradient

MViV = mitral valve-in-valve

NYHA = New York Heart Association

STS = Society of Thoracic Surgeons

THV = transcatheter heart valve

TMVR = transcatheter mitral valve replacement

Multiple studies have demonstrated that the risk for repeat mitral valve (MV) surgery is high, with procedural mortality ranging between 6.3% and 15% (1–5). Third and fourth redo mitral operations carry even higher mortality risk of 17.3% and 40%, respectively (6). A recent analysis of 11,973 patients from the Society of Thoracic Surgeons (STS) database revealed a 30-day mortality rate of 6.5% in patients who underwent MV replacement for the first time versus 11.1% in those who underwent redo MV surgery ($p < 0.0001$) (7).

Transcatheter mitral valve replacement (TMVR) using balloon-expandable aortic transcatheter heart valves (THVs) has emerged as an alternative to surgery for patients with severe MV disease due to degenerated bioprostheses or failed surgical repairs with annuloplasty rings, as well as native MV disease with severe mitral annular calcification (MAC) in patients who are not good candidates for conventional MV surgery. The VIVID (Valve-in-Valve International Database) registry, the STS/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry, and other registries collected early outcomes of mitral valve-in-valve (MViV) in high-risk patients (8–10). Transapical access was used in the majority of procedures in the initial experience using first- and second-generation devices, but the use of transseptal access has increased with the third-generation SAPIEN 3 valve (Edwards Lifesciences, Irvine, California). Whether outcomes could be improved with transeptal access use was unknown until recently.

The MITRAL (Mitral Implantation of Transcatheter Valves; IDE G140136; NCT02370511) trial is the first prospective study to evaluate the safety and feasibility of transseptal MViV using the third-generation SAPIEN 3 valve in patients at high surgical risk. We present herein the 1-year outcomes of transseptal MViV in this trial.

SEE PAGE 873

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. The MITRAL early feasibility study is a physician-initiated, prospective, multicenter clinical trial designed to evaluate the safety and feasibility of TMVR using the SAPIEN XT and SAPIEN 3 valves. The study has 3 treatment arms, including native MV disease with severe MAC treated with a valve-in-MAC procedure, failing surgical repairs with annuloplasty rings treated with mitral valve-in-ring, and MViV in failed surgical bioprostheses. A total of 91 patients at high surgical risk were enrolled (valve-in-MAC, n = 31; mitral valve-in-ring, n = 30; MViV, n = 30) and treated between March 2015 and December 2017 at 13 sites in the United States. We present herein the results of the MViV arm. Patients were considered eligible for the study if they had symptoms of New York Heart Association (NYHA) functional class II or greater due to severe mitral stenosis, defined as MV area <1.5 cm^2 on transthoracic echocardiography or at least moderate to severe mitral regurgitation (MR). A list of inclusion and exclusion criteria is provided in Supplemental Appendix 1.

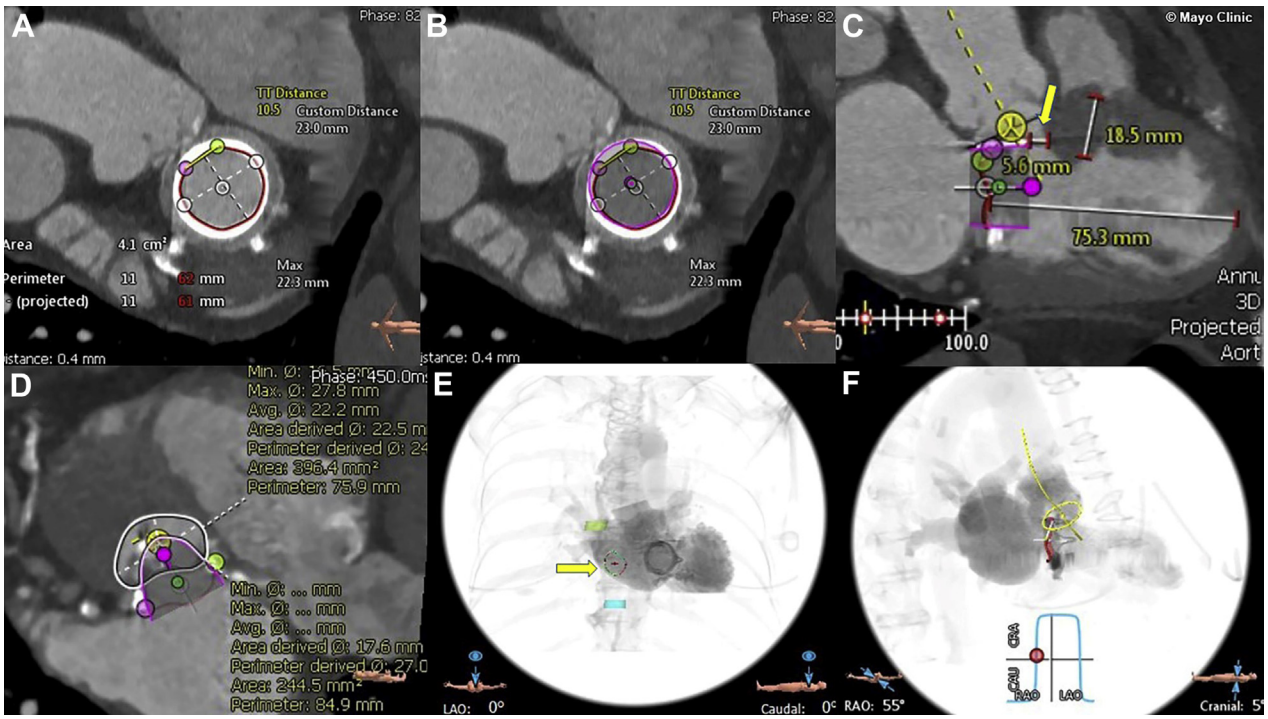
Candidates were presented in a live case-review conference call to a subject eligibility committee (including a cardiac surgeon, interventional cardiologists, an advanced cardiac imaging expert, and a computed tomography core laboratory director) to determine eligibility. Baseline echocardiographic and computed tomographic (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 echocardiograms were obtained according to published guidelines and analyzed at an independent core laboratory according to the American Society of Echocardiography standard for echocardiography

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.

Manuscript received December 8, 2020; revised manuscript received February 11, 2021, accepted February 16, 2021.

