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# Early Outcomes of Percutaneous Transvenous Transseptal Transcatheter Valve Implantation in Failed Bioprosthetic Mitral Valves, Ring Annuloplasty, and Severe Mitral Annular Calcification

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## ABSTRACT

**OBJECTIVES** The aim of this study was to examine 1-year outcomes of transseptal balloon-expandable transcatheter heart valve implantation in failed mitral bioprosthesis, ring annuloplasty, and mitral annular calcification (MAC).

**BACKGROUND** Immediate outcomes following transseptal mitral valve implantation in failed bioprostheses are favorable, but data on subsequent outcomes are lacking.

**METHODS** Percutaneous transseptal implantation of balloon-expandable transcatheter heart valves was performed in 87 patients with degenerated mitral bioprostheses (valve in valve [VIV]) (n = 60), previous ring annuloplasty (valve in ring) (n = 15), and severe MAC (valve in MAC) (n = 12).

**RESULTS** The mean Society of Thoracic Surgeons risk score was 13 ± 8%, and the mean age was 75 ± 11 years. Acute procedural success was achieved in 78 of 87 patients (90%) in the overall group and 58 of 60 (97%) in the VIV group, with a success rate of 20 of 27 (74%) in the valve in ring/valve in MAC group. Thirty-day survival free of death and cardiovascular surgery was 95% (95% confidence interval [CI]: 92% to 97%) in the VIV subgroup and 78% (95% CI: 70% to 86%) in the valve in ring/valve in MAC group (p = 0.008). One-year survival free of death and cardiovascular surgery was 86% (95% CI: 81% to 91%) in the VIV group compared with 68% (95% CI: 58% to 78%) (p = 0.008). At 1 year, 36 of 40 patients (90%) had New York Heart Association functional class I or II symptoms, no patients had more than mild residual mitral prosthetic or periprosthetic regurgitation, and the mean transvalvular gradient was 7 ± 3 mm Hg.

**CONCLUSIONS** One-year outcomes following successful transseptal balloon-expandable transcatheter heart valve implantation in high-risk patients with degenerated mitral bioprostheses are excellent, characterized by durable symptom relief and prosthesis function. Although mitral valve in ring and valve in MAC have higher operative morbidity and mortality, 1-year outcomes after an initially successful procedure are favorable in carefully selected patients. (J Am Coll Cardiol Intv 2017;10:1932–42) © 2017 by the American College of Cardiology Foundation.

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Structural degeneration requiring repeat intervention in the first 10 years following mitral valve surgery may be required in up to 35% of patients (1,2). Given the high risk of redo mitral valve surgery, particularly in patients with severe medical comorbidities, alternative, less invasive therapies are needed. Nonrheumatic mitral stenosis or regurgitation due to mitral annular calcification (MAC) presents unique challenges and carries a higher procedural mortality with mitral valve replacement (3,4). Transcatheter valve-in-valve implantation is a promising therapy for such patients, with emerging evidence suggesting feasibility of this approach (5–7). We have recently reported a series of patients undergoing transvenous transseptal implantation of balloon-expandable transcatheter heart valves (THVs) showing high procedural success rates and rapid recovery, particularly in patients with degenerated mitral bioprostheses (8). However, the 1-year durability of balloon-expandable THVs designed for the treatment of aortic stenosis in the mitral position is unknown.

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We sought to evaluate the 1-year outcomes of percutaneous antegrade transvenous transseptal mitral valve implantation using commercially available balloon-expandable THVs in patients with failed mitral bioprostheses, ring annuloplasty, and mitral stenosis due to MAC.

## METHODS

**PATIENT POPULATION.** From January 2014 through March 2017, 46 consecutive patients underwent percutaneous transvenous transseptal implantation of the balloon-expandable SAPIEN, SAPIEN XT, or SAPIEN 3 THV (Edwards Lifesciences, Irvine, California) into the mitral position at the Mayo Clinic (Rochester, Minnesota), 19 at Intermountain Heart Institute (Salt Lake City, Utah), 10 at New York University Medical Center (New York, New York), 6 at Centre Cardiologique du Nord (Saint-Denis, France), 4 at St. Michael's Hospital (Toronto, Ontario, Canada), and 3 at the University of Alabama (Birmingham, Alabama). Each center included in this study performed the procedure using the same technique (described later) and patient selection criteria. Patients who had significant bioprosthetic mitral valve or annuloplasty repair dysfunction (stenosis, regurgitation, or both) or severe mitral stenosis due to MAC, with comorbid conditions that would preclude a repeat sternotomy and valve replacement, were considered candidates for the procedure. Exclusion criteria for patients with bioprosthetic valve failure included the presence of active endocarditis or prosthetic valve thrombosis. Exclusion criteria for patients with annuloplasty rings included a high predicted risk for left ventricular outflow tract (LVOT) obstruction on the basis of pre-procedural imaging or the presence of an annular area too large to allow 5% to 10% oversizing with a balloon-expandable THV. Exclusion criteria for patients with MAC included insufficient circumferential calcification (<270° of annular circumference), a high predicted risk for LVOT obstruction on the basis of pre-procedural imaging (anticipated ≥50% reduction in LVOT area), or the presence of an annular area too large to allow 5% to 10% oversizing with a balloon-expandable THV. All patients were evaluated by a cardiovascular surgeon before proceeding with percutaneous valve therapy. All patients received detailed instruction on potential risks of the procedure and the off-label use of the THVs. Alternatives, including repeat open surgery and medical therapy, were carefully discussed. All patients provided informed consent for the procedure. Patients were counseled about the need for long-term anticoagulation with warfarin after valve implantation (in the absence of contraindications). All procedures were performed electively, with the exception of 2 urgent mitral valve implantations. Four procedures were performed using planned venoarterial extracorporeal membrane oxygenation; the remaining were performed without hemodynamic support devices. This retrospective study was approved by the Mayo Clinic Institutional Review Board.

