Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings

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ABSTRACT

BACKGROUND Limited data exist regarding transcatheter mitral valve replacement (TMVR) for patients with failed mitral valve replacement and repair.

OBJECTIVES This study sought to evaluate the outcomes of TMVR in patients with failed mitral bioprosthetic valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]).

METHODS From the TMVR multicenter registry, procedural and clinical outcomes of mitral ViV and ViR were compared according to Mitral Valve Academic Research Consortium criteria.

RESULTS A total of 248 patients with mean Society of Thoracic Surgeons score of 8.9 ± 6.8% underwent TMVR. Transseptal access and the balloon-expandable valve were used in 33.1% and 89.9%, respectively. Compared with 176 patients undergoing ViV, 72 patients undergoing ViR had lower left ventricular ejection fraction (45.6 ± 17.4% vs. 55.3 ± 11.1%; p < 0.001). Overall technical and device success rates were acceptable, at 92.3% and 85.5%, respectively. However, compared with the ViV group, the ViR group had lower technical success (83.3% vs. 96.0%; p = 0.001) due to more frequent second valve implantation (11.1% vs. 2.8%; p = 0.008), and lower device success (76.4% vs. 89.2%; p = 0.009) due to more frequent reintervention (16.7% vs. 7.4%; p = 0.03). Mean mitral valve gradients were similar between groups (6.4 ± 2.3 mm Hg vs. 5.8 ± 2.7 mm Hg; p = 0.17), whereas the ViR group had more frequent post-procedural mitral regurgitation moderate or higher (19.4% vs. 6.8%; p = 0.003). Furthermore, the ViR group had more frequent life-threatening bleeding (8.3% vs. 2.3%; p = 0.03), acute kidney injury (11.1% vs. 4.0%; p = 0.03), and subsequent lower procedural success (58.3% vs. 79.5%; p = 0.001). The 1-year all-cause mortality rate was significantly higher in the ViR group compared with the ViV group (28.7% vs. 12.6%; log-rank test, p = 0.01). On multivariable analysis, failed annuloplasty ring was independently associated with all-cause mortality (hazard ratio: 2.70; 95% confidence interval: 1.34 to 5.43; p = 0.005).

CONCLUSIONS The TMVR procedure provided acceptable outcomes in high-risk patients with degenerated bio-prostheses or failed annuloplasty rings, but mitral ViR was associated with higher rates of procedural complications and mid-term mortality compared with mitral ViV. (J Am Coll Cardiol 2017;70:1121–31) © 2017 by the American College of Cardiology Foundation.

It is estimated that valvular heart disease affects >100 million patients worldwide, which will increase further with the aging population and a subsequent increase in degenerative valve disease. Currently, >40,000 mitral valve replacements are performed annually in the United States, and an analysis of the Society of Thoracic Surgeons (STS) National Database indicated a massive shift from mechanical to bioprosthetic valve replacements (1). Owing to a considerable shift toward bioprosthesis implantation, coupled with frequent repeat operation after mitral valve replacement or repair, it is expected that a growing number of patients will present with degenerated bioprostheses or failed annuloplasty rings (2,3). Although reoperation is considered the standard of care for degenerated bioprostheses or failed annuloplasty rings, these patients are frequently elderly, and repeat cardiac surgery carries significant morbidity and mortality risks (4).

Since the first successful transcatheter aortic valve replacement was introduced by Alain Cribier in 2002 (5), this procedure has already been performed in >250,000 patients worldwide, and it has become

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the standard treatment in inoperable and high surgical risk patients (6-9). Furthermore, this technology is being increasingly applied to a variety of pathologies such as degenerated bioprostheses (10).

Transcatheter mitral valve replacement (TMVR) for degenerated mitral bioprostheses and failed annuloplasty rings has emerged as a less invasive alternative to repeat cardiac surgery in selected patients deemed at high surgical risk, but the experience of TMVR is limited to small series (11-14). Although previous studies showed the feasibility of TMVR for degenerated mitral bioprostheses and failed annuloplasty rings, the diverse etiologies (stenosis, regurgitation, or a combination of both) and device advancements mandate comprehensive evaluation of clinical outcomes of TMVR with a large cohort. Therefore, we created an international multicenter registry of patients undergoing TMVR.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The
TMVR registry is an international, multicenter, observational study that enrolled all consecutive patients with mitral degenerated bioprostheses and failed annuloplasty rings undergoing TMVR. The registry was initiated in November 2015, and a total of 25 centers from Europe and North America participated in the registry. Patients were considered candidates for the procedure if they had significant bioprosthetic mitral valve or annuloplasty ring dysfunction (stenosis, regurgitation, or both), with comorbid conditions that would preclude a repeat sternotomy and valve replacement. We collected data retrospectively for cases performed before initiation and prospectively thereafter. This study was approved by the institutional review board of each institution, and all patients provided written informed consent for TMVR and the use of anonymous clinical, procedural, and follow-up data for research. For retrospective analysis of clinically acquired and anonymized data, the institutional review board of some institutions waived the need for written patient informed consent.

STUDY DEVICES AND TMVR PROCEDURE. Patients
were selected for TMVR at the institutional level after discussions by the multidisciplinary heart team. Device size was selected based on a combination of the manufacturer's reported internal diameter and true internal diameter as well as computed tomographic and transesophageal echocardiographic measurements (13,15,16). In addition, the valve-in-valve (ViV) software application was used to ensure the proper device size selection. The access site and type of device were determined by the multidisciplinary heart team. All TMVR procedures were conducted in accordance with local guidelines using standard techniques via transseptal, transapical, or transatrial access, and the balloon-expandable transcatheter valves (Sapien, Sapien XT, and Sapien 3 [Edwards Lifesciences, Irvine, California], and Melody [Medtronic, Minneapolis, Minnesota]) or other transcatheter valves (Lotus [Boston Scientific, Natick, Massachusetts], and Direct Flow [Direct Flow Medical, Santa Rosa, California]) were implanted (17-22).

