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Prosthetic Mitral Surgical Valve in Transcatheter Aortic Valve Replacement Recipients

A Multicenter Analysis

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ABSTRACT

OBJECTIVES The aim of this study was to determine the prognosis and specific complications of patients with prosthetic mitral valves (PMVs) undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND TAVR is performed relatively often in patients with PMVs, but specific risks are not well described.

METHODS A multicenter analysis was conducted, including patients with severe symptomatic aortic stenosis who underwent TAVR at 10 centers. Patients' clinical characteristics and outcomes were evaluated according to the presence of a PMV.

RESULTS The mean age of the study population (n = 2,414) was 81 ± 8 years, and 48.8% were men. A total of 91 patients (3.77%) had PMVs. They were more commonly women, younger, and had higher surgical risk. PMVs were implanted a median of 14 years before TAVR, and most patients had mechanical prostheses (73.6%). Eighty-six patients (94.5%) were on long-term vitamin K inhibitor therapy, and bridging antithrombotic therapy was administered in 59 (64.8%). TAVR device embolization occurred in 6.7% (vs. 3.3% in the non-PMV group; p = 0.127), in all instances when distance between the PMV and the aortic annulus was <7 mm. Mortality rates did not show a difference, but the rate of bleeding was higher in patients with PMV (24.2% vs. 16.1%; p = 0.041), even in those treated via the transfemoral approach (22.2% vs. 13.9%; p = 0.048). Indeed, bleeding complications, prior atrial fibrillation, chronic obstructive pulmonary disease, surgical risk, and New York Heart Association functional class were independent predictors of mortality.

CONCLUSIONS TAVR presents similar mortality irrespective of the presence of a PMV. However, patients with PMVs had higher bleeding risk that was independently associated with higher mortality. Risk for valve embolization was relatively high, but it occurred only in patients with PMV–to–aortic annulus distances <7 mm. (J Am Coll Cardiol Intv 2017;10:1973–81) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

LMWH = low-molecular weight heparin

PMV = prosthetic mitral valve

TAVR = transcatheter aortic valve replacement

UFH = unfractionated heparin

Prior cardiac surgery in surgical aortic valve replacement candidates increases operative risk by up to 70% (1). In particular, the presence of a prosthetic mitral valve (PMV) doubles the mortality rate compared with isolated surgical aortic valve replacement (2). Hence, reoperation represents the single factor that most increases risk in nonemergent valvular surgery, especially in elderly patients (1). For this reason, transcatheter aortic valve replacement (TAVR) in this scenario has been extensively used because of its proven efficacy in high- and intermediate-risk patients with severe aortic stenosis (3,4). Conversely, evidence is still scarce for these patients, given that they were excluded from pivotal trials (3,5) and are underrepresented in large registries (6).

Although TAVR has been often performed in the presence of a PMV since the first reported case in 2008 (7), several specific considerations that may affect outcomes are still poorly understood, including the potential interaction between TAVR and a PMV at the time of implantation, the role of imaging tests for optimization of results, the most adequate device and approach, and the best antithrombotic regimen before and after TAVR (8,9).

Therefore, we aimed to describe using a real-world multicenter registry the proportion, main characteristics, and outcomes following TAVR among patients with PMVs. Also, we searched for predictors of procedural success by conducting a central imaging analysis including echocardiography and cardiac computed tomography.

METHODS

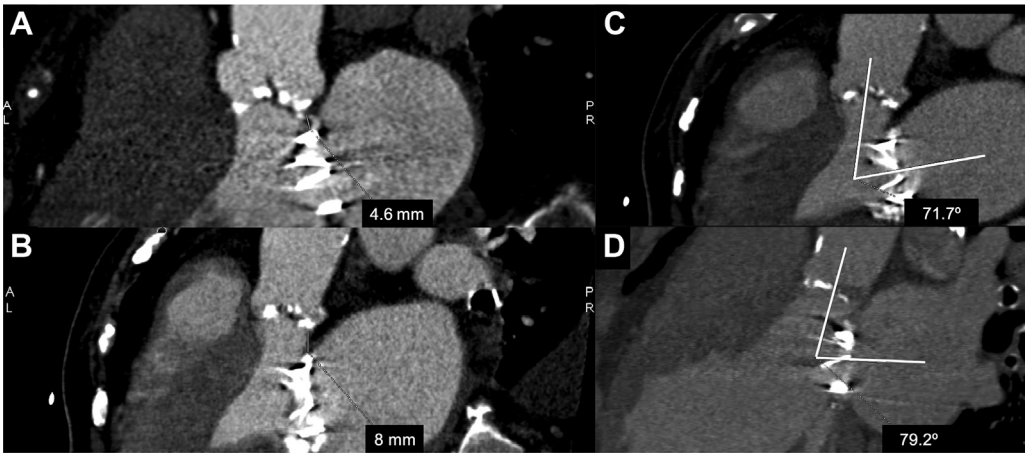
STUDY POPULATION. Between April 2008 and January 2017, 2,414 consecutive patients with diagnoses of aortic stenosis underwent TAVR at 10 centers. Severe aortic stenosis was defined on transthoracic echocardiography following the European guidelines for valvular disease (10). Baseline, procedural, in-hospital, and 1-, 6-, and 12-month follow-up details were obtained through clinical visits and prospectively recorded. Longer term follow-up was also available for most patients. Procedural success and complications were defined according to Valve Academic Research Consortium 2 criteria (as pre-specified in the database) and adjudicated according to the investigator's discretion (11). Patients were classified into 2 groups according to the presence of a PMV. In the PMV group, a retrospective search for the mitral prostheses technical features, including type (mechanical or biological), size, specific model, and time from implantation, was conducted.