**PROCEDURAL PLANNING.** In most cases, transcatheter valve size was selected on the basis of a combination of the manufacturer's reported internal dimension and true internal dimension as well as computed tomography–derived and transesophageal echocardiography (TEE)–derived measurements (9). The valve-in-valve app was consulted for each case to ensure proper valve size selection (Bapat V, Valve in Valve Mitral app, UBQO Limited, London, United Kingdom). We typically added 1 to 2 ml of additional volume to the deployment balloon and determined the amount of volume on the basis of the visual appearance of the valve, aiming to achieve mild flaring of the ends of the valve stent on the ventricular and atrial sides. For patients with calcific mitral stenosis or mitral annuloplasty rings, 3-dimensional computed tomographic evaluation of the mitral annulus and leaflets was essential to determine the presence of adequate calcification or ring coverage of

### ABBREVIATIONS AND ACRONYMS

**CI** = confidence interval

**LV** = left ventricular

**LVOT** = left ventricular outflow tract

**MAC** = mitral annular calcification

**MR** = mitral regurgitation

**MVARC** = Mitral Valve Academic Research Consortium

**NYHA** = New York Heart Association

**TEE** = transesophageal echocardiography

**THV** = transcatheter heart valve

at least 75% of the circumference of the valve in all 4 quadrants to facilitate transcatheter valve anchoring, as well as risk for LVOT obstruction. Different valve sizes were overlaid using a 3-dimensional computed tomographic model (in some cases, a printed model was created) to determine optimal valve size that would result in 5% to 10% oversizing. A predicted reduction in LVOT area of ≥50% with simulated valve implantation was considered an exclusion criterion.

**MITRAL VALVE-IN-VALVE PROCEDURE.** The mitral valve-in-valve procedure was performed in the cardiac catheterization laboratory according to our recently reported technique (8). Patients were placed under general endotracheal anesthesia. Intraprocedural imaging was performed using TEE. Two Perclose ProGlide devices (Abbott Vascular, Santa Rosa, California) were deployed in a pre-close fashion in the right common femoral vein, and the 14- or 16-F sheath was introduced. A 5-F pacing catheter was advanced into the right ventricle via the femoral vein for rapid pacing during valve deployment. Transseptal puncture was performed using standard techniques with guidance by TEE. The atrial septum was sequentially dilated with a 14-F dilator, followed by a 10- to 14-mm Mustang balloon depending on the size of the SAPIEN valve being used. An 8.5-F medium curve Agilis sheath (St. Jude Medical, St. Paul, Minnesota) or 9-F Dexterity steerable introducer (Spirus Medical, West Bridgewater, Massachusetts) was placed in the left atrium over an Inoue wire (Toray Industries, Tokyo, Japan) through which a Safari wire (Boston Scientific, Marlborough, Massachusetts) was introduced into the left ventricle. Unfractionated heparin (200 U/kg) was administered to ensure adequate systemic anticoagulation, and the activated clotting time was monitored regularly to maintain a time >300 s. The THV was positioned and deployed within the bioprosthesis, annuloplasty ring, or MAC to achieve a conical deployment with flaring of the prosthesis on the ventricular side and in most cases with 20% of the prosthesis on the atrial side of the sewing ring/MAC and 80% ventricular after final deployment. Immediate procedural results, including immediate prosthesis function, were assessed using TEE.

The majority (n = 84) of cases were performed without obtaining transapical access to avoid complications associated with transapical access and to simplify procedural technique, as described in detail previously (8). Three cases were performed with the use of a transapical rail, as described in detail previously (8).

**DEFINITIONS.** Complications including conversion to open surgery, myocardial infarction, stroke, emergency surgery, bleeding, and vascular complications were reported according to the Mitral Valve Academic Research Consortium (MVARC) criteria (10). Device success was defined as the absence of procedural mortality, the correct positioning of a single transcatheter valve, and the absence of residual moderate or severe prosthetic regurgitation or stenosis. Prosthetic function was assessed before discharge by transthoracic echocardiography. Transcatheter prosthesis and periprosthetic or intervalvular regurgitation was graded as absent, trace, mild, moderate, or severe.

**FOLLOW-UP.** In-hospital and post-discharge adverse events were prospectively recorded. All patients were prescribed indefinite oral anticoagulation (warfarin) with a goal international normalized ratio of 2.0 to 3.0 and single-antiplatelet therapy (aspirin 81 mg/day or clopidogrel 75 mg/day if indicated for other purposes). Bridging anticoagulation was not required before hospital dismissal. The 30-day and 1-year follow-up medical evaluations were performed at the treating institution or through the patient's local physician. Thirty-day and 1-year transthoracic echocardiographic data were collected.

**DATA ANALYSIS.** Society of Thoracic Surgeons risk score was calculated using the mitral valve replacement algorithm. Continuous variables are expressed as mean ± SD if normally distributed or as median (interquartile range) if skewed. Paired Student *t* tests and Wilcoxon signed rank tests compared pre- and post-procedural variables within patients. Repeated-measures analysis was used to compare variables measured at multiple time points. We defined the surveillance period as the time between the procedure and the last clinical contact with the patient. Analyses were performed using JMP version 9 (SAS Institute, Cary, North Carolina).

## RESULTS

**PATIENT POPULATION.** A total of 87 patients underwent percutaneous transvenous mitral balloon-expandable THV implantation during the study period. The mean age of the overall group was 75 ± 11 years, and 48 (56%) were women. The mean Society of Thoracic Surgeons risk score was 13 ± 8%. A total of 40 patients (46%) reached 1 year of follow-up during the study period. Characteristics of each group are shown in **Tables 1 to 3**.