ENDPOINTS AND DEFINITIONS. The primary end-
points of the present study were all-cause mortality rates at 30 days and 1 year. Secondary endpoints were technical, device, and procedural success and other 30-day major clinical endpoints defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria (23,24). Technical success was determined at exit from the catheterization/operating room and defined as a procedure meeting all of the following: absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment and correct positioning of the first intended device; and freedom from emergency surgery or reintervention related to the device or access procedure. Device success was assessed at 30 days and at all later post-procedural intervals. This success was defined as follows: absence of procedural mortality or stroke; proper placement and positioning of the device; freedom from unplanned surgical or interventional procedures related to the device or access procedure continued intended safety and performance of the device, including: 1) no evidence of structural or functional failure; 2) no specific device-related technical failure issues and complications; and 3) reduction of mitral regurgitation to acceptable levels without significant mitral stenosis and with no greater than moderate (2+) paravalvular mitral regurgitation (and without associated hemolysis). Although the original MVARC criteria defined significant mitral stenosis as a post-procedural transmitral gradient ≥5 mm Hg or an effective orifice area <1.5 cm², a post-procedural transmitral gradient ≥5 mm Hg was relatively common in post-mitral valve replacement and repair (25). Therefore, for the purpose of the present study, we used modified criteria for significant mitral stenosis defined as a transmitral gradient ≥10 mm Hg and/or an effective orifice area ≤1.0 cm² according to the American Society of Echocardiography guidelines (26). Procedural success was determined at 30 days, and it was defined as a procedure that has achieved device success without major clinical complications,

TABLE 1 Baseline Characteristics				
	Overall (N = 248)	ViV (n = 176)	ViR (n = 72)	p Value
Age, yrs	72.5 ± 12.1	72.9 ± 12.8	71.4 ± 10.2	0.36
Female	141 (56.9)	111 (63.1)	30 (41.7)	0.002
NYHA functional class III or IV	221 (89.1)	155 (88.1)	66 (91.7)	0.41
Logistic EuroSCORE, %	26.9 ± 15.8	26.2 ± 15.6	28.2 ± 16.2	0.44
STS score, %	8.9 ± 6.8	9.3 ± 7.0	8.1 ± 6.2	0.24
Diabetes mellitus	58 (23.4)	46 (26.1)	12 (16.7)	0.11
Creatinine, mg/dl	1.5 ± 1.2	1.4 ± 1.1	1.7 ± 1.4	0.08
Hypertension	150 (60.5)	109 (61.9)	41 (56.9)	0.47
Peripheral vascular disease	18 (7.3)	11 (6.3)	7 (9.7)	0.34
Previous cerebrovascular accident	41 (16.5)	37 (21.0)	4 (5.6)	0.003
Chronic pulmonary disease	63 (25.4)	43 (24.4)	20 (27.8)	0.58
Coronary artery disease	93 (37.5)	57 (32.4)	36 (50.0)	0.009
Previous myocardial infarction	38 (15.3)	16 (9.1)	22 (30.6)	<0.001
Previous PCI	37 (14.9)	21 (11.9)	16 (22.2)	0.04
Previous CABG	66 (26.6)	39 (22.2)	27 (37.5)	0.013
Echocardiographic findings				
Mean gradient, mm Hg	11.0 ± 6.1	12.4 ± 5.8	6.9 ± 5.1	<0.001
LVEF, %	52.5 ± 13.9	55.3 ± 11.1	45.6 ± 17.4	<0.001
Mitral regurgitation moderate or higher	190 (76.6)	125 (71.0)	65 (90.3)	0.001
Mechanism of failure				
Regurgitation	120 (48.4)	64 (36.4)	56 (77.8)	<0.001
Stenosis	66 (26.6)	63 (35.8)	3 (4.2)	<0.001
Combined	62 (25.0)	49 (27.8)	13 (18.1)	0.11

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; ViR = valve-in-ring; ViV = valve-in-valve.

including death, stroke, life-threatening/fatal bleeding, major vascular complications, stage 2 or 3 acute kidney injury, severe congestive heart failure, valve-related dysfunction, or other complications requiring surgery or repeat intervention.

Other endpoints included procedure- and device-related complications, as well as echocardiographic assessment of the valve and cardiac function immediately after the procedure and 30 days' post-procedurally. All echocardiographic, procedural, and clinical data were assessed at each institution according to MVARC criteria (23,24). The severity of regurgitation was qualitatively assessed and graded by using transthoracic echocardiography at each institution according to established guidelines and MVARC criteria (23,24,26).

DATA COLLECTION. Data collection included baseline clinical, laboratory, echocardiographic, and computed tomographic data, as well as procedural data, antithrombotic treatment, and clinical follow-up data, at pre-specified time points (1, 6, and 12 months and yearly thereafter). Follow-up was obtained by clinical visits and/or through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data provided by each institution were anonymized and centrally collected, and all inconsistencies were resolved directly with local investigators and on-site data monitoring.

STATISTICAL ANALYSIS. Patients were stratified according to whether they had TMVR for failed mitral bioprosthetic valves or annuloplasty rings. Continuous variables are presented as mean ± SD and were compared by using the Student *t* test or Mann-Whitney *U* test. Categorical variables are presented as counts or percentages and were compared by using the chi-square or Fisher exact test. Cumulative rates of death were calculated by using the Kaplan-Meier survival analysis, and the log-rank test was used for comparisons across the groups. Univariable Cox regression models were used to evaluate potential predictors of all-cause mortality at 1 year. Statistically significant variables with a p value <0.10 by univariable analysis were included in the multivariable model. The final model was determined by backward elimination procedures with a threshold p value <0.10. The proportional hazards assumption was confirmed by examination of log (–log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. The estimated hazard ratio (HR) with 95% confidence interval (CI) was provided by the Cox model. All statistical analyses were performed by using SPSS version 24.0 (IBM SPSS Statistics [IBM Corporation, Armonk, New York]). A 2-sided p value <0.05 was considered to be statistically significant.