FIGURE 1 **Cardiac CT Analysis**

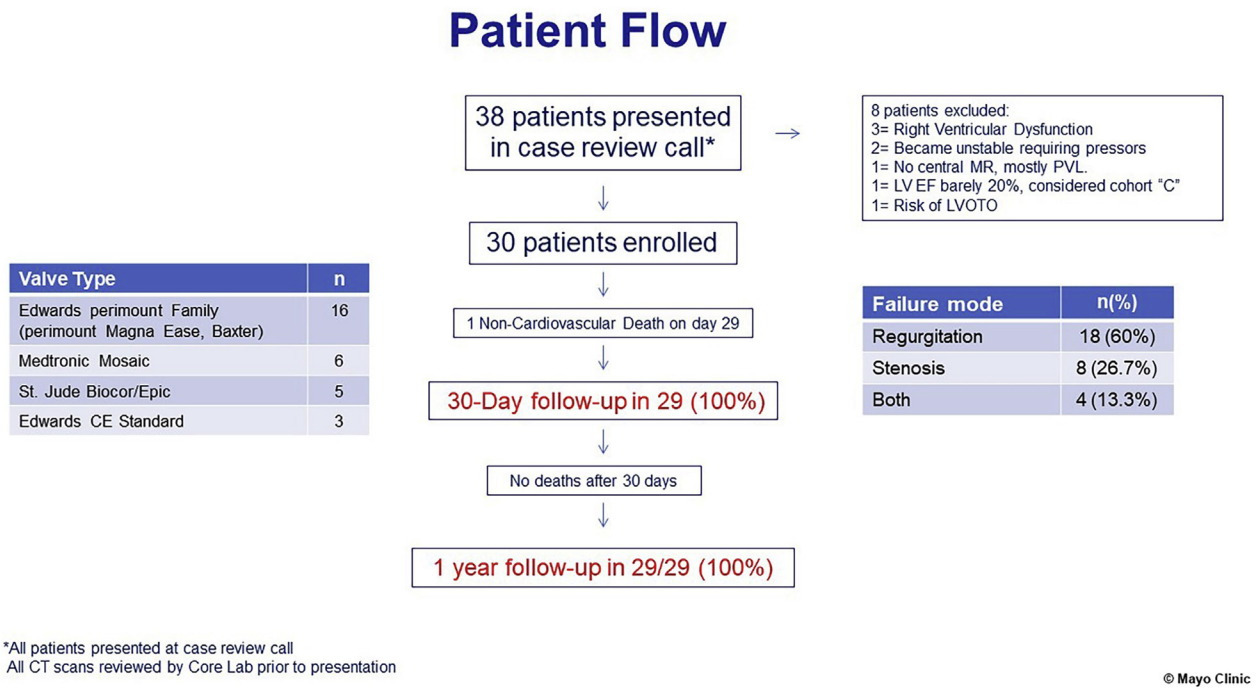


Measurements of the mitral annulus made using 3mensio Structural Heart Workflow version 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). **(A)** The mitral valve "neoannulus" area of the surgical bioprosthesis measurement is shown from the surgeon's short-axis view during diastole. **(B)** A 23-mm virtual SAPIEN 3 transcatheter heart valve (THV) is placed in the mitral surgical bioprosthesis **(pink)**; the size was selected according to neoannulus/surgical bioprosthesis area. **(C)** The virtual valve placed in the mitral annulus is visualized in the left ventricular outflow tract (LVOT) long-axis view. The LVOT space is measured at the site where the THV stent frame is in closest proximity of the septum **(arrow)**. **(D)** Neo-LVOT area measurement shown in short-axis view during systole. After placing the virtual valve **(pink)**, the remaining LVOT area is measured **(white)**. **(E)** Fluoroscopic simulation of transseptal access **(arrow)** for procedural planning purposes. **(F)** Fluoroscopic simulation of a coplanar view of the mitral bioprosthesis representing the valve deployment angle to be used during mitral valve-in-valve implantation procedure.

core laboratories (11,12). The cardiac CT image acquisition protocol was similar to CT protocols for transcatheter aortic valve replacement (13), with adjustments for MV analysis (14), summarized in Supplemental Appendix 3 and illustrated in **Figure 1**. Although the MViV software application was used in the evaluation (15), the THV size was selected according to the mitral neoannulus area (the inner area of the surgical bioprosthetic ring) as determined by cardiac CT analysis (**Figure 1**) (14). All patients were treated with transseptal access and received intravenous heparin during the procedure to maintain an activated clotting time greater then 250 s. We have previously published the technique of transseptal MViV (14,16). The patients received single-antiplatelet therapy indefinitely after MViV, and anticoagulation was recommended for at least 3 months for patients who did not have indications for long-term anticoagulation prior to TMVR.

OUTCOMES. The primary safety endpoint was technical success at exit from the cardiac catheterization laboratory, 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 THV with residual MR grade <2+ and mean MV gradient (MVG) <10 mm Hg, no need for surgery or additional reintervention, and patient exits the procedure room alive. The primary THV performance endpoint was absence of MR grade ≥2+ or mean MVG ≥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

FIGURE 2 Patient Flowchart



CT = computed tomographic; EF = ejection fraction; LV = left ventricular; LVOTO = left ventricular outflow tract obstruction; MR = mitral regurgitation; PVL = paravalvular leak.

of secondary endpoints are provided in Supplemental Appendix 4.

STATISTICAL ANALYSIS. Continuous variables are expressed as median (interquartile range [IQR]). Categorical variables are expressed as frequency (percentage). Comparisons between time points were made using a Wilcoxon test. Comparisons of median mean MVG among THV sizes were made using Kruskal-Wallis 1-way analysis of variance on ranks. A Kaplan-Meier curve was generated for all-cause mortality and for the composite endpoint of all-cause mortality and hospitalization for heart failure. For the purposes of this paper, all p values were 2 sided, and p values <0.05 were considered to indicate statistical significant. All analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between July 2016 and October 2017, 38 subjects were screened and presented at a case-review conference call for subject eligibility determination. Eight patients were excluded for the following reasons: severe right ventricular dysfunction (n = 3, considered to have very poor prognosis because of severe right ventricular dysfunction), hemodynamic instability requiring intravenous pressors (n = 2), lack of central MR with mostly paravalvular regurgitation (n = 1), left ventricular ejection fraction <20% (n = 1), and risk for left ventricular outflow tract (LVOT) obstruction (n = 1). Thirty patients were enrolled (the patient flowchart is illustrated in **Figure 2**). Baseline clinical characteristics, including the types of surgical valves implanted, are presented in **Table 1**; median age was 77.5 years (IQR: 70.3 to 82.8 years), and 63.3% were women. Multiple comorbidities were present, including atrial fibrillation in 60%. The median STS Predicted Risk of Mortality score for MV replacement was 9.4% (IQR: 5.8% to 12.0%), and 80% of patients were in NYHA functional class III or IV. Baseline echocardiographic characteristics are listed in **Table 2**. Median left ventricular ejection fraction was 56.2% (IQR: 48.7% to 64.5%). Mitral stenosis was the predominant pathology, present in 73.3% of the subjects.