**MITRAL VALVE IMPLANTATION IN FAILED BIOPROSTHETIC VALVES.** A total of 60 patients underwent percutaneous transseptal implantation of balloon-expandable THVs within dysfunctional

**TABLE 1 Mitral Valve-in-Valve Patient Characteristics (n = 60)**

| | |
|---|---|
| Age (yrs) | 75 ± 11 |
| Female | 34 (57) |
| Previous cardiac surgery | 60 (100) |
| Chronic lung disease | 21 (35) |
| Previous stroke | 5 (8) |
| Diabetes mellitus | 13 (22) |
| Hypertension | 51 (85) |
| Peripheral arterial disease | 10 (17) |
| Atrial fibrillation | 41 (68) |
| Creatinine (mg/dl) | 1.3 ± 0.5 |
| Hemoglobin (g/dl) | 11.2 ± 1.8 |
| NT-proBNP (ng/l) | 3,482 ± 4,978 |
| Mode of prosthesis failure | |
| Regurgitation | 38 (63) |
| Stenosis | 19 (32) |
| Combined | 3 (5) |
| Prosthesis type | |
| Mosaic | 21 (35) |
| Hancock | 11 (18) |
| Perimount | 8 (13) |
| Epic | 7 (12) |
| Carpentier Edwards | 7 (12) |
| Biocor | 3 (5) |
| Other | 3 (5) |
| Ejection fraction (%) | 57 ± 11 |
| Right ventricular systolic pressure (mm Hg) | 61 ± 16 |
| STS risk score | 12.5 ± 7.2 |
| NYHA functional class | |
| III | 27 (45) |
| IV | 33 (55) |

Values are mean ± SD or n (%).
NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

**TABLE 2 Mitral Valve-in-Ring Patient Characteristics (n = 15)**

| | |
|---|---|
| Age (yrs) | 72 ± 8 |
| Female | 9 (60) |
| Previous cardiac surgery | 15 (100) |
| Chronic lung disease | 6 (40) |
| Previous stroke | 1 (7) |
| Diabetes mellitus | 2 (13) |
| Hypertension | 11 (73) |
| Peripheral arterial disease | 3 (20) |
| Atrial fibrillation | 7 (47) |
| Creatinine (mg/dl) | 1.7 ± 1.6 |
| Hemoglobin (g/dl) | 10.6 ± 2.7 |
| NT-proBNP (ng/l) | 2,476 ± 3,555 |
| Mode of failure | |
| Regurgitation | 11 (73) |
| Stenosis | 3 (20) |
| Combined | 1 (7) |
| Ring type | |
| Physio | 7 (47) |
| Annuloflex | 3 (20) |
| Tailor/Seguin | 2 (13) |
| CG Future | 1 (7) |
| Duran AnCore | 1 (7) |
| Cosgrove Band | 1 (7) |
| Ring characteristics | |
| Complete | 12 (80) |
| Incomplete | 3 (20) |
| Rigid | 3 (20) |
| Semirigid | 9 (60) |
| Flexible | 3 (20) |
| Ejection fraction (%) | 50 ± 19 |
| Right ventricular systolic pressure (mm Hg) | 55 ± 23 |
| STS risk score | 11.4 ± 7.3 |
| NYHA functional class | |
| III | 7 (47) |
| IV | 8 (53) |

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

mitral bioprosthetic valves (mode of failure regurgitation in 38, stenosis in 19, combined in 3). Characteristics of this population are shown in Table 1. Of these procedures, 58 (97%) were successful, whereas 2 patients (3%) died during valve deployment of left ventricular (LV) apical perforation because of wire or catheter nosecone injury (Table 4). No patient experienced stroke or myocardial infarction after the procedure. One patient developed a hemothorax early after the procedure related to transapical access for the rail delivery, which was successfully managed with a tube thoracostomy. Two other patients had vascular access-related bleeding requiring blood transfusion.

Mild periprosthetic mitral regurgitation (MR) was present in 2 patients, and moderate periprosthetic MR in 1 patient, with the remaining patients having either trivial or no periprosthetic MR (Figure 1). One patient had mild prosthetic regurgitation, with the remaining patients having no or trivial prosthetic regurgitation.

Three patients (5%) had LVOT obstruction (with maximum instantaneous gradients of 30, 30, and 52 mm Hg, respectively), with the remaining patients having no LVOT obstruction. Of the patients with LVOT obstruction, 1 had New York Heart Association (NYHA) functional class IV symptoms at 30 days, with the remaining 2 having NYHA functional class I symptoms at last follow-up. One patient developed hemolytic anemia believed to be due to LVOT obstruction, which resolved spontaneously after 2 months. In all cases, LVOT obstruction was managed conservatively, with no need for operative intervention. The mean mitral valve gradient immediately post-procedure was 6.2 ± 2.9 mm Hg, with mean mitral valve effective orifice area of 2.1 ± 0.6 $cm^2$ (Figure 1). Thirty patients (50%) met MVARC criteria for mitral stenosis (mean gradient >5 mm Hg

**TABLE 3 Mitral Valve-in-Mitral Annular Calcification Patient Characteristics (n = 12)**

| | |
|---|---|
| Age (yrs) | 79 ± 9 |
| Female | 5 (42) |
| Previous cardiac surgery | 7 (58) |
| Chronic lung disease | 8 (67) |
| Previous stroke | 2 (17) |
| Diabetes mellitus | 4 (33) |
| Hypertension | 10 (83) |
| Peripheral arterial disease | 4 (33) |
| Atrial fibrillation | 5 (42) |
| Creatinine (mg/dl) | 1.5 ± 0.5 |
| Hemoglobin (g/dl) | 11.7 ± 2.3 |
| NT-proBNP (ng/l) | 1,357 ± 1,113 |
| Mitral valve dysfunction type | |
| Regurgitation | 1 (8) |
| Stenosis | 8 (67) |
| Combined | 3 (25) |
| Ejection fraction (%) | 64 ± 10 |
| Right ventricular systolic pressure (mm Hg) | 50 ± 15 |
| STS risk score | 16.5 ± 12 |
| NYHA functional class | |
| III | 7 (58) |
| IV | 5 (42) |

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

or valve area <1.5 $cm^2$) (Table 5). Median hospital length of stay post-procedure was 3 days.