RESULTS

BASELINE CHARACTERISTICS. A total of 248 patients with previous mitral valve surgery were treated with TMVR across 25 participating centers between February 2009 and February 2017. The baseline characteristics of the study population are shown in Table 1. Of the study population, 176 patients (71.0%) had TMVR for degenerated mitral bioprosthetic valves (ViV), and 72 patients (29.0%) had TMVR for failed annuloplasty rings (valve-in-ring [ViR]). In the overall cohort, the majority of patients were female (56.9%), with a mean age of 72.5 years, and had a high surgical risk with a mean STS score of 8.9 ± 6.8% and a logistic European System for Cardiac Operative Risk Evaluation of 26.9 ± 15.8%. Surgical risk scores were similar between the ViV and ViR groups (STS score: 9.3 ± 7.0% vs. 8.1 ± 6.2%; p = 0.24; logistic European System for Cardiac Operative Risk Evaluation:

TABLE 2 Procedural Data

	Overall (N = 248)	ViV (n = 176)	ViR (n = 72)	p Value
Access site				
Transseptal access	82 (33.1)	62 (65.2)	20 (27.8)	0.26
Transapical access	165 (66.5)	113 (64.2)	52 (72.2)	0.23
Transatrial access	1 (0.4)	1 (0.6)	0 (0.0)	>0.99
Device type				
Balloon-expandable valves	223 (89.9)	166 (94.3)	57 (79.2)	<0.001
Sapien*	24 (9.7)	19 (10.8)	5 (6.9)	0.35
Sapien XT*	93 (37.5)	68 (38.6)	25 (34.7)	0.56
Sapien 3*	102 (41.1)	75 (42.6)	27 (37.5)	0.46
Melody†	4 (1.6)	4 (2.3)	0 (0.0)	0.33
Lotus‡	14 (5.6)	8 (4.5)	6 (8.3)	0.24
Direct Flow§	11 (4.4)	2 (1.1)	9 (12.5)	<0.001
Balloon pre-dilatation	21 (8.5)	18 (10.2)	3 (4.2)	0.12
Balloon post-dilatation	16 (6.5)	7 (4.0)	9 (12.5)	0.013

Values are n (%). *Edwards Lifesciences, Irvine, California. †Medtronic, Minneapolis, Minnesota. ‡Boston Scientific, Natick, Massachusetts. §Direct Flow Medical, Santa Rosa, California.

Abbreviations as in **Table 1**.

TABLE 3 Procedural Outcomes

	Overall (N = 248)	ViV (n = 176)	ViR (n = 72)	p Value
Procedure-related death	3 (1.2)	2 (1.1)	1 (1.4)	>0.99
Conversion to conventional surgery	5 (2.0)	2 (1.1)	3 (4.2)	0.15
LVOT obstruction	8 (3.2)	4 (2.3)	4 (2.3)	0.18
Valve embolization	4 (1.6)	2 (1.1)	2 (2.8)	0.58
Need for second valve implantation	13 (5.1)	5 (2.8)	8 (11.1)	0.008
Left ventricular perforation	1 (0.4)	1 (0.6)	0 (0.0)	>0.99
Technical success	229 (92.3)	169 (96.0)	60 (83.3)	0.001
Re-intervention	25 (10.1)	13 (7.4)	12 (16.7)	0.03
Paravalvular leak closure	9 (3.6)	4 (2.3)	5 (6.9)	0.07
Atrial septal defect closure	10 (4.0)	7 (4.0)	3 (4.2)	0.95
Surgical mitral valve replacement	4 (1.6)	2 (1.1)	2 (2.8)	0.58
Others	2 (0.8)	0 (0.0)	2 (2.8)	0.08
Echocardiographic findings				
Mean gradient, mm Hg	6.0 ± 2.6	5.8 ± 2.7	6.4 ± 2.3	0.17
Mean gradient ≥10 mm Hg	16 (6.5)	11 (6.3)	5 (6.9)	0.84
Mitral valve area, cm^2	2.1 ± 0.8	2.1 ± 0.8	2.0 ± 0.6	0.37
LVEF, %	50.3 ± 13.6	52.8 ± 12.0	44.1 ± 15.4	<0.001
Mitral regurgitation moderate or higher after procedure	26 (10.3)	12 (6.8)	14 (19.4)	0.003
Mitral regurgitation moderate or higher at 30 days*	15 (6.5)	6 (3.6)	9 (13.6)	0.005
Device success (modified)	212 (85.5)	157 (89.2)	55 (76.4)	0.009

Values are n (%) or mean ± SD. *Two-hundred thirty-two patients survived at 30 days were included.

LVOT = left ventricular outflow tract; other abbreviations as in **Table 1**.

26.2 ± 15.6 vs. 28.2 ± 16.2; p = 0.44). The ViV group was more likely to be female (63.1% vs. 41.7%; p = 0.002) and had more frequent previous cerebrovascular accidents (21.0% vs. 5.6%; p = 0.003) compared with the ViR group. However, the ViR group had more extensive coronary artery disease (50.0% vs. 32.4%; p = 0.009) with more frequent previous myocardial infarction (30.6% vs. 9.1%; p < 0.001), previous percutaneous coronary intervention (22.2% vs. 11.9%; p = 0.04), previous coronary artery bypass graft surgery (37.5% vs. 22.2%; p = 0.013), and lower left ventricular ejection fraction (45.6 ± 17.4% vs. 55.3 ± 11.1%; p < 0.001). In terms of failure mode, predominant mitral regurgitation was more frequent in the ViR group compared with the ViV group (77.8% vs. 36.4%; p < 0.001), whereas mitral stenosis was more frequent in the ViV group (35.8% vs. 4.2%; p < 0.001).