TABLE 1 Baseline Patient Characteristics (n = 30)

Age (yrs)	77.5 (70.3–82.8)
Female	19/30 (63.3)
Diabetes	6/30 (20)
Atrial fibrillation	18/30 (60)
Chronic kidney disease	6/30 (20)
Chronic obstructive pulmonary disease	6/30 (20)
Home oxygen therapy	3/30 (10)
Receiving long-term anticoagulation	17/30 (56.7)
Hospitalization for heart failure during prior 12 months	14/30 (46.7)
Prior stroke	4/30 (13.3)
Prior CABG	11/30 (36.7)
Prior AVR	6/30 (20)
TAVR	2 (33.3)
SAVR	4 (66.7)
Type of surgical bioprosthesis	
Edwards Perimount (Perimount, Magna Ease, Baxter)	16/30 (53.3)
Medtronic Mosaic	6/30 (20)
S. Jude Biocor/Epic	5/30 (16.7)
Edwards CE Standard	3/30 (10)
STS score for MVR	9.4 (5.8–12.0)
NYHA functional class	
I	0 (0)
II	6/30 (20)
III	20/30 (66.7)
IV	4/30 (13.3)

Values are median (interquartile range) or n/N (%).
AVR = aortic valve replacement; CABG = coronary artery bypass grafting; 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 (n = 30)

Ejection fraction (%)	56.2 (48.7–64.5)
Stroke volume (ml)	59.4 (43.5–77.5)
Cardiac output (l/min)	3.3 (1.6–4.6)
Mean MVG (mm Hg)	11.1 (7.4–13.7)
MVA (cm^2)	1.4 (1.2–1.8)
Pulmonary artery systolic pressure (mm Hg)	40.1 (32.8–54.0)
Peak LVOT gradient (mm Hg)	4.1 (3.0–5.9)
Mean LVOT gradient (mm Hg)	2.0 (1.3–2.6)
Predominant pathology (mode of bioprosthesis failure)	
Stenosis	22 (73.3)
Regurgitation	3 (10)
Both stenosis and regurgitation	5 (16.7)
Severity of mitral regurgitation	
None or trace	12/30 (40)
1+	8/30 (26.7)
2+	4/30 (13.3)
3+	0/30 (0)
4+	6/30 (20)

Values are median (interquartile range) or n/N (%).
LVOT = left ventricular outflow tract; MVA = mitral valve area; MVG = mitral valve gradient.

PROCEDURAL RESULTS AND PRIMARY SAFETY ENDPOINT. All patients underwent transseptal MViV with the SAPIEN 3 THV. Procedural results are presented in Table 3. The size of the THV was chosen according to cardiac CT analysis, coinciding with the size recommended by the MViV app in 63.3% of cases. A different size than the one recommended by the MViV app was chosen in 36.7% (1 size smaller in all). The THV was prepared with additional contrast volume in the delivery system balloon catheter in 36.7% of cases to flare the THV in the left ventricle to decrease the risk for valve embolization to the left atrium and to optimize valve performance. The primary safety endpoint of technical success at exit from the procedure room was achieved in 100% of patients. There were no cases of LVOT obstruction, need for a second THV during index procedure, intraprocedural mortality, or conversion to open heart surgery. Atrial septostomy was closed percutaneously in 1 patient during the index procedure (3.3%), at the discretion of the operator.

ADDITIONAL ENDPOINTS. The primary THV performance endpoint of absence of MR grade 2+ or greater or mean MVG ≥10 mm Hg was achieved in 96.6% of survivors at 30 days (28 of 29) and in 82.8% of patients alive at 1 year (24 to 29). The reason for not meeting the performance endpoint at 30 days or 1 year was a mean MVG ≥10 mm Hg in all 5 patients (3 treated with the 26-mm and 2 with the 29-mm SAPIEN 3). One of those 5 patients was treated with a size smaller than recommended by the MViV app (a 27-mm Magna, which has a true internal diameter of 26 mm, and developed a stenosis that was treated with a 26-mm THV instead of a 29-mm THV), and the remaining were treated with THV sizes recommended by the MViV app. The secondary safety endpoint of procedural success was achieved in 93.3% (28 of 30). Reasons for not achieving procedural success in 2 subjects included 1 death and a mean MVG of 10.4 mm Hg at 30 days in 1 subject. All-cause mortality at 30 days was 3.3% and remained unchanged at 1 year (Kaplan-Meier survival curves are presented in Figure 3 and the Central Illustration).

TABLE 3 Intraprocedural Results (n = 30)

Device	
SAPIEN 3	30/30 (100)
Device size	
23 mm	4/30 (13.3)
26 mm	13/30 (43.3)
29 mm	13/30 (43.3)
Access	
Transseptal	30/30 (100)
Pre-dilation*	7/30 (23.3)
Additional contrast during initial deployment	
No	19/30 (63.3)
Yes	11/30 (36.7)
Amount (ml)	0.0 (0.0–3.0)
Post-dilatation	4/30 (13.3)
Septostomy closed	1/30 (3.3)
Results	
In-hospital mortality	1/30 (3.3)
Cardiovascular	0
Noncardiovascular	1/30 (3.3)
Technical success at exit from catheterization laboratory	30/30 (100)
LVOT obstruction with hemodynamic compromise	0 ()
Need for a second valve	0 ()
≥2+ MR on procedural TEE	0 ()
Paravalvular leak closure during index procedure	0 ()
Vascular complications	0/30 (0)
Conversion to open heart surgery	0 ()
Valve embolization	0 ()
Left ventricular perforation	0 ()
Pericardial effusion requiring pericardiocentesis	0 ()
New pacemaker requirement	1/30 (3.3)
Myocardial infarction requiring intervention	0 ()
Echocardiographic characteristics post-TMVR	
Mean MVG (mm Hg)	2.9 (2.0–3.9)
Peak LVOT gradient (mm Hg)†	5.4 (3.9–8.9)
Mean LVOT gradient (mm Hg)†	2.5 (2.0–4.4)
Residual total MR at end of procedure	
Trace or none	28/30 (93.3)
1+	2/30 (6.7)
2+	0/30 (0)
≥3+	0/30 (0)
Amount of paravalvular MR at end of procedure	
Trace or none	29/30 (96.7)
1+	1/30 (3.3)
2+	0/30 (0)
≥3+	0/30 (0)