Thirty-day survival following the procedure was 95%, with no patients lost to follow-up at 30 days. The mean follow-up duration of the entire group was 283 ± 252 days (range 1 to 931 days). One-year survival following the procedure was 86%, with 27 patients (45%) reaching 1-year follow-up, 1 patient lost to follow-up after reaching 30-day follow-up, and 26 patients not yet reaching 1-year follow-up. Of the 6 patients who died during the first year of follow-up, 2 were acute procedure-related deaths, 1 death was related to a drug reaction, 1 was due to sepsis, 1 was due to congestive heart failure, and 1 was due to an unknown cause. There was 1 case of prosthetic valve leaflet dysfunction despite a therapeutic international normalized ratio in the setting of urosepsis occurring 2 months after a mitral valve-in-valve procedure. This patient died 1 month later of congestive heart failure and chronic respiratory failure due to interstitial pneumonitis and emphysema. There were no requirements for redo cardiac surgery during the first year of follow-up. At 1 year of follow-up, 18 patients (68%) reported NYHA functional class I symptoms, 8 (28%) had NYHA functional class II symptoms, and 1 (2%) had NYHA functional class III symptoms. The mean echocardiographic mitral valve gradient at 1-year follow-up was 7.3 ± 2.4 mm Hg, with effective orifice area of 1.9 ± 0.6 $cm^2$. No patients had periprosthetic MR, and no patient had more than mild prosthetic MR at 1 year.

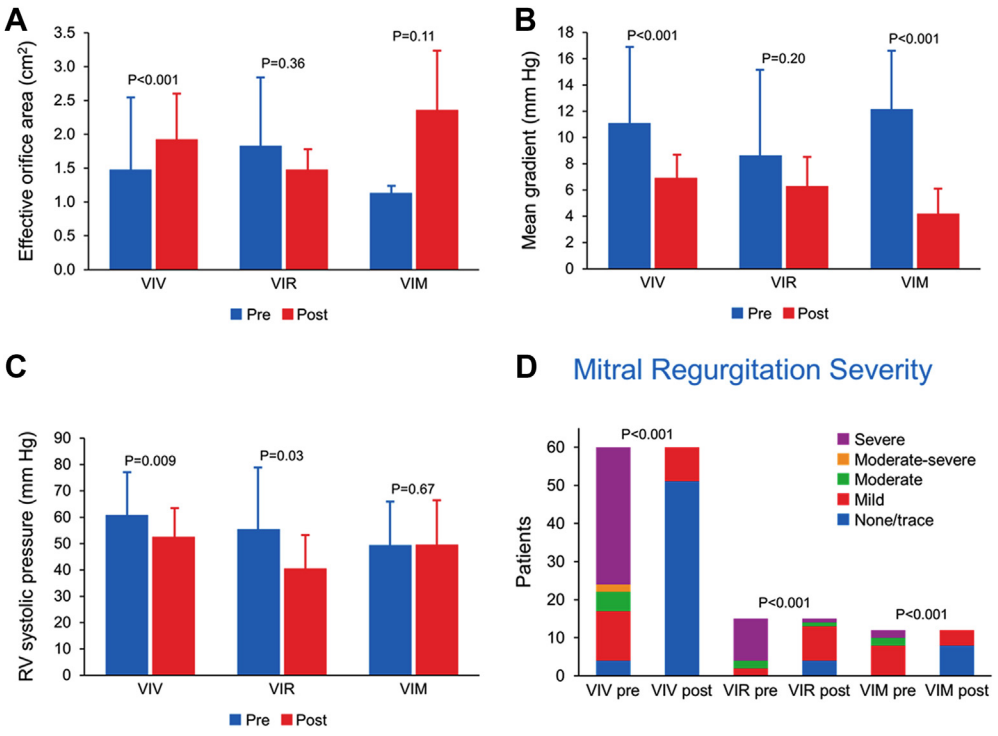
**TABLE 4 Clinical Outcomes According to Procedure**

| | Total (N = 87) | Mitral VIV (n = 60) | Mitral VIR (n = 15) | Mitral VIM (n = 12) | p Value |
|---|---|---|---|---|---|
| Procedural success | 78 (90) | 58 (97) | 11 (73) | 9 (75) | 0.03 |
| Periprocedural mortality | 5 (5) | 2 (3) | 0 (0) | 2 (17) | 0.13 |
| Major bleeding | 9 (10) | 4 (7) | 2 (13) | 3 (25) | 0.17 |
| Left ventricular outflow tract obstruction | 8 (9) | 3 (5) | 3 (20) | 2 (17) | 0.20 |
| Second valve required | 5 (6) | 1 (2) | 2 (13) | 2 (17) | 0.02 |
| Cardiac surgery | 5 (6) | 1 (2) | 3 (20) | 1 (8) | 0.03 |
| Prosthetic valve thrombosis | 2 (2) | 1 (2) | 1 (7) | 0 (0) | 0.31 |
| 30-day survival | 82 (94) | 57 (95) | 15 (100) | 10 (83) | 0.19 |

Values are n (%).
VIM = valve in mitral annular calcification; VIR = valve-in-ring; VIV = valve in valve.