IMAGING EVALUATION. Imaging data were collected for the entire study population. In patients with PMVs, color Doppler and 2-dimensional echocardiography were retrospectively evaluated at baseline, post-procedurally, and at 1, 6, and 12 months after TAVR by an expert in echocardiography blinded to further data of the post-TAVR outcomes. The degree of mitral regurgitation, mean gradient, and pressure half-time were estimated before and after the procedure according to the guidelines for evaluation of prosthetic valves of the American Society of Echocardiography (12).

Multidetector computed tomography was performed in most patients following each center's protocol as a part of the standard pre-TAVR evaluation. Central off-line analysis in TAVR patients with PMVs was performed by an independent core laboratory (ICICORELAB, Valladolid, Spain) and included the analysis of the distance between the PMV and the aortic annulus as measured in the 3-chamber view at the closest distance and also the angle between the aortic root and the mitral valve (2 lines orthogonal to the annular planes, respectively) as schematically depicted in **Figure 1**.

STATISTICAL ANALYSIS. Data are expressed as absolute frequency and percentage in the case of qualitative variables. Quantitative variables are described as mean ± SD or as median (interquartile range), depending on variable distribution. Group comparisons were analyzed using the Student *t* test or its nonparametric equivalent, the Mann-Whitney *U* test, for continuous variables and the chi-square test or Fisher exact test for categorical variables. Multivariate analysis through Cox regression was used to evaluate independent predictors of mortality in the global population and in the PMV group. Less than 1 variable for every 10 events was included to avoid overfitting. Adjusted hazards ratio and 95% confidence interval was calculated for each variable. Proportional risks and the C statistic were calculated for the adjusted model. Centers with more than 5% missing data at follow-up were excluded from the multivariate analysis. A propensity score was estimated using a logistic regression model with PMV as the dependent variable and baseline characteristics with statistically significant difference or clinically relevant as independent variables, including age, logistic European System for Cardiac Operative Risk Evaluation score, diabetes mellitus, chronic obstructive pulmonary disease, prior atrial fibrillation, and left ventricular ejection fraction (Online Figure 1).

FIGURE 1 **Computed Tomographic Images of Transcatheter Aortic Valve Replacement Patients With Mitral Prostheses**



Distance from the aortic annulus to the mitral prosthesis **(A,B)** and angle between the aortic root and the mitral valve **(C,D)**.