PROCEDURAL DATA. Patients treated with TMVR had a variety of mitral bioprostheses and annuloplasty rings (Online Table 1). The median label size and internal diameter of mitral bioprostheses were 29 mm and 27 mm, respectively. In terms of property of annuloplasty rings, rigid, semi-rigid, and flexible rings were used in 14 patients (19.4%), 41 patients (56.9%), and 9 patients (12.5%). Complete annuloplasty rings were used in 52 patients (72.2%), and the median commissure-to-commissure distance of ring was 29 mm.

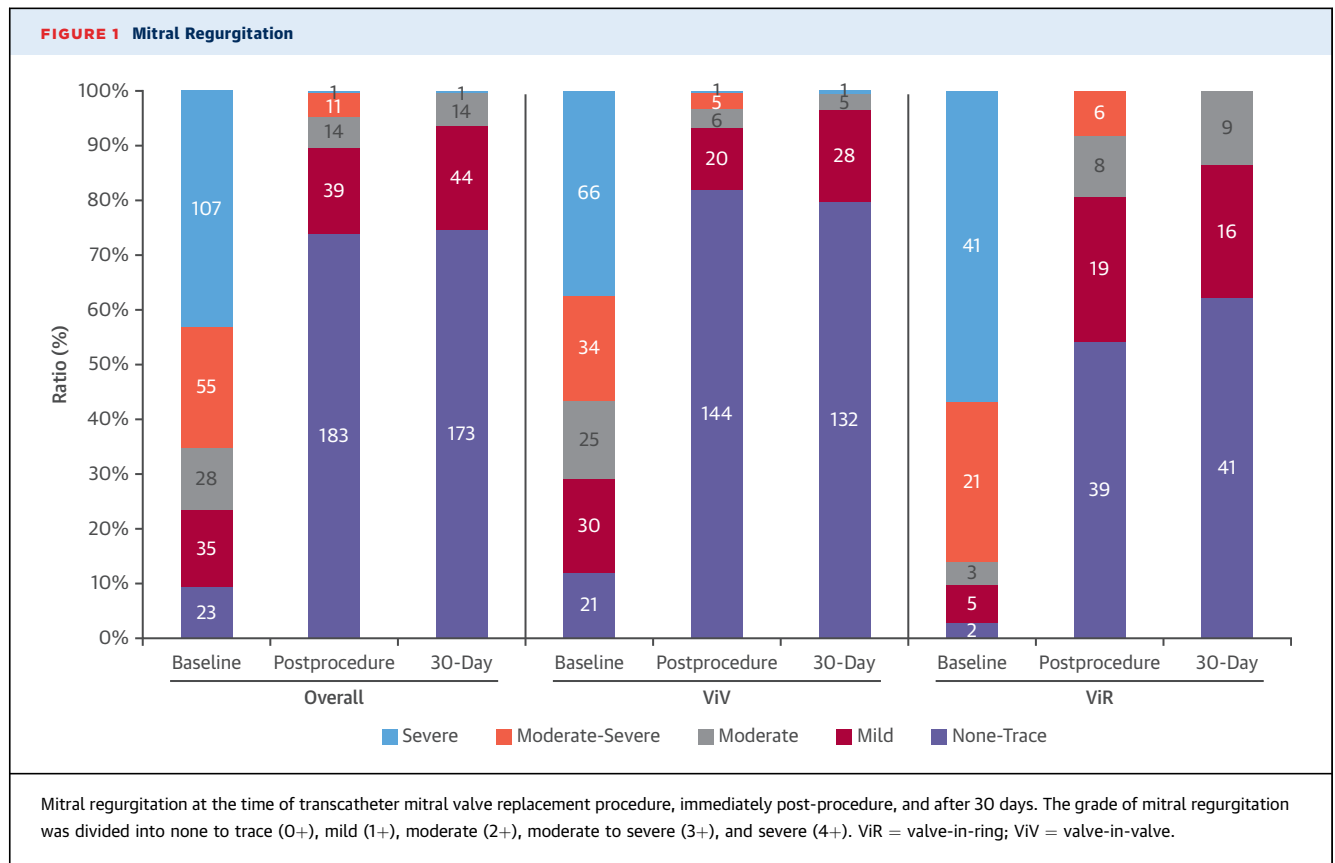The procedural data are summarized in **Table 2**. With respect to access site, the majority of patients were treated via transapical access (66.5%), and the remaining patients were treated via transseptal (33.1%) and transatrial (0.4%) access. Among patients treated with transseptal access, an apical rail technique with wire externalization from venous access to apical site was used in 4 patients (4.9%). The most frequently used transcatheter valves were the balloon-expandable valves (89.9%), followed by the Lotus (5.6%) and the Direct Flow (4.4%). Balloon pre-dilatation was performed in 8.5%, with no significant difference between the ViV and ViR groups, whereas balloon post-dilatation was more frequently performed in the ViR group compared with the ViV group (12.5% vs. 4.0%; p = 0.013).

PROCEDURAL AND CLINICAL OUTCOMES. The procedural outcomes of the study population are summarized in **Table 3**. Composite endpoints of technical, device, and procedural success were assessed according to MVARC criteria (Online Table 2). In the overall group, procedure-related death, conversion to conventional surgery, left ventricular outflow tract (LVOT) obstruction, valve embolization, and left ventricular perforation were observed in 3 (1.2%), 5 (2.0%), 8 (3.2%), 4 (1.6%), and 1 patient (0.4%), respectively. Technical success was achieved in the majority of patients (92.3%). However, the ViR group had a significantly lower technical success rate compared with the ViV group (83.3% vs.