**MITRAL VALVE IMPLANTATION IN FAILED ANNULOPLASTY RINGS.** Fifteen patients with failed mitral annuloplasty rings (11 for regurgitation, 3 for stenosis, 1 for combined regurgitation and stenosis) underwent percutaneous balloon-expandable THV implantation (Table 2). Of these procedures, 2 were complicated by valve migration into the left atrium within minutes after deployment. Both patients remained hemodynamically stable and underwent surgery using conventional open sternotomy to remove the SAPIEN valve and replace the mitral valve. Both of these cases were in patients with incomplete rings, and in the 1 patient who underwent pre-procedural cardiac computed tomographic angiography, predicted percentage oversizing using 3-dimensional modeling was −5%. Two other patients required implantation of a second valve immediately after first valve implantation because of residual periprosthetic regurgitation. The remaining 11 procedures were successful (73%) (Table 4). One of the 7 successful procedures was complicated by an incidentally noted LV apical pseudoaneurysm discovered on transthoracic echocardiography the next day, likely caused by the LV Lunderquist anchor wire. The pseudoaneurysm was successfully treated with percutaneous closure using a 14-mm Amplatzer Vascular Plug II device (Medtronic, Minneapolis, Minnesota) 1 day after the valve-in-valve procedure. Two patients had vascular access site-related bleeding requiring blood transfusion. Nine patients (60%) met MVARC criteria for mitral stenosis (mean gradient >5 mm Hg or valve area <1.5 $cm^2$) immediately post-procedure (Table 5).

**FIGURE 1 Hemodynamic Changes Following Percutaneous Mitral Valve Implantation**




**(A to C)** Significant changes were observed in effective orifice area, mean gradient, and right ventricular systolic pressure. **(D)** Mitral regurgitation severity decreased in all groups. VIM = valve in mitral annular calcification; VIR = valve in ring; VIV = valve in valve.

Of the 13 procedures not requiring cardiac surgery, the mean gradient was reduced to 6.8 ± 2.8 mm Hg, and 12 patients had no more than mild prosthetic or periprosthetic regurgitation, with 1 patient having moderate residual prosthetic regurgitation (Figure 1). One patient had LVOT obstruction due to anterior leaflet displacement immediately after valve deployment but remained hemodynamically stable. Because of persistent symptoms and a peak gradient of 61 mm Hg, the patient underwent a successful elective surgery to resect the anterior leaflet through an aortotomy, leaving the transcatheter mitral valve in place with a post-operative LVOT gradient of 16 mm Hg. In this patient, baseline cardiac computed tomographic angiography measured the native LVOT at 5.61 $cm^2$ and the projected neo-LVOT measured at 2.14 $cm^2$. Two other patients developed mild dynamic LVOT obstruction due to anterior leaflet displacement that was noticed at 30-day follow-up (resting maximal instantaneous gradients 23 and 25 mm Hg and Valsalva gradients 36 and 34, respectively) that were managed successfully with hydration and were NYHA functional class I at last follow-up. One of these patients underwent pre-procedural cardiac computed tomographic angiography showing native LVOT area of 4.37 $cm^2$ with projected neo-LVOT of 3.78 $cm^2$.

**TABLE 5 Echocardiographic Data During Follow-Up**

| | Immediate | 30 Days | 1 Year | p Value |
|---|---|---|---|---|
| Mitral VIV | | | | |
| Mean gradient (mm Hg) | 6.3 ± 2.9 | 6.9 ± 1.8 | 7.3 ± 2.5 | 0.08 |
| Mitral valve area ($cm^2$) | 2.1 ± 0.6 | 1.9 ± 0.7 | 1.8 ± 0.6 | 0.58 |
| Ejection fraction (%) | 57 ± 11 | 53 ± 11 | 57 ± 11 | 0.82 |
| RVSP (mm Hg) | 55 ± 16 | 48 ± 12 | 48 ± 17 | 0.009 |
| Mitral VIR | | | | |
| Mean gradient (mm Hg) | 6.6 ± 2.8 | 6.3 ± 2.2 | 8.2 ± 4.1 | 0.41 |
| Mitral valve area ($cm^2$) | 1.7 ± 0.4 | 1.5 ± 0.3 | NA | 0.36 |
| Ejection fraction (%) | 50 ± 19 | 46 ± 17 | 59 ± 5 | 0.31 |
| RVSP (mm Hg) | 51 ± 16 | 41 ± 13 | 49 ± 23 | 0.03 |
| Mitral VIM | | | | |
| Mean gradient (mm Hg) | 4.2 ± 1.9 | 6.7 ± 3.2 | 4.7 ± 1.5 | 0.25 |
| Mitral valve area ($cm^2$) | 2.8 ± 1.6 | 3.6 ± 2.3 | NA | 0.50 |
| Ejection fraction (%) | 64 ± 10 | 54 ± 2 | 55 ± 10 | 0.47 |
| RVSP (mm Hg) | 50 ± 17 | 34 ± 4 | 48 ± 21 | 0.16 |

Values are mean ± SD.
NA = not applicable; RVSP = right ventricular systolic pressure; other abbreviations as in Table 4.

All patients were alive at 30-day follow-up, and none were lost to follow-up. Mean follow-up duration was 309 ± 202 days. At 30-day follow-up, 1 patient remained hospitalized after requiring emergency cardiac surgery and had NYHA functional class IV heart failure symptoms, 1 patient continued to have NYHA functional class III dyspnea, 8 had NYHA functional class II dyspnea, and the remaining 5 had no residual symptoms. The mean mitral valve gradient was 6.5 ± 2.2 mm Hg, with a mean effective orifice area of 1.5 ± 0.3 $cm^2$. Three patients had mild prosthetic MR, 1 patient had mild periprosthetic MR, and the remaining patients had trace or no residual MR at 30-day follow-up.