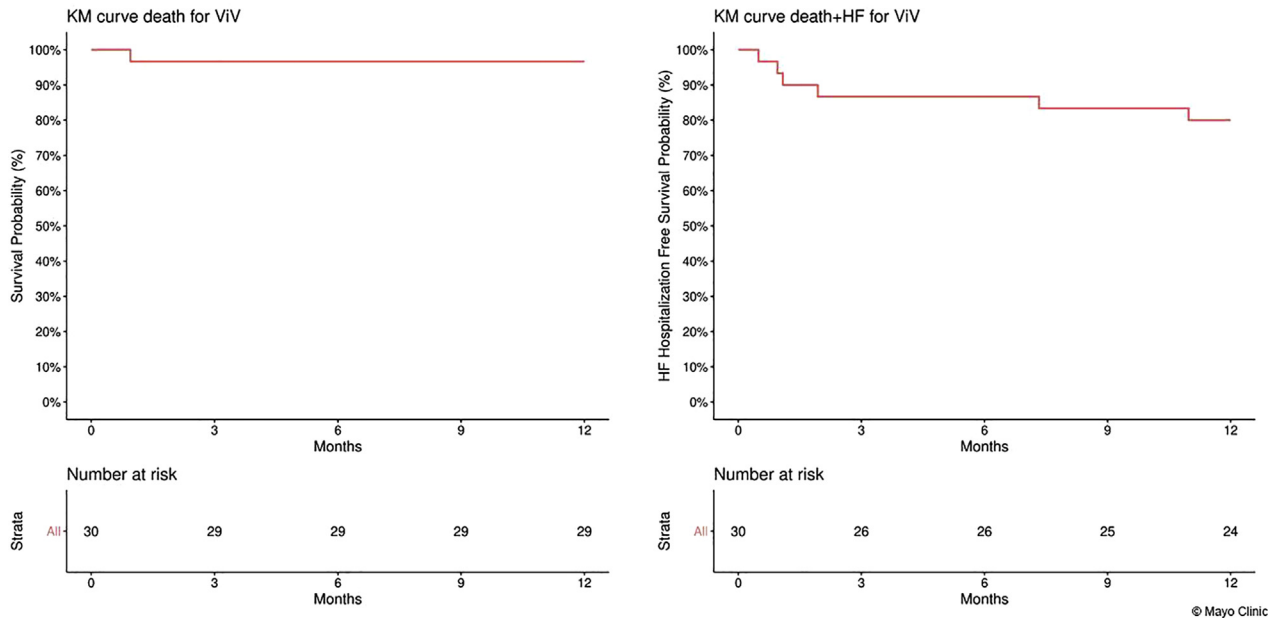
Values are n/N (%) or median (interquartile range). *Performed in patients with very severe mitral stenosis to avoid hemodynamic decompensation during valve positioning and deployment. †Eight missing values.

MR = mitral regurgitation; TEE = transesophageal echocardiogram; TMVR = transcatheter mitral valve replacement; other abbreviations as in Tables 1 and 2.

30-DAY OUTCOMES. At 30-day follow-up, 96.7% of patients (29 of 30) were alive, and 82.8% were in New York Heart Association functional class I or II. The single death observed within 30 days occurred on day 29 post-MViV, due to asphyxia when the patient swallowed 6 pills at the same time at home. This was confirmed by autopsy and was adjudicated as noncardiovascular death. Clinical events at 30 days and 1 year are presented in Table 4 and echocardiographic characteristics in Table 5. One patient had spontaneous intracranial microhemorrhage within 30 days found on brain magnetic resonance imaging done for headache (with no focal deficit per a neurologist's evaluation). No patient required MV reintervention. There were no THV thrombosis, hemolysis, or THV endocarditis events.

1-YEAR OUTCOMES. At 1-year follow-up (median 1.1 years; IQR: 1.0 to 1.9 years), 96.7% of patients (29 of 30) were alive, and 89.3% were in NYHA functional class I or II. There were no deaths after 30-day follow-up (Table 4). A descriptive summary of each patient, including essential baseline characteristics and outcomes, is provided in Table 6. A total of 5 patients had rehospitalization for heart failure (16.7%), 1 within 30 days because of decompensated diastolic heart failure and 4 after 30 days (2 because of acute on chronic diastolic heart failure, 1 because of preexisting underlying systolic heart failure, and 1 with suspected contribution from a left-to-right shunt who underwent percutaneous closure of the iatrogenic interatrial septal defect). Three of these patients met the THV performance endpoint at 1 year, and 2 did not because of mean MVG ≥10 mm Hg (11.6 and 14.7 mm Hg at heart rates of 90 and 81 beats/min, respectively; heart rate unchanged from baseline). Two patients underwent septostomy closure after 30 days because of left-to-right shunt and suspected right ventricular overload. Additional adverse events were rare. One patient had an intracranial hemorrhage after 30 days subsequent to trauma after a fall. There were no late THV migration or embolization events, endocarditis, or THV thrombosis (systematically searched for using transthoracic echocardiography). No hemolytic anemia events were detected with routine biological markers, including haptoglobin and plasma free hemoglobin levels. Patients who were alive at 1 year experienced significant improvement in NYHA functional class (Figure 4), improvement in 6-min walk distance (Figure 5), and improvement in quality-of-life scores (Figure 6). Most patients continued oral anticoagulation (Figure 7). Left ventricular function remained unchanged. TMVR device function remained stable, with a median mean MVG of 6.6 mm Hg (IQR: 5.5 to 8.9 mm Hg) in the entire cohort, but mean MVG was greater for the smaller 23-mm THVs (8.4 mm Hg [IQR: 7.3 to 9.6 mm Hg] vs. 6.0 mm Hg [IQR: 5.0 to 7.7 mm Hg] for the 29-mm

FIGURE 3 **Kaplan-Meier Survival Curves**



HF = heart failure; KM = Kaplan-Meier; ViV = valve-in-valve.

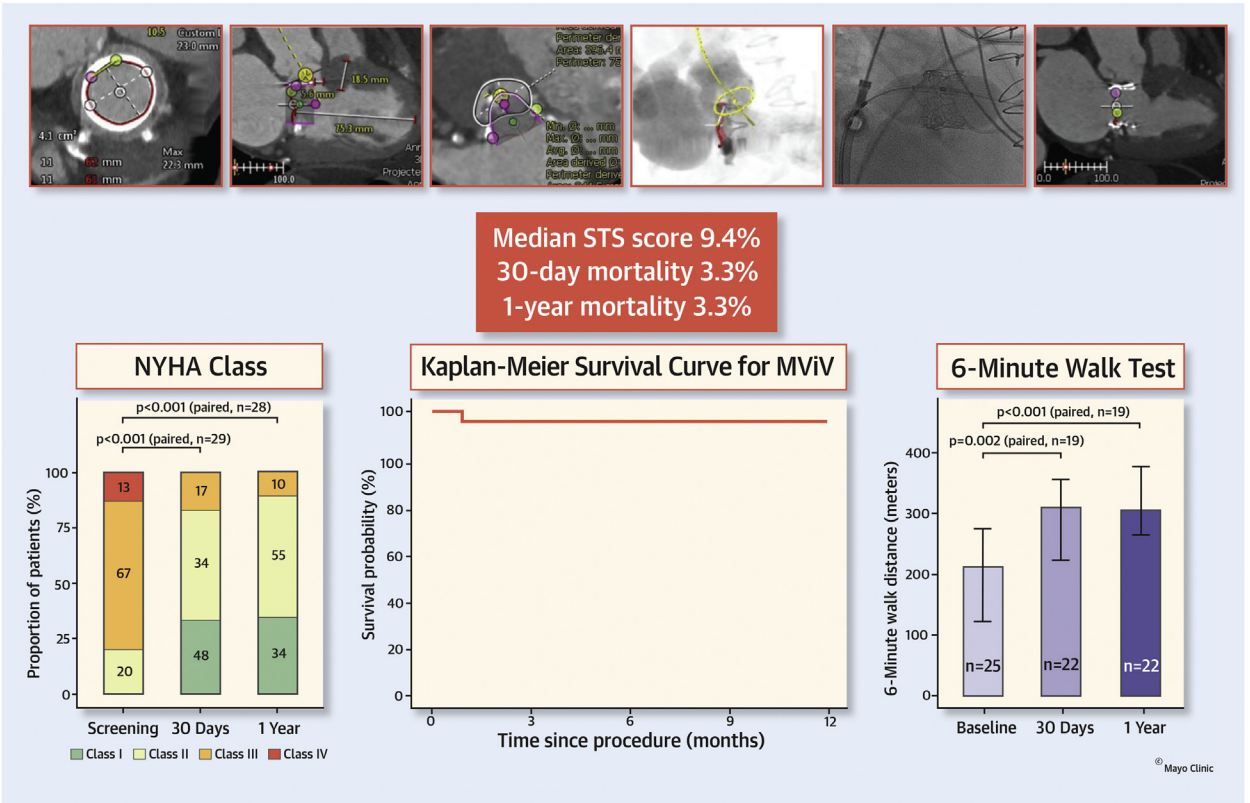
THV) (Figure 8). All patients had grade 1+ or less total MR at 1 year.