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FIGURE 1 Mitral Regurgitation

Mitral regurgitation at the time of transcatheter mitral valve replacement procedure, immediately post-procedure, and after 30 days. The grade of mitral regurgitation was divided into none to trace (0+), mild (1+), moderate (2+), moderate to severe (3+), and severe (4+). ViR = valve-in-ring; ViV = valve-in-valve.

96.0%; p = 0.001) due to more frequent second valve implantation (11.1% vs. 2.8%; p = 0.008). Reintervention was required in 25 patients (10.1%) and was more frequent in the ViR group compared with the ViV group (16.7% vs. 7.4%; p = 0.03). Paravalvular leak closure tended to be more frequent in the ViR group compared with the ViV group (6.9% vs. 2.3%; p = 0.07), whereas there were no significant differences between the ViV and ViR groups in atrial septal defect closure (4.0% vs. 4.2%; p = 0.95) and surgical mitral replacement (1.1% vs. 2.8%; p = 0.58).

With respect to echocardiographic findings, postprocedural left ventricular ejection fraction was lower in the ViR group compared with the ViV group (44.1 ± 15.4% vs. 52.8 ± 12.0%; p < 0.001), whereas there were no significant differences between the 2 groups in mitral valve mean gradient (5.8 ± 2.7 mm Hg vs. 6.4 ± 2.3 mm Hg; p = 0.17) and mitral valve area (2.1 ± 0.8 cm^2 vs. 2.0 ± 0.6 cm^2; p = 0.37). However, the incidence of moderate or greater mitral regurgitation at post-procedure was significantly higher in the ViR group compared with the ViV group (19.4% vs. 6.8%; p = 0.003), which remained significantly higher at 30 days even after the closure of

paravalvular leakage (13.6% vs. 3.6%; p = 0.005) (Figure 1). Among 9 patients (4 patients in the ViV group and 5 patients in the ViR group) who received paravalvular leak closure after TMVR for the correction of significant mitral regurgitation, 7 patients (77.8%) showed improvement of mitral regurgitation to less than moderate (ViV: 75.0%; ViR: 80.0%; p > 0.99). In the ViR group, mitral regurgitation moderate or higher at 30 days was more frequent in patients with flexible rings compared with those with semi-rigid rings (44.4% vs. 10.8%; p = 0.02) (Online Figure 1). It is noteworthy that there was no patient who had significant mitral stenosis with a transmitral mean gradient ≥10 mm Hg and mitral valve area ≤1.0 cm^2. Due to more frequent reintervention and lower technical success rate, the device success rate was significantly lower in the ViR group compared with the ViV group (76.4% vs. 89.2%; p = 0.009).

Clinical outcomes are summarized in Table 4. There were no significant differences between the ViV and ViR groups in 30-day all-cause mortality (5.7% vs. 8.3%; p = 0.44), stroke (2.3% vs. 0%; p = 0.33), major or extensive bleeding (6.3% vs. 4.2%; p = 0.52), or major vascular complication (1.7% vs.

TABLE 4 Clinical Outcomes

	Overall (n = 248)	ViV (n = 176)	ViR (n = 72)	p Value
All-cause mortality at 30 days	16 (6.5)	10 (5.7)	6 (8.3)	0.44
Stroke	4 (1.6)	4 (2.3)	0 (0.0)	0.33
Bleeding				
Major or extensive	14 (5.6)	11 (6.3)	3 (4.2)	0.52
Life-threatening or fatal	10 (4.0)	4 (2.3)	6 (8.3)	0.03
Major vascular complication	4 (1.6)	3 (1.7)	1 (1.4)	>0.99
Acute kidney injury (stage 2 or 3)	15 (6.0)	7 (4.0)	8 (11.1)	0.03
Procedure success	182 (73.4)	140 (79.5)	42 (58.3)	0.001
All-cause mortality at 1 year*	33 (16.9)	18 (12.6)	15 (28.7)	0.01

Values are n (%). *Cumulative rates and p value were calculated using the Kaplan-Meier survival analysis and log-rank test, respectively.

Abbreviations as in **Table 1**.

1.4%; p > 0.99). However, the ViR group had more frequent life-threatening or fatal bleeding (8.3% vs. 2.3%; p = 0.03) and stage 2 or 3 acute kidney injury (11.1% vs. 4.0%; p = 0.03) compared with the ViV group, which resulted in a significantly lower procedural success rate in the ViR group (58.3% vs. 79.5%; p = 0.001).

IMPACT OF ACCESS SITE AND LEARNING CURVE. With stratification according to whether patients were treated via transseptal or transapical access, procedural and clinical outcomes are shown in Online Figure 2. There were no significant differences between transseptal and transapical access in procedural-related death, conversion to surgery, LVOT obstruction, second valve implantation, and technical success. However, patients in the transseptal group required more frequent closure of an iatrogenic atrial septal defect compared with the transapical group (12.2% vs. 0.0%; p < 0.001), which resulted in lower device success rate (78.0% vs. 89.1%; p = 0.02). Nevertheless, there were no significant differences between the 2 groups in clinical outcomes at 30 days and procedural success. Given that the median number of TMVR procedures at each institution was 8, patients were divided into the early experience group (the first 7 cases) and the late experience group (the 8th case and thereafter). There were no significant differences between the early and late experience groups in terms of procedural and 30-day clinical outcomes for the overall cohort as well as the transseptal cohort (Online Figures 3 and 4).