One-year survival following the valve-in-ring procedure was 82%, with 9 patients (60%) reaching 1 year of follow-up and 2 patients not yet reaching 1 year of follow-up. Seven patients (70%) had NYHA functional class I or II dyspnea, with 2 patients (30%) having NYHA functional class III or IV heart failure symptoms at 1 year of follow-up. Six patients underwent transthoracic echocardiography at 1 year of follow-up; among these patients, 3 had mild prosthetic, with no patients having more than mild prosthetic MR or periprosthetic MR. The mean mitral valve gradient at 1 year was 9 ± 4 mm Hg.

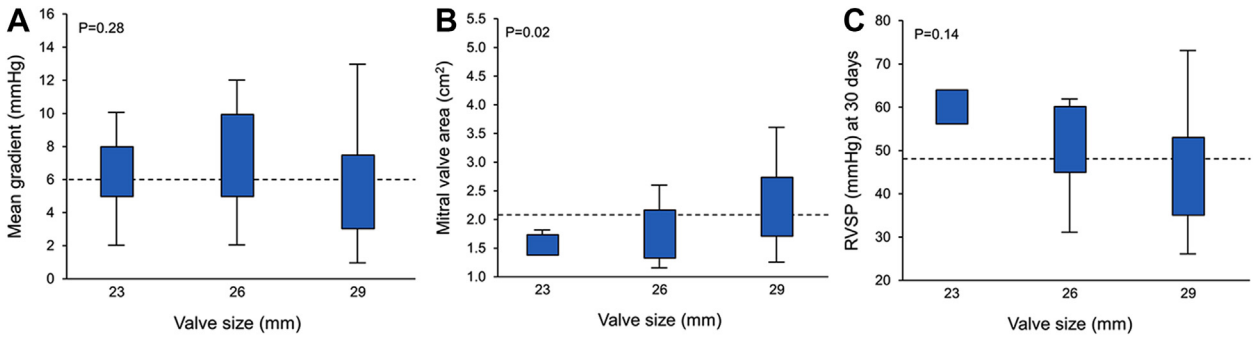
One patient developed prosthetic valve thrombosis 15 months after THV implantation despite therapeutic warfarin anticoagulation and aspirin therapy, and died of complications related to prosthetic valve thrombosis.

**MITRAL VALVE IMPLANTATION IN SEVERE MAC.** Twelve patients with severe MAC underwent percutaneous THV implantation (Table 3). The first procedure in an 80-year-old woman was complicated by apical perforation from the delivery system nosecone after valve deployment with development of cardiac tamponade that could not be successfully repaired surgically. Despite chest compressions during cardiopulmonary resuscitation, the deployed SAPIEN XT valve remained in situ. Another procedure was performed on an 85-year-old woman with severe MAC and was complicated by severe regurgitation of the initially deployed valve, requiring a second valve that embolized in the left atrium, subsequently requiring urgent open surgical repair. In this case, mitral annular area measured 589 $mm^2$ with perimeter of 99 mm, with estimated 15% oversizing, and the mechanism of valve embolization was believed to be due to an inadequate amount of circumferential MAC that occupied only 50% of the annular circumference. A third patient developed severe LVOT obstruction following THV implantation and died 2 days later because of LVOT obstruction. In this case, the baseline computed tomography–derived LVOT area was 281 $mm^2$, with an aortomitral angle of 115°, with a projected neo-LVOT area on the basis of implantation of a 29-mm S3 valve of 165 $mm^2$. One patient had an initially successful procedure but developed severe mitral periprosthetic regurgitation due to slight valve migration, requiring valve-in-valve implantation 6 days later, which was completed successfully. One patient had vascular access site–related bleeding requiring blood transfusion. The other 8 of these procedures (67%) were successful and uncomplicated, with all patients experiencing reductions in mean gradients, patients having either mild or no residual prosthetic or periprosthetic regurgitation, and alleviation of symptoms (Table 4). Two patients (17%) met MVARC criteria for mitral stenosis (mean gradient >5 mm Hg or valve area <1.5 $cm^2$) immediately post-procedure (Table 5). One of the 12 procedures was performed using planned venoarterial extracorporeal membrane oxygenation, which was successfully weaned at the end of the procedure, with the remaining 7 performed without extracorporeal membrane oxygenation. At 30 days, no patients were lost to follow-up, and 10 patients were alive, with 9 of 10 experiencing reduction in symptoms. One patient subsequently developed moderate-to-severe symptomatic mitral paravalvular leak 60 days post-procedure, likely due to slight valve migration, and was successfully treated with paravalvular leak closure. The 1 patient requiring emergency surgery developed persistent heart failure requiring readmission and continued to have NYHA functional class IV symptoms. One patient subsequently died 48 days after the procedure of complications related to a fall and cervical vertebral fracture. The mean follow-up duration of the group was 258 ± 321 days.

One-year survival was 57%, with 4 patients reaching 1 year of follow-up, 1 patient lost to follow-up, and 4 patients not yet reaching 1 year of follow-up. Of these, 3 patients had NYHA functional class I or II symptoms, and 1 patient had NYHA functional class III symptoms. Echocardiographic mean mitral valve gradients in these patients were 4.7 ± 1.5 mm Hg, with 1 patient meeting MVARC criteria for mitral stenosis (mean gradient >5 mm Hg or valve area <1.5 $cm^2$). No patients had periprosthetic MR or more than mild prosthetic MR at 1 year. Two of these patients have also had 2-year follow-up and continue to have NYHA functional class II symptoms. One patient was lost to follow-up.