DISCUSSION

This is the first prospective, multicenter, U.S. Food and Drug Administration-approved early feasibility clinical trial with independent imaging core laboratories and independent clinical event adjudication to evaluate the safety and feasibility of transseptal MViV using the SAPIEN 3 balloon-expandable aortic THV. The main findings of this study are as follows: 1) Transseptal MViV in selected patients at high surgical risk was associated with a 100% technical success rate, a low procedural complication rate, and a low mortality rate (3.3%) at 1 year in a patient population with a median STS score of 9.4%; 2) transseptal MViV was associated with alleviation of symptoms, improvement in 6-min walk distance, and improvement in quality-of-life scores; and 3) the performance of the THV was acceptable and remained stable at 1 year.

The findings of this trial are different from those of prior published studies that evaluated the early experience of MViV procedures. In those early reports of retrospective studies, procedure-related complications and mortality rates were higher than in this prospective study. The initial 30-day all-cause mortality rate in the VIVID registry was 7.7% in a patient population with an STS score of 13.4% (8). Similarly, the initial 30-day mortality rate in the TVT Registry was 8.1% in patients with an STS score of 10% (10). The VIVID registry and initial analysis of the TVT Registry included patients treated with first- and second-generation devices, and a large proportion of patients were treated via transapical access (64.4% and 46.8%, respectively) (10,17). A subsequent multicenter retrospective registry study of 60 MViV patients all treated with a transseptal approach demonstrated better outcomes, with a 30-day mortality rate of 5% and a procedural success rate of 97% (9). Two additional contemporary retrospective registries reported similar 30-day mortality rates of 5.9% and 6.2%, with all-cause mortality rates at 1 year of 13.2% and 23.5%, respectively (18,19). The all-cause 1 year mortality rate of 3.3% in our study was significantly lower than those in the earlier studies.

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



Guerrero, M. et al. J Am Coll Cardiol Intv. 2021;14(8):859-72.

Early and late outcomes for functional capacity (New York Heart Association functional class; **left**) and 6-min walk distance (**right**; median and interquartile range). Both measures were significantly improved compared with baseline and remained stable. The early mortality (depicted as Kaplan-Meier survival; **center**) was better than expected on the basis of the Society of Thoracic Surgeons score.

The patient populations in prior studies were heterogenous, with different delivery access routes and valve types used. A difference in outcomes related to type of delivery access (transapical vs. transseptal) was not demonstrated until recently. A contemporary analysis of the TVT Registry including only patients treated with the SAPIEN 3 valve found a 30-day mortality rate of 8.1% in patients treated with transapical MViV versus 5.0% in patients treated with transseptal access ($p = 0.07$). The difference in mortality was even more pronounced at 1 year (21.7% with transapical access vs. 15.7% with transseptal access; $p = 0.03$) (20).

With 100% transseptal access and careful patient selection in the present study, the investigators were able to reduce the mortality rate to 3.3% at 1 year. The only death was noncardiovascular (asphyxia after taking 6 pills simultaneously on day 29 post-MViV). The very low mortality at 1 year in our study is equivalent to one-fifth of the 15.7% mortality rate observed in the TVT Registry with transseptal MViV, suggesting significant progress in this field. In addition, technical success in this study was 100%. There were no intraprocedural deaths, need for a second valve, THV device embolization, LVOT obstruction, or conversion to open heart surgery during the index procedure. We attribute the improved outcomes in this study to careful patient selection, including cardiac CT analysis in all patients to identify patients at risk for complications such as LVOT obstruction.

Another factor that may have contributed to improved outcomes is the experience of the operators participating in this trial. We have previously described the technique used (14,16). Ongoing education and proctoring of new operators during these procedures may allow the overall outcomes to continue to improve in the real-world experience outside the confines of a clinical trial.

REPEAT MITRAL SURGERY VERSUS MViV. An analysis from the STS database including 11,973 patients showed that 30-day mortality among patients undergoing redo MV surgery was higher (11.1%) than among patients who underwent first-time mitral surgery (6.5%) (7). However, there are no data from randomized prospective studies comparing outcomes of patients who undergo repeat MV surgery versus MViV. Limited data exist from small retrospective studies that have demonstrated no significant difference in mortality between these approaches. In a retrospective study, Kamioka et al. (21) compared 62 patients who underwent MViV (STS score 12.7%, 48 transseptal and 14 transapical) with 59 patients treated with repeat surgery (STS score 8.7%) and found 1-year mortality rates of 11.3% versus 11.9%, respectively ($p = 0.92$). In a similar study, Simonetto et al. (22) compared the outcomes of 29 patients who underwent redo MV surgery (STS score 3.6%) and 49 patients who underwent MViV (27 transseptal [STS score 8.5%] and 22 transapical [STS score 8.9%]) and found no significant difference in mortality at 1 year (17.2%, 14.8%, and 18.2%; $p = 1.00$).

It is unlikely that a randomized study evaluating transseptal MViV in high-risk patients will be conducted considering the low mortality rate observed in our study. The Food and Drug Administration has already approved MViV for high-risk patients. However, a prospective study evaluating intermediate-risk patients is already ongoing (PARTNER [Placement of Aortic Transcatheter Valve] 3 Trial - Mitral Valve in Valve; NCT03193801).