MID-TERM MORTALITY. Over a median follow-up period of 220 days (interquartile range, 40 to 560 days), 48 patients died in the overall cohort

(28 patients in the ViV group and 20 patients in the ViR group). The cumulative event rate for all-cause mortality at the 1-year follow-up was 16.9%, with significantly higher all-cause 1-year mortality in the ViR group compared with the ViV group (28.7% vs. 12.6%; log-rank test, p = 0.01) (Central Illustration). There were no significant differences between the transseptal and transapical access groups in 1-year all-cause mortality (16.2% vs. 17.4%; log-rank test, p = 0.74) (Figure 2). On univariable analysis, the factors associated with 1-year all-cause mortality were age, predominant mitral regurgitation at baseline, left ventricular ejection fraction, failed annuloplasty ring, and moderate or greater post-procedural mitral regurgitation. After adjustment with multivariable analysis, age (HR: 1.04; 95% CI: 1.00 to 1.08; p = 0.03) and failed annuloplasty ring (HR: 2.70; 95% CI: 1.34 to 5.43; p = 0.005) were independently associated with 1-year all-cause mortality (Table 5).

ANTITHROMBOTIC THERAPY AND CLINICAL THROMBOSIS. Information regarding anticoagulation and post-procedural thrombosis was available in 236 patients (95.2%: 166 patients in the ViV group and 70 patients in the ViR group). Among them, 152 patients (64.4%) received anticoagulation (warfarin or direct oral anticoagulant agents) for at least 3 months after TMVR, and 84 patients (35.6%) received antiplatelet agents only after TMVR (Figure 3). Among patients receiving only antiplatelet agents, 3 patients presented with symptomatic mitral valve thrombosis within 1 month after TMVR (3.6%), whereas no patients had clinical mitral valve thrombosis when receiving anticoagulant agents (p = 0.04).

DISCUSSION

The present study is, to the best of our knowledge, the first large-scale study that evaluated the safety, efficacy, and clinical outcomes of TMVR in patients with degenerated mitral bioprostheses and failed annuloplasty rings. The major findings of the present study are as follows: 1) in the overall cohort, the procedural and clinical outcomes of TMVR for patients with degenerated mitral bioprostheses and failed annuloplasty rings were acceptable despite high surgical risk with multiple comorbidities; 2) compared with patients with degenerated mitral bioprostheses, TMVR for patients with failed annuloplasty rings was associated with lower rates of technical, device, and procedural success; and 3) the cumulative event rates for all-cause mortality after TMVR at the 1-year follow-up were higher in patients with failed annuloplasty rings compared with those with degenerated mitral bioprostheses.

CENTRAL ILLUSTRATION Kaplan-Meier Curves for Mortality After Mitral Valve-in-Valve and Valve-in-Ring
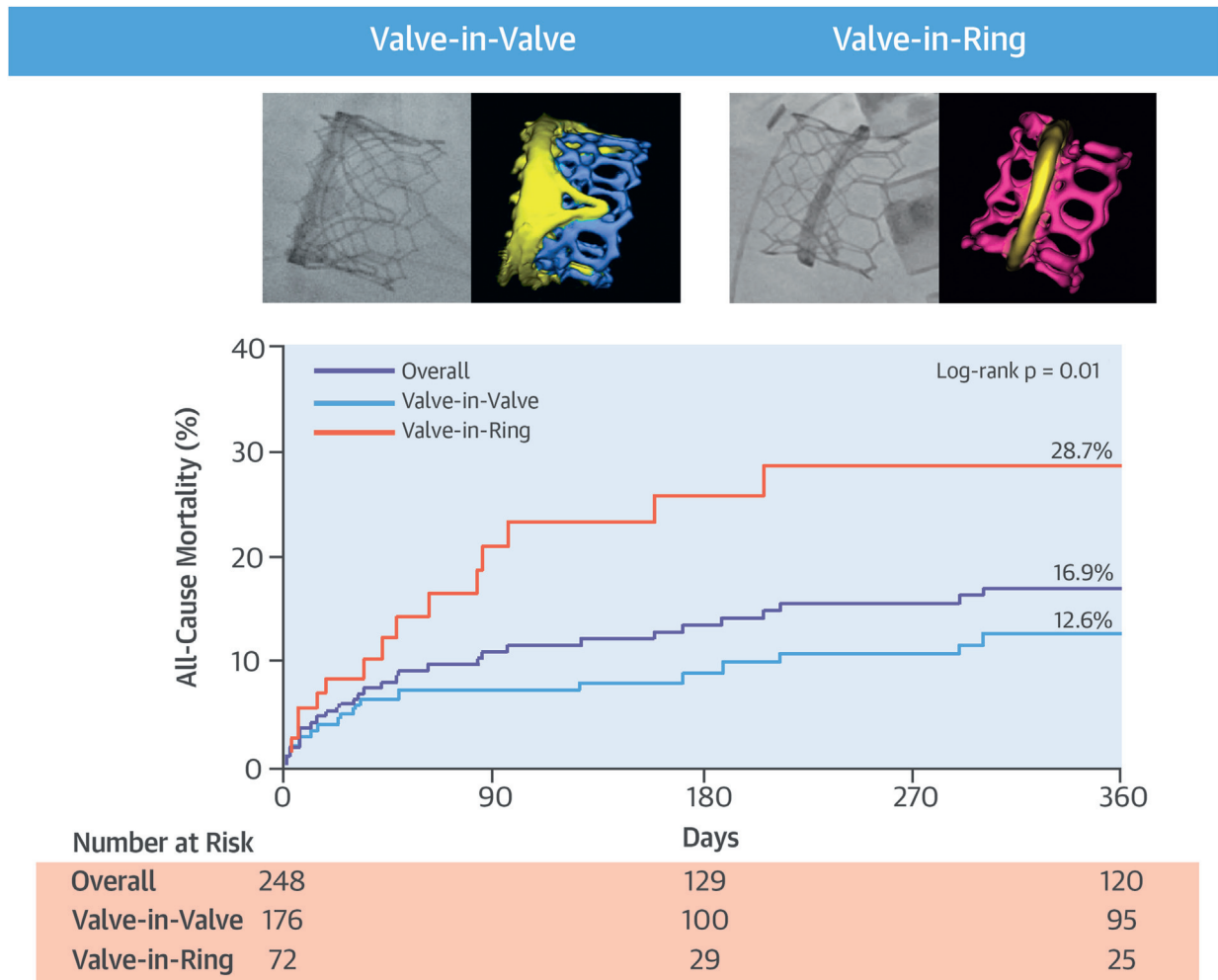
Yoon, S.-H. et al. J Am Coll Cardiol. 2017;70(9):1121–31.