**COMPARISON BY THV SIZE.** Immediate post-procedural mean gradient was similar among valve sizes,

**FIGURE 2 Hemodynamic Results According to Valve Size**




Mean gradient and mitral valve area immediately post-procedure **(A,B)** and right ventricular systolic pressure (RVSP) **(C)** in the entire cohort. Increasing valve size was associated with larger mitral valve area, but mean gradient and RVSP were similar among groups.

although gradient tended to be lower with larger valve sizes (p = 0.28) (Figure 2). Mitral valve area was larger with the 29-mm valve compared with other groups (2.4 ± 0.2 $cm^2$ for 29 mm vs. 1.7 ± 0.2 and 1.5 ± 0.3 $cm^2$ for 26 and 23 mm, respectively; p = 0.02). There was a trend toward lower right ventricular systolic pressure at 30-day follow-up for patients receiving larger valves (46 ± 2 mm Hg for 29-mm valves vs. 51 ± 4 and 59 ± 7 mm Hg for 26- and 23-mm valves, respectively; p = 0.12) (Figure 2). NYHA functional status at 1 year was similar between patients receiving 23- or 26-mm THVs and those receiving 29-mm THVs (p = 0.61).

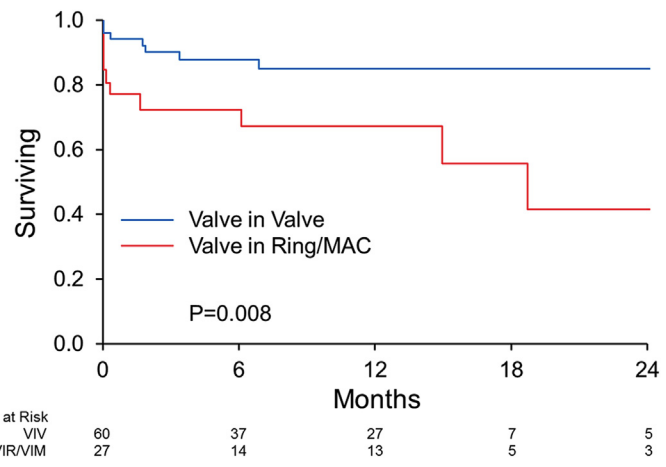
**PREDICTORS OF LVOT OBSTRUCTION.** Patients who developed LVOT obstruction had significantly higher ejection fractions compared with patients without LVOT obstruction (66 ± 6 mm Hg vs. 56 ± 12 mm Hg; p = 0.002). LVOT obstruction tended to be more common in patients undergoing valve-in-ring or valve-in-MAC compared with valve-in-valve procedures (19% vs. 5%; p = 0.10). There were no differences in other baseline variables between groups. Most of the cases of LVOT obstruction were minimally symptomatic and managed conservatively with gradients decreasing over time, but 2 cases (1 valve in ring and 1 valve in MAC) had severe obstruction related to anterior mitral leaflet displacement; 1 was treated successfully with surgery, and the other resulted in hemodynamic compromise and congestive heart failure-related death.

**SURVIVAL AND NEED FOR CARDIAC SURGERY.** Thirty-day survival free of death and cardiovascular surgery was 78% (95% confidence interval [CI]: 70% to 86%) in the mitral valve in ring/valve in MAC group and 95% (95% CI: 92% to 97%) in the failed bioprosthetic mitral valve subgroup (p = 0.008) (Figure 2). One-year survival free of death and cardiovascular surgery was 68% (95% CI: 58% to 78%) in the mitral valve in ring/valve in MAC group and 86% (95% CI: 81% to 91%) in the failed bioprosthetic mitral valve group (p = 0.008) (Figure 3).

## DISCUSSION

In this analysis of early and 1-year outcomes of percutaneous balloon-expandable THV implantation in the mitral position, we made the following

**FIGURE 3 Survival Free of Death or Cardiovascular Surgery**




Survival free of death or cardiovascular surgery was significantly better with mitral valve in valve (VIV) compared with valve in ring (VIR) or valve in mitral annular calcification (VIM). MAC = mitral annular calcification.

observations: 1) antegrade transvenous transseptal balloon-expandable THV implantation for failed mitral bioprosthesis is associated with 97% acute procedural success, 95% 30-day survival, 86% 1-year survival, and durable prosthesis function at 1 year of follow-up; 2) transvenous transseptal balloon-expandable THV implantation for failed annuloplasty rings and severe MAC is feasible but associated with significant rates of LVOT obstruction, need for a second THV, and/or subsequent cardiovascular surgery; 3) in patients with initially successful procedures, 1-year prosthesis function was favorable, with no patients having more than mild prosthetic or periprosthetic regurgitation; 4) a 2% incidence of prosthetic valve thrombosis was observed despite therapeutic anticoagulation, supporting the current recommendation for systemic anticoagulation therapy in all patients undergoing percutaneous mitral valve implantation; and 5) higher LV ejection fraction with associated smaller cavity size was associated with development of LVOT obstruction.

The present study is the largest series of percutaneous transvenous transseptal implantation of balloon-expandable THVs in the mitral position. The high success rate in patients with bioprostheses was demonstrated in a wide range of prosthesis types and sizes and in modes of failure, demonstrating the versatility of the transvenous transseptal balloon-expandable THV technique. At 1 year of follow-up, the majority of patients continued to experience improvements in functional status. From a hemodynamic standpoint, prosthesis function remained stable, with no significant change in the mean gradient or effective orifice area at 1 year and a persistent reduction in estimated right ventricular systolic pressure by echocardiography. Of note, patients receiving smaller THVs (23 and 26 mm), as expected, tended to have higher resting mean gradients and estimated right ventricular systolic pressure, but there was no significant difference in NYHA functional class symptoms at 1 year in these patients compared with those receiving 29-mm THVs. Importantly, warfarin (in conjunction with single-antiplatelet therapy) was prescribed for all patients to minimize the risk for prosthetic valve thrombosis.

The transvenous transseptal delivery of balloon-expandable THVs for patients with failed mitral annuloplasty rings was successful in the majority of patients (73%) despite a higher risk for LVOT obstruction, need for a second valve, or cardiac surgery. Some cases that required surgery were related to the early learning curve of the procedure when important lessons were learned, including avoidance of patients with incomplete rings, consistent use of pre-procedural cardiac computed tomographic angiography, and optimal positioning of the THV in a more ventricular position to minimize embolization risk.