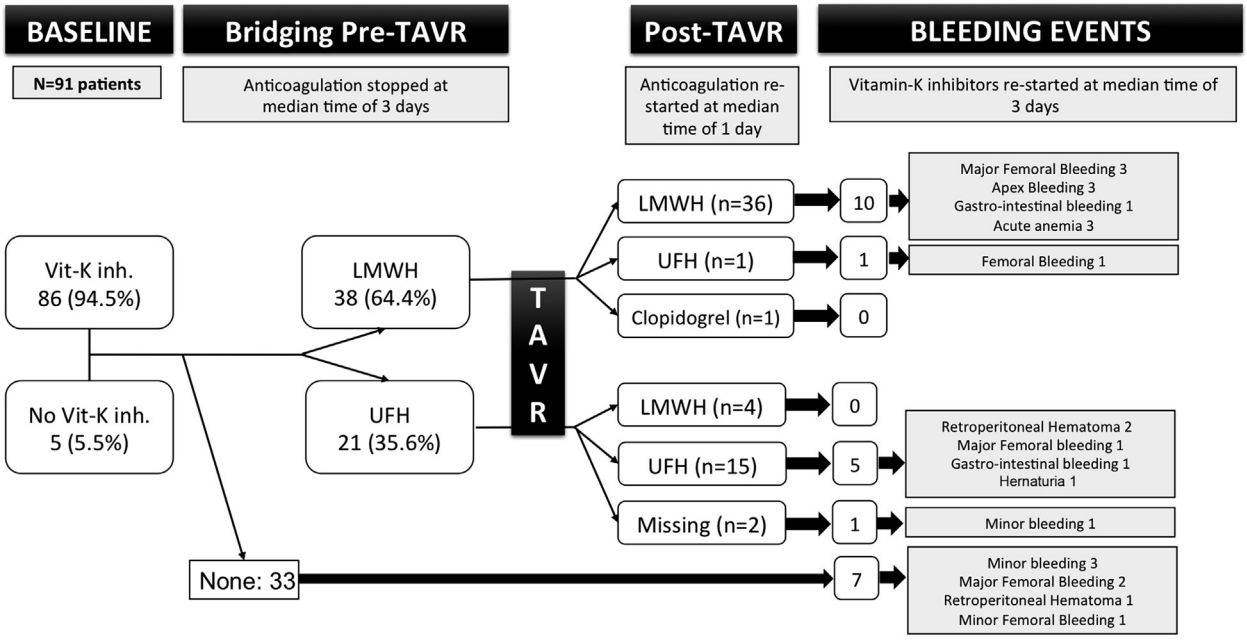
TABLE 1 **Baseline Characteristics of the Global Study Population According to the Presence of a Prosthetic Mitral Valve**

		Entire Cohort			Propensity-Matched Cohort*		
	Global Population (n = 2,414 [100%])	**Non-PMV Group (n = 2,323 [96.2%])**	**PMV Group (n = 91 [3.8%])**	**p Value†**	**Non-PMV Group (n = 80)**	**PMV Group (n = 80)**	**p Value†**
Clinical variables							
Age (yrs)	80.5 ± 7.7	80.8 ± 7.6	74.8 ± 8.4	**<0.001**	72.7 ± 10.8	74.2 ± 8.7	0.241
Female	1,236 (51.2)	1,171 (50.4)	65 (71.4)	**<0.001**	41 (51.3)	55 (68.8)	**0.020**
Weight (kg)	71.32 ± 15.0	71.45 ± 15.1	67.33 ± 12.8	**0.017**	76.1 ± 19.9	67.4 ± 12.9	**0.001**
BMI (kg/m^2)	26.77 ± 5.1	26.8 ± 5.1	26.5 ± 4.7	0.594	28.4 ± 6.9	26.4 ± 4.8	**0.027**
STS score (%)	7.55 ± 5.4	7.50 ± 5.3	8.88 ± 7.5	0.12	7.9 ± 5.9	8.3 ± 5.1	0.642
Logistic EuroSCORE (%)	20.57 ± 13.5	20.30 ± 13.36	27.43 ± 15.31	**<0.001**	24.7 ± 16.7	27.4 ± 15.3	0.233
Diabetes mellitus	745 (31.1)	707 (30.6)	38 (46.9)	**0.002**	41 (51.3)	37 (46.3)	0.608
COPD	711 (29.7)	690 (29.8)	21 (25.9)	0.451	17 (21.3)	21 (26.3)	0.541
Stroke/TIA	258 (16.6)	250 (17.0)	8 (9.9)	0.094	10 (19.6)	7 (13.7)	0.549
Prior cardiac surgery	474 (20.9)	383 (17.6)	91 (100.0)	**<0.001**	14 (17.5)	80 (100.0)	**<0.001**
Prior AF	763 (32.0)	692 (30.1)	71 (78.0)	**<0.001**	56 (70.0)	60 (75.0)	0.454
ASA	473 (23.0)	447 (22.6)	26 (34.2)	**0.018**	13 (18.1)	25 (34.7)	**0.043**
Clopidogrel	263 (16.3)	257 (16.7)	6 (7.9)	**0.042**	11 (25.0)	3 (6.8)	0.057
Vitamin K inhibitors	778 (32.6)	692 (30.1)	86 (94.5)	**<0.001**	56 (70.0)	76 (95.0)	**<0.001**
NYHA functional class III or IV	1,411 (64.6)	1,360 (64.7)	51 (63.0)	0.753	54 (69.2)	48 (63.2)	0.324
Echocardiographic variables							
AVA BL (cm^2)	0.65 ± 0.2	0.65 ± 0.2	0.70 ± 0.2	**0.041**	0.66 ± 0.18	0.71 ± 0.23	0.144
Peak. gradient (mm Hg)	75.0 ± 25.5	75.12 ± 25.6	73.46 ± 23.1	0.551	67.7 ± 22.2	71.6 ± 25.1	0.307
Mean gradient (mm Hg)	45.78 ± 16.9	45.87 ± 17.0	43.48 ± 14.7	0.192	43.1 ± 16.4	43.3 ± 15.2	0.909
LVEF (%)	54.09 ± 14.2	54.06 ± 14.2	54.75 ± 13.8	0.651	55.3 ± 14.1	54.2 ± 13.0	0.711
SPAP (mm Hg)	44.0 ± 13.1	44.5 ± 14.5	53.2 ± 16.0	**<0.001**	46.5 ± 15.7	51.1 ± 15.8	0.076
Mitral regurgitation 3 or 4	406 (17.2)	402 (17.7)	4 (4.7)	**0.002**	19 (25.0)	4 (5.3)	**<0.001**
Aortic regurgitation 3 or 4	238 (10.2)	217 (9.6)	21 (25.0)	**<0.001**	1 (1.6)	2 (3.3)	0.999