Procedural and post-procedural computed tomography images of mitral valve-in-valve and valve-in-ring are shown **(upper panel)**. The cumulative all-cause mortality rates of the overall cohort **(purple line)**, patients undergoing mitral valve-in-valve **(orange line)**, and valve-in-ring **(blue line)** are shown **(lower panel)**.

Recently, several studies reported the acceptable clinical outcomes of TMVR for patients with degenerated bioprosthesis or failed annuloplasty rings (11,27-29). However, these studies were limited in sample size, type of previous mitral valve surgery (replacement or repair), and access site. A substantial portion of patients required reoperation after either mitral valve replacement or repair (30), but reoperation after mitral valve surgery is associated with increased perioperative mortality and morbidity in elderly patients (4), which leads to a large number of undertreated patients with degenerated mitral bioprostheses and dysfunctional annuloplasty rings. Therefore, comprehensive understanding of outcomes of TMVR for both degenerated bioprosthesis and failed annuloplasty ring is essential. Furthermore, advancements in transcatheter valves with smaller profiles have enabled easier transseptal access; this approach needs further assessment of its efficacy and safety compared with the conventional transapical approach.
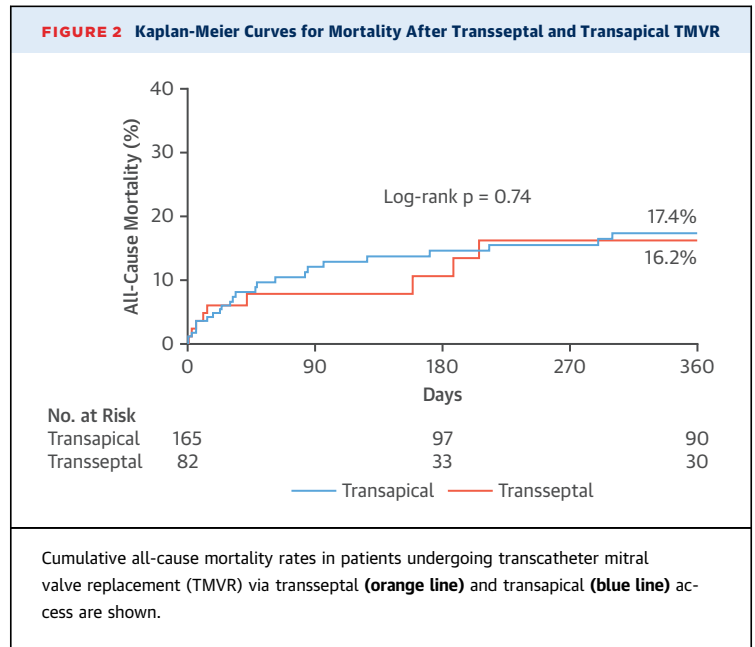
In the present study, patients with degenerated mitral bioprosthesis and failed annuloplasty rings both exhibited high surgical risk, with mean STS scores of 9.3% and 8.1%, respectively. However,

there were significant differences in baseline characteristics: female subjects and previous cerebrovascular accidents were more frequent in the ViV group; and the ViR group had more frequent predominant mitral regurgitation with extensive coronary artery disease and lower left ventricular ejection fraction compared with the ViV group, which may reflect the recurrence and progression of ischemic mitral regurgitation after mitral valve repair with ring annuloplasty. In the present study, high technical and device success rates of mitral ViV were observed in a variety of types and sizes of mitral bioprostheses as well as mode of failure. Although anatomical challenges with the transseptal approach or more invasive transapical approach are required in TMVR, the accumulated experience and evidence from "aortic" ViV may help to select appropriate device size and accurate deployment of transcatheter valves. However, compared with mitral ViV, mitral ViR was associated with lower technical, device, and procedure success.

The challenges of the mitral ViR procedure may be attributable to several factors: 1) initially elliptical annuloplasty rings need to become circular during the TMVR procedure, but the various degrees of rigidity of annuloplasty rings and the absence of definite recommendations regarding the appropriate size and type of transcatheter devices led to difficulties in predicting the ring deformability and resulted in more frequent mitral regurgitation; and 2) the optimal implantation of a transcatheter valve is limited due to the existence of native anterior mitral leaflet and insufficient fixation with annuloplasty rings, resulting in more frequent need for second valve implantation or LVOT obstruction with too low deployment in the left ventricular cavity.

The mitral ViV was initially performed via a transseptal and transatrial approach by Webb et al. (31), but difficulties in achieving a coaxial alignment of the transcatheter valve and mitral bioprosthesis has established the transapical approach as a more feasible route thereafter (13). Nevertheless, the present study showed that the procedural and clinical outcomes of the transseptal approach were comparable to those of the transapical approach, except for the more frequent requirement of closure of an iatrogenic atrial septal defect. The challenges in achieving coaxiality and stabilization of a balloon-expandable valve with transseptal access may be overcome by the optimized transseptal puncture guided by intraoperative transesophageal echocardiography (16). Although the present study did not show improved outcomes with increased experience,

FIGURE 2 Kaplan-Meier Curves for Mortality After Transseptal and Transapical TMVR