We also noted favorable application of this technique in patients with semirigid or flexible rings because of the ability to deform the ring to a circular shape and minimize paravalvular leak. LVOT obstruction due to either anterior leaflet displacement into the LVOT or the ventricular aspect of valve stent obstructing LV outflow remains a concern and was observed in 3 patients in this series. Important factors that contribute to this risk include the aortomitral angle, LV geometry, anterior mitral leaflet length and mobility, and transcatheter valve depth and flaring within the ventricle. Our study is the first to demonstrate that patients who developed LVOT obstruction had higher ejection fractions compared with patients who did not, confirming that smaller LV cavity size is a risk factor for the development of this complication. Preliminary data from the VIVID (Valve in Valve International Data) registry have similarly shown higher rates of LVOT obstruction, all-cause mortality, and additionally higher rates of residual MR in patients undergoing mitral valve-in-ring procedures. Potential measures to prevent LVOT obstruction include slightly more atrial THV deployment (while ensuring adequate prosthesis anchoring and ring coverage to minimize paravalvular leak) and pre-procedural alcohol septal ablation (11). Despite the higher morbidity of the valve-in-ring procedure, the long-term outcomes of these patients were favorable, with 90% 1-year survival and the majority of patients' having resolution of symptoms (70%) and favorable THV hemodynamic status. Accordingly, these data support that with careful patient selection, comprehensive pre-procedural imaging including mandatory cardiac computed tomography to determine LVOT obstruction risk and to optimize prosthesis sizing, and contingency planning for potential complications, transvenous transseptal can be a highly effective and successful therapy.

The results of our series of patients with MAC suggest that percutaneous balloon-expandable THV implantation holds promise but has important limitations as a therapy for this challenging group of patients. Although initial procedural success was 75%, complications including valve migration or instability requiring a second valve occurred in 17%, and LVOT and paravalvular leak requiring

percutaneous closure each occurred in 17% and 9% of patients, respectively. These complications closely mirror the results of a worldwide registry that included 64 patients undergoing balloon-expandable THV for MAC (12). In the few patients who reached 1 year of follow-up, however, valve hemodynamic status by transthoracic echocardiography was favorable. Given the small sample size of this group of patients, larger cohorts will be necessary to more fully understand the role of balloon-expandable THV therapy for severe MAC. However, it is clear from available data thus far that careful patient selection with the use of pre-procedural imaging is critical to ensure adequate THV anchoring and to minimize the risk for paravalvular leak and LVOT obstruction (11). Cardiac computed tomography is essential to assess the risk for LVOT obstruction and degree of circumferential annular calcification, and to aim for 5% to 10% THV-annular area oversizing. Using cutoffs of minimum 270° (75%) of annular calcification, 5% to 10% area oversizing and a minimum neo-LVOT area of 250 $mm^2$, complications including valve embolization and LVOT obstruction can be prevented. More insight into optimal thresholds for these variables is anticipated from the results of the ongoing MITRAL (Mitral Implantation of Transcatheter Valves) trial (NCT02370511).

Alternative transcatheter mitral valve delivery approaches including transapical and transatrial approaches have also been successfully used. Advantages of these approaches include more direct delivery (transapical), direct visualization (transatrial), and the ability to immediately manage complications surgically. Additionally, the transatrial approach allows removal of the anterior mitral leaflet and subvalvular apparatus in patients with high risk for LVOT obstruction. However, these approaches have the potential for more surgery-related complications (e.g., respiratory failure, major bleeding) and longer recovery times.

**STUDY LIMITATIONS.** This study represents the largest series to date of transvenous transseptal mitral valve implantation and includes patients from selected tertiary referral centers, but the relatively small sample size is an inherent limitation. This report reflects very early experience with this procedure, and refined computed tomographic protocols, procedural techniques, and operator experience may further improve on these excellent outcomes, especially with annuloplasty ring and MAC procedures. Although only 46% of patients reached 1-year follow-up, and not all patients had undergone 1-year echocardiography at the time of submission of this article, long-term outcome data after mitral valve-in-valve have not been available until now and are critical to better understand the role of this therapy in clinical practice. Follow-up TEE was not performed routinely, so it is possible that MR could be underestimated in some cases by transthoracic echocardiography performed at follow-up. Future series of a larger number of patients treated using similar techniques and with longer follow-up duration will be necessary to continually assess outcomes of this exciting and novel therapy. Furthermore, these data are expected to aid in the development of dedicated devices and clinical trials for transseptal mitral valve implantation.

## CONCLUSIONS

One-year outcomes following successful transfemoral percutaneous transvenous balloon-expandable mitral valve implantation in high-risk patients with degenerated bioprostheses are excellent, characterized by durable symptom relief and prosthesis function. Although mitral valve in ring and valve in MAC have higher operative morbidity and mortality, 1-year outcomes after an initially successful procedure are favorable in carefully selected patients.

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## PERSPECTIVES

**WHAT IS KNOWN?** Surgical mitral valve replacement in patients with previous mitral valve surgery or severe MAC is often associated with high or prohibitive risk.

**WHAT IS NEW?** Transfemoral percutaneous transvenous transseptal mitral valve implantation in high-risk patients with degenerated bioprostheses was associated with durable symptom relief and prosthesis function at 1 year of follow-up. Treatment of patients with failed annuloplasty rings and MAC was associated with higher complication rates but successful 1-year outcomes in a subset of patients.

**WHAT IS NEXT?** Larger scale studies and data on long-term outcomes of patients undergoing percutaneous mitral valve-in-valve implantation are needed, as well as the development of dedicated devices for transseptal mitral valve implantation. Further study of valve-in-ring and valve-in-MAC therapy is necessary.

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**KEY WORDS** **mitral valve implantation, percutaneous, transcatheter valve, transseptal**