THV PERFORMANCE. The primary THV performance endpoint of absence of MR grade ≥2+ or mean MVG ≥10 mm Hg was achieved in 96.6% of patients alive with echocardiographic data available at 30 days (28 of 29) and 82.8% at 1 year (24 of 29). Five patients did not meet the performance endpoint at 1 year, and the reason was a mean MVG >10 mm Hg. Three of those were treated with 26-mm and 2 with 29-mm SAPIEN 3 THVs (3 had mitral stenosis as predominant mode of failure at baseline, 1 had MR, and 1 had mixed pathology at baseline). Importantly, 80% of these patients had alleviation of symptoms despite high residual gradients and were in NYHA functional

TABLE 4 30-Day and 1-Year Clinical Outcomes

	30 Days (n = 30)	1 Year (n = 30)
All-cause mortality	1/30 (3.3)	1/30 (3.3)
Cardiovascular	0/30 (0)	0/30 (0)
Noncardiovascular	1/30 (3.3)	1/30 (3.3)
Device success	28/30 (93.3)	Not applicable
Procedural success	28/30 (93.3)	Not applicable
Primary performance endpoint in survivors	28/29* (96.6)	24/29* (82.8)
Stroke	1/30 (3.3)	2/30 (6.7)
Ischemic	0/30 (0)	0/30 (0)
Hemorrhagic†	1/30 (3.3)	2/30 (6.7)
Myocardial infarction requiring revascularization	0/30 (0)	0/30 (0)
Mitral valve reintervention after index procedure	0/30 (0)	0/30 (0)
Septostomy closed‡	1/30 (3.3)	3/30 (10)
Acute kidney injury requiring hemodialysis	0/30 (0)	0/30 (0)
Blood transfusion	3/30 (10)	6/30 (20)
Major vascular complication§	1/30 (3.3)	1/30 (3.3)
New permanent pacemaker requirement	1/30 (3.3)	1/30 (3.3)
New-onset atrial fibrillation	0/30 (0)	0 (0)
New hospitalization for heart failure	1/30 (3.3)	5/30 (16.7)
Device embolization or migration	0/30 (0)	0/30 (0)
Hemolytic anemia	0/30 (0)	0/30 (0)
Valve thrombosis	0/30 (0)	0/30 (0)
Endocarditis	0/30 (0)	0/30 (0)
New York Heart Association functional class‖		
I	14/29 (48.3)	10/28 (35.7)
II	10/29 (34.5)	15/28 (53.6)
III	5/29 (17.2)	3/28 (10.7)
IV	0/29 (0)	0/28 (0)

Values are n/N (%). *1 patient died on day 29 after transcatheter mitral valve replacement. †1 spontaneous intracranial microhemorrhage found on magnetic resonance imaging done for headache (no focal deficit per neurologist's evaluation) and 1 hemorrhage after a fall. ‡11 during index procedure and 2 between 30-day and 1-year follow-up. §Pulmonary embolism on post-operative day 2. ‖1 died and one subject missing New York Heart Association functional class at 1 year.

TABLE 5 Echocardiographic Characteristics at 30 Days and 1 Year

	30 Days (n = 29*)	1 Year (n = 29*)
Ejection fraction (%)	56.6 (47.0–66.2)	57.7 (45.8–62.3)
Stroke volume (ml)	54.0 (45.0–69.0)	65.6 (52.6–79.3)†
Cardiac output (l/min)	3.1 (1.7–4.3)	4.6 (3.7–5.2)†
Mean MVG (mm Hg)	6.0 (4.7–7.3)	6.6 (5.5–8.9)
Pulmonary artery systolic pressure (mm Hg)	32.2 (27.8–39.0)	45.3 (35.8–54.8)
Peak LVOT gradient (mm Hg)	4.9 (4.0–8.0)	4.1 (2.6–6.8)
Mean LVOT gradient (mm Hg)	2.9 (1.8–4.5)	2.4 (1.5–3.9)
Severity of total mitral regurgitation		
None to trace	28/29 (96.6)	26/29 (89.6)
1+	1/29 (3.4)	3/29 (3.4)
2+	0/29 (0)	0/29 (0)
≥3+	0/29 (0)	0/29 (0)
Severity of paravalvular mitral regurgitation		
None to trace	29/29 (100.0)	27/29 (93.1)
1+	0/29 (0.0)	2/29 (6.9)
2+	0/29 (0)	0/29 (0)
≥3+	0/29 (0)	0/29 (0)

Values are median (interquartile range) or n/N (%). *1 died on post-operative day 29. †15 missing values.
Abbreviations as in Table 2.

TABLE 6 Summary of Individual Patient Data

Patient #	Sex	Age (yrs)	Bioprosthesis Brand	Bioprosthesis Size (mm)	Pathology	SAPIEN 3 Size Recommended by MViV App (mm)	Mitral Annular Area by CT (mm^2)	SAPIEN 3 Size Chosen (mm)
1	F	69	Perimount 6900	25	MS	26	391.5	23
2	M	67	Mosaic	29	MS	26/29	480	26
3	M	77	Mosaic	29	MR	26/29	581	29
4	F	84	Biocor	29	MS	29	510	29
5	F	64	Epic	27	MS	26	443.5	26
6	M	75	Perimount 6900	33	MS	29/NA	586.5	29
7	F	82	Perimount 6900	27	MS	29	453	26
8	M	96	Biocor	29	MR	29	538.5	26
9	M	78	Mosaic	31	MR	29	680	29
10	M	58	Baxter (Edwards)	31	MS	29/NA	635	29
11	F	88	Mosaic	31	MR	29	655.5	29
12	M	73	Perimount	31	Mixed	29	620	29
13	F	82	Perimount	27	MS	29	486	26
14	F	75	Perimount	25	Mixed	26	415	23
15	F	89	Perimount	27	MS	29	476	26
16	F	85	Epic	31	MS	29	605.5	29
17	F	53	Perimount	31	MS	29/NA	587.5	29
18	F	78	Epic	29	MR	29	500	26
19	F	78	Perimount	25	MS	26	392	23
20	M	75	Perimount	25	MS	26	400	26
21	F	86	Mosaic	27	MR	26	480	26
22	F	83	Perimount	25	MS	26	406.5	23
23	F	76	Perimount	25	MS	26	408.5	26
24	M	81	CE Standard	31	MR	29	640	29
25	M	66	CE Standard	33	Mixed	29/NA	678	29
26	M	81	CE Standard	33	Mixed	29/NA	660	29
27	F	87	Perimount	31	MS	29/NA	657	29
28	F	70	Mosaic	27	MR	26	417.5	26
29	F	71	Magna Ease	27	MS	29	500.5	26
30	F	65	Perimount	27	MS	29	480	26

*Patient died on day 29 post-MViV from asphyxia after taking 6 pills together.

CT = computed tomography; MR = mitral regurgitation; MS = mitral stenosis; MVG = mitral valve gradient; MViV = mitral valve-in-valve; NA = not applicable; THV = transcatheter heart valve.

Continued on the next page

class I or II at 1 year. Only 1 patient remained in NYHA functional class III at 1 year.