Cumulative all-cause mortality rates in patients undergoing transcatheter mitral valve replacement (TMVR) via transseptal **(orange line)** and transapical **(blue line)** access are shown.
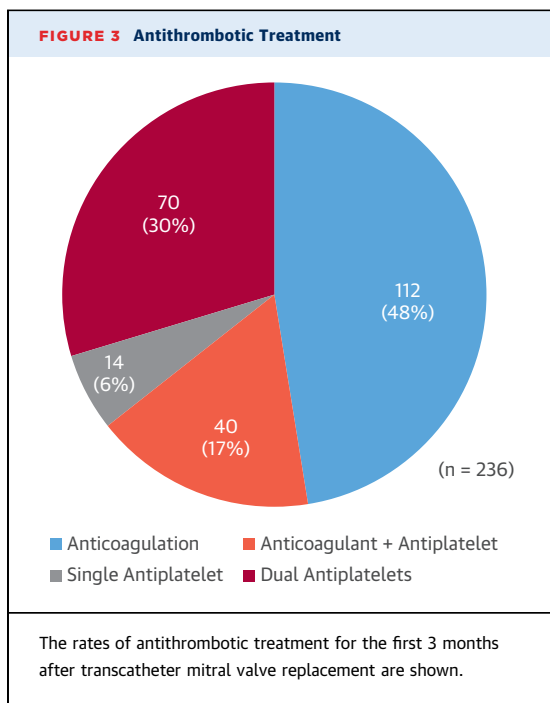
the impact of a less invasive procedure on clinical outcomes should be evaluated in a larger cohort with longer term follow-up.

Mid- and long-term mortality may be affected by procedural complications in combination with baseline comorbidities and underlying mitral valve disease. The higher mid-term mortality of ViR compared

TABLE 5 Predictors of All-Cause Mortality

	Univariable Model		Multivariable Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.03 (0.99–1.07)	0.07	1.04 (1.00–1.08)	0.03
Female	0.84 (0.42–1.67)	0.62		
NYHA functional class III or IV	0.86 (0.30–2.46)	0.78		
STS score, %	1.03 (0.99–1.07)	0.14		
Creatinine, mg/dl	1.10 (0.88–1.37)	0.39		
Peripheral vascular disease	0.74 (0.18–3.10)	0.68		
Previous cerebrovascular accident	0.81 (0.31–2.11)	0.67		
Chronic pulmonary disease	1.08 (0.50–2.33)	0.84		
Previous CABG surgery	0.89 (0.40–1.97)	0.77		
Predominant mitral regurgitation at baseline	2.15 (1.04–4.44)	0.04		
LVEF per increase of 10%	0.80 (0.63–1.01)	0.06		
Transseptal access	0.88 (0.41–1.90)	0.75		
Failed annuloplasty ring	2.39 (1.20–4.75)	0.01	2.70 (1.34–5.43)	0.005
Post-procedural mitral regurgitation moderate or higher	2.32 (0.90–6.01)	0.08		

CI = confidence interval; HR = hazard ratio; other abbreviations as in **Table 1**.

FIGURE 3   Antithrombotic Treatment

70 (30%)

112 (48%)

14 (6%)

40 (17%)

(n = 236)

■ Anticoagulation   ■ Anticoagulant + Antiplatelet
■ Single Antiplatelet   ■ Dual Antiplatelets

The rates of antithrombotic treatment for the first 3 months after transcatheter mitral valve replacement are shown.

with ViV warrants careful selection of patients for a ViR procedure. LVOT obstruction was a potentially devastating complication, and its prediction still poses a challenge (32,33). In addition, the need for second valve implantation in the mitral position raises the concern for increase of transmitral pressure gradient or risk of intra-atrial thrombosis (25,34). Furthermore, the nature of the underlying mitral valve disease could affect the long-term outcomes. Nevertheless, given the early experience and lack of knowledge and evidence in TMVR fields, further improvements in procedural and consequently better clinical outcomes of TMVR are awaited in the future. These improvements will be achieved through comprehensive understanding of the TMVR procedure, accumulation of experience and appropriate technique for the successful procedure, establishment of guidelines for size and type of transcatheter valves, and technical device advancement.

The risk of thrombosis has been increasingly recognized after transcatheter valve replacement in the setting of ViV implantations (32), particularly in the mitral position (33,34). According to the recently updated 2014 American Heart Association/American College of Cardiology guidelines, anticoagulation therapy with warfarin is reasonable for the first 3 months after surgical bioprosthetic mitral valve

replacement as well as transcatheter "aortic" valve replacement (Class IIa) (35). However, limited data exist regarding antithrombotic treatment for ViV procedures. In the present study, the absence of anticoagulation was associated with early mitral valve thrombosis, which may be attributable to low transvalvular pressure. The present results do not allow for provision of recommendations on the duration of anticoagulant treatment after TMVR. Future studies are awaited to assess the optimal duration of anticoagulation treatment after TMVR.

STUDY LIMITATIONS. First, this study had the inherent limitations of an observational study without center-independent adjunction of adverse events and an independent core laboratory to assess mitral regurgitation. In addition, the outcomes in this study could differ from those in "real-world" practice due to potential selection biases. Moreover, device selection was not randomized but left at the operator's discretion, and patient selection as well as operator experience may have affected the observed outcomes.

CONCLUSIONS

The TMVR procedure provided acceptable outcomes in high-risk patients with degenerated bioprostheses or failed annuloplasty rings, but mitral ViR was associated with higher rates of procedural complications and mid-term mortality compared with mitral ViV.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TMVR provided acceptable outcomes in high-risk patients with degenerated bioprostheses or annuloplasty rings, but ViR procedures were associated with higher rates of complications and mid-term mortality than ViV replacement.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the long-term outcomes and optimal antithrombotic treatment of patients undergoing TMVR for degenerated bioprostheses or failed annuloplasty rings.

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KEY WORDS annuloplasty ring, degenerated bioprostheses, mitral valve, transcatheter valve implantation

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