Values are mean ± SD or n (%). *Matched variables age, logistic EuroSCORE, diabetes mellitus, COPD, prior AF, and LVEF. †Significant p values (<0.05) are in **bold**.

ASA = acetylsalicylic acid; AVA = aortic valve area; BL = baseline; BMI = body index mass; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PMV = prosthetic mitral valve; SPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TIA = transient ischemic accident.

FIGURE 2 Management of Antithrombotic Therapy



Flowchart summarizing the management of antithrombotic therapy during index hospitalization and the related bleeding complications. LMWH = low-molecular weight heparin; TAVR = transcatheter aortic valve replacement; UFH = unfractionated heparin; Vit-K inh. = vitamin K inhibitors.

A propensity score-matched cohort was created with a 1:1 ratio and nearest neighbor matching. A difference in the propensity scores of <0.2 times the SD of the logistic scores was established as a caliper. Comparison of categorical and continuous variables between the matched cohorts was performed using the McNemar test and Wilcoxon rank test, respectively. Survival analysis using the Kaplan-Meier method was used to determine differences according to the presence of a PMV. Statistical significance was defined as $p < 0.05$. All analyses were conducted using the statistical package SPSS Statistics version 23.0 (IBM, Armonk, New York) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. The mean age of the study population (n = 2,412) was 80.5 ± 7.7, years and 48.8% (n = 1,178) were men. A total of 91 patients (3.77%) had PMVs. The main baseline characteristics of the global study population according to the presence of a PMV are summarized in Table 1. Most patients with PMVs were women (71.4%), with lower rate of concomitant mitral regurgitation (4.7% vs. 17.7%; $p < 0.001$) and higher use of vitamin K inhibitors (94.5% vs. 30.1%; $p < 0.001$).

In the PMV cohort (n = 91), 24 patients (26.4%) had biological prostheses and 67 patients (73.6%) had mechanical prostheses (19.4% monodisc, 80.6% bidisc). The most common prosthesis type was Carbomedics (20.8%). All PMV interventions were performed a median of 14 years before TAVR. The mean size of PMVs was 27.15 ± 1.93 mm, and 9 patients (9.9%) also underwent tricuspid annuloplasty within the same intervention. Before TAVR, mean mitral transprosthetic gradient and pressure half-time at baseline were 4.8 ± 2.4 mm Hg and 129.3 ± 88.8 ms, respectively. Also, moderate or severe mitral regurgitation was detected in 1 (1.2%) and 3 (3.5%) patients with PMVs, respectively. Concerning antithrombotic regimen before TAVR, 86 patients (94.5%) received vitamin K inhibitors, 24 patients (26.4%) received aspirin plus vitamin K inhibitors, and 2 patients (2.2%) were receiving triple therapy. Patients with concomitant coronary artery disease were more often receiving antiplatelet treatment (66.7% vs. 21.0%; p = 0.001).

PROCEDURAL AND IN-HOSPITAL OUTCOMES. Management of antithrombotic therapy and related bleeding events along the hospitalization are

summarized in Figure 2. Bridging antithrombotic agents were administered in 59 patients (64.8%), including low-molecular weight heparin (LMWH) (65.4%) and unfractionated heparin (UFH) (34.6%). For the procedure, UFH was used in all patients, and following TAVR, anticoagulation was restarted within the first 24 h in 64.8% of patients (n = 59), mainly with LMWH (69%). No differences in bleeding events were found irrespective of the use of UFH or LMWH.

Main procedural and in-hospital outcomes are summarized in Table 2. Bleeding complications occurred more often in patients with PMVs (24.2% vs. 16.1%; p = 