Although the mean MVG in the entire cohort was higher than reported for THVs designed for the mitral position (7.3 ± 2.7 mm Hg vs. 3.0 ± 1.1 mm Hg) (23), it was similar to the gradients observed at 1 year in the VIVID registry (6.7 ± 2.7 mm Hg) (17) and the TVT Registry (7.0 ± 2.94 mm Hg) (20). The mechanism for mitral higher gradients has not been elucidated. Factors contributing may include restricted expansion limited by the surgical prosthesis, undersizing, and thrombosis. However, thrombosis was not observed by the echocardiography core laboratory in these patients. Nevertheless, routine transesophageal echocardiographic or cardiac CT imaging was not performed at 1-year follow-up, which could have helped confirm the presence or absence of valve thrombosis. Valve fracture using a high-pressure balloon to optimize gradients during the index procedure has been reported (24). However, valve fracture was not used in this study, because of limited data and lack of high mitral gradients observed on

TABLE 6 Continued

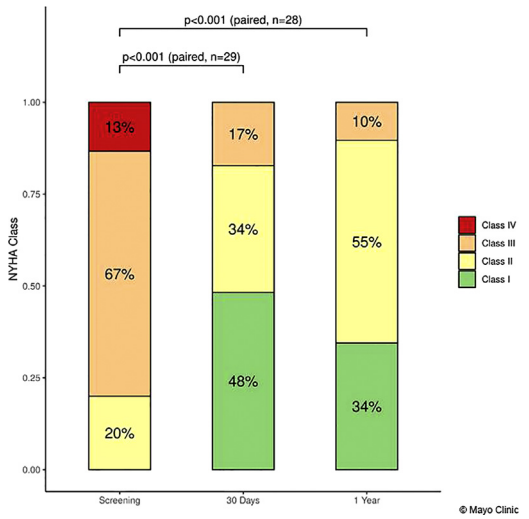
Technical Success	Need for Second Valve	Alive at 30 Days	Procedural Success	THV Performance Endpoint Met at 30 Days	Alive at 1 Year	THV Performance Endpoint Met at 1 Year
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	No (mean MVG >10 mm Hg)	No (mean MVG >10 mm Hg)	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	No (MVG >10 mm Hg)
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	No (MVG >10 mm Hg)
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	No*	No*	No (not available)*	No*	No*
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	No (MVG >10 mm Hg)
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	No (MVG >10 mm Hg)
Yes	No	Yes	Yes	Yes	Yes	Yes
	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	Yes	Yes	Yes	No (MVG >10 mm Hg)
Yes	No	Yes	Yes	Yes	Yes	Yes

transesophageal echocardiography immediately after MViV deployment. The long-term significance of the high residual mitral gradients in these patients is not known. This prospective trial may provide further insights about this finding.

STUDY LIMITATIONS. First, this was an early feasibility study with a small number of patients enrolled. Because the trial design was not randomized and controlled, the results cannot provide evidence that MViV in high-risk patients with failed surgical bioprostheses is superior to repeat standard MV surgery. The patient population as well as the operators in this study were highly selected. Therefore, the results cannot be applied to the general population. The residual MVGs after MViV appeared to be higher than gradients after surgical MV replacement or TMVR with dedicated mitral THVs used for native MV replacement. The long-term significance of this finding is unknown. Follow-up cardiac CT imaging was not performed at 1 year; long-term follow-up CT analysis could have helped identify the mechanism of higher mitral gradients.

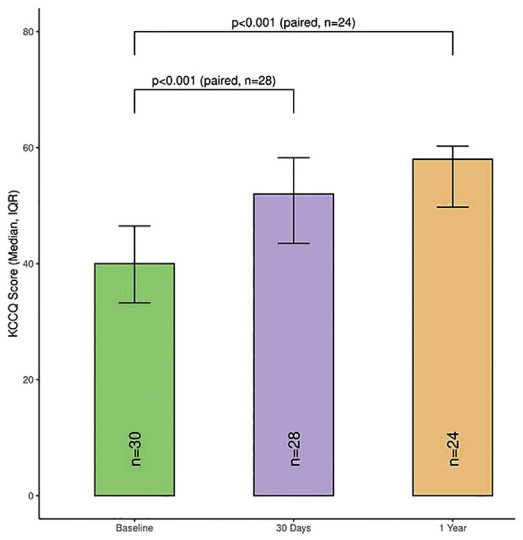
NEXT STEPS. Further studies are needed to evaluate the outcomes of MViV in lower surgical risk patients. The PARTNER 3 Trial - Mitral Valve in Valve is a multicenter prospective registry evaluating the safety and effectiveness of MViV in patients at intermediate surgical risk.

FIGURE 4 NYHA Functional Class



NYHA = New York Heart Association.

FIGURE 6 Quality-of-Life Scores

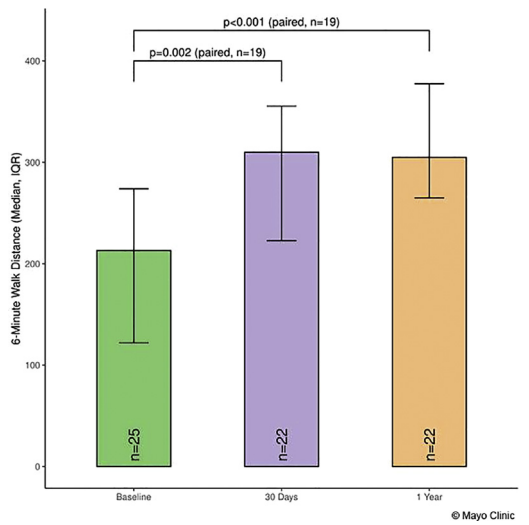


IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire.

CONCLUSIONS

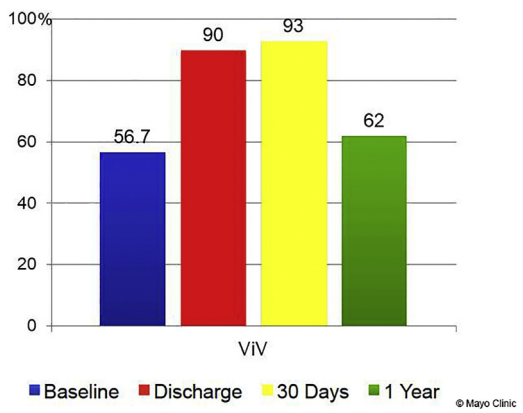
Transseptal MViV in high-risk patients was associated with 100% technical success, low procedural complication rates, and very low mortality at 1 year. Most patients experienced significant alleviation of symptoms, and THV performance remained stable at 1 year. Transseptal MViV may be considered the standard of care for high-risk patients with degenerated mitral bioprostheses who have favorable anatomy pending longer term results.

FIGURE 5 6-Min Walk Test



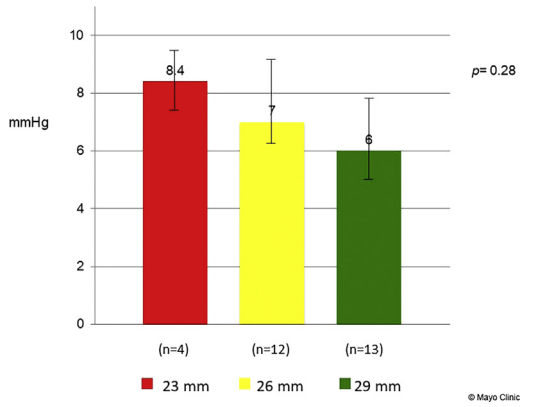
IQR = interquartile range.

FIGURE 7 Percentage of Patients Receiving Oral Anticoagulation



ViV = valve-in-valve.

FIGURE 8 Mean Mitral Valve Gradient at 1-Year Follow-Up According to Transcatheter Heart Valve Size



Values are median mean gradient. Error bars represent interquartile range.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Guerrero has received research grant support from Abbott Vascular and Edwards Lifesciences. Dr. Wang has served as a consultant for Edwards Lifesciences and Boston Scientific; has received research grant support from Boston Scientific assigned to her employer, Henry Ford Health; and holds equity in Encompass Technologies. Dr. Kodali has served as a consultant for Admedus, Meril Lifesciences, Abbott Vascular, JenaValve, and Claret Medical; and has ownership interest in Dura Biotech, Thubrikar Aortic Valve, Micro Interventional Devices, and Supira Medical. Dr. George has served as consultant for Cardiomech, VDyne, MitreMedical, and Neptune Medical. Dr. Meduri has served as a consultant for Medtronic and Boston Scientific; and has served on the advisory board for Boston Scientific. Dr. Reisman has served as consultant for Edwards Lifesciences. Dr. Hahn has received speaker fees from Baylis Medical, Edwards Lifesciences, and Medtronic; is a consultant for Abbott Structural, Edwards Lifesciences, Gore & Associates, Medtronic, Navigate, and Philips Healthcare; has received nonfinancial support from 3mensio; holds equity in Navigate; and is the chief scientific officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she receives no direct industry compensation. Dr. O'Neill has served as a consultant for Abiomed, Boston Scientific, and Edwards Lifesciences. Dr. Feldman is an employee of Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Mayra Guerrero, Mayo Clinic College of Medicine, Department of Cardiovascular Medicine, Mayo Clinic Hospital, 1216 2nd Street SW, Rochester, Minnesota 55905, USA. E-mail: mayraguerrero@icloud.com.

PERSPECTIVES

WHAT IS KNOWN? Patients with failed mitral bioprostheses who need repeat MV surgery often have high surgical risk.

WHAT IS NEW? Transseptal MViV in high-risk patients was associated with 100% technical success, low procedural complication rates, and very low all-cause mortality at 1 year.

WHAT IS NEXT? Further studies are needed to confirm the safety and efficacy of MViV in lower risk patients and to evaluate the durability of THV performance.

REFERENCES

1. Jamieson WR, Burr LH, Miyagishima RT, et al. Reoperation for bioprosthetic mitral structural failure: risk assessment. Circulation 2003;108 suppl 1:II98–102.

2. Albeyoglu SC, Filizcan U, Sargin M, et al. Determinants of hospital mortality after repeat mitral valve surgery for rheumatic mitral valve disease. Thorac Cardiovasc Surg 2006;54:244–9.

3. Vohra HA, Whistance RN, Roubelakis A, et al. Outcome after redo-mitral valve replacement in adult patients: a 10-year single-centre experience. Interact Cardiovasc Thorac Surg 2012;14:575–9.

4. Ejiofor JI, Hirji SA, Ramirez-Del Val F, et al. Outcomes of repeat mitral valve replacement in patients with prior mitral surgery: a benchmark for transcatheter approaches. J Thorac Cardiovasc Surg 2018;156:619–27.e1.

5. Kilic A, Acker MA, Gleason TG, et al. Clinical outcomes of mitral valve reoperations in the United States: an analysis of the Society of Thoracic Surgeons national database. Ann Thorac Surg 2019;107:754–9.

6. Exposito V, Garcia-Camarero T, Bernal JM, et al. Repeat mitral valve replacement: 30-years' experience. Rev Esp Cardiol 2009;62:929–32.

7. Mehaffey HJ, Hawkins RB, Schubert S, et al. Contemporary outcomes in reoperative mitral valve surgery. Heart 2018;104:652–6.

8. Dvir D. Transcatheter mitral valve-in-valve/valve-in-ring. Available at: https://wwwtctmdcom/slide/tav-mitral-surgical-valves-and-rings-lessons-vivid-registry. Accessed August 27, 2018.

9. Eleid MF, Whisenant BK, Cabalka AK, et al. Early outcomes of percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. J Am Coll Cardiol Intv 2017;10:1932–42.

10. Guerrero M, Vemulapalli S, Xiang Q, et al. Thirty-day outcomes of transcatheter mitral valve replacement for degenerated mitral bioprostheses (valve-in-valve), failed surgical rings (valve-in-ring), and native valve with severe mitral annular calcification (valve-in-mitral annular calcification) in the United States: data from the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. Circ Cardiovasc Interv 2020;13:e008425.

11. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

12. Douglas PS, DeCara JM, Devereux RB, et al. Echocardiographic imaging in clinical trials: American Society of Echocardiography standards for echocardiography core laboratories: endorsed by the American College of Cardiology Foundation. J Am Soc Echocardiogr 2009;22:755–65.

13. Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). J Cardiovasc Comput Tomogr 2012;6:366–80.

14. Guerrero M, Salinger M, Pursnani A, et al. Transseptal transcatheter mitral valve-in-valve: a step by step guide from preprocedural planning to postprocedural care. Catheter Cardiovasc Interv 2018;92:E185–96.

15. Bapat V. Valve-in-valve apps: why and how they were developed and how to use them. EuroIntervention 2014;10 suppl U:U44–51.

16. Michelena HI, Alli O, Cabalka AK, Rihal CS. Successful percutaneous transvenous antegrade mitral valve-in-valve implantation. Catheter Cardiovasc Interv 2013;81:E219–24.

17. Simonato M, Whisenant B, Barbosa Ribeiro H, et al. Transcatheter mitral valve replacement after surgical repair or replacement: comprehensive mid-term evaluation of valve-in-valve and valve-in-ring implantation from the VIVID registry. Circulation 2021;143:104–16.

18. Urena M, Brochet E, Lecomte M, et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. Eur Heart J 2018;39:2679–89.

19. Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2019;40:441–51.

20. Whisenant B, Kapadia SR, Eleid MF, et al. One-year outcomes of mitral valve-in-valve using the SAPIEN 3 transcatheter heart valve. JAMA Cardiol 2020;5:1245–52.

21. Kamioka N, Babaliaros V, Morse MA, et al. Comparison of clinical and echocardiographic outcomes after surgical redo mitral valve replacement and transcatheter mitral valve-in-valve therapy. J Am Coll Cardiol Intv 2018;11:1131–8.

22. Simonetto F, Purita PAM, Malerba M, et al. Surgical redo versus transseptal or transapical transcatheter mitral valve-in-valve implantation for failed mitral valve bioprosthesis. Catheter Cardiovasc Interv. 2021;97:714–22.

23. Sorajja P, Moat N, Badhwar V, et al. Initial feasibility study of a new transcatheter mitral prosthesis: the first 100 patients. J Am Coll Cardiol 2019;73:1250–60.

24. Kaneko T, Piccirillo B, Golwala H, et al. Balloon fracture of a surgical mitral bioprosthesis during valve-in-valve transcatheter mitral valve replacement: first-in-human report. Circ Cardiovasc Interv 2018;11:e006273.

KEY WORDS mitral valve-in-valve, surgical mitral valve replacement, transcatheter mitral valve replacement

APPENDIX For inclusion and exclusion criteria, MITRAL trial valve-in-valve arm trial operations, supplemental methods (cardiac computed tomography), study endpoints, and supplemental references, please see the online version of this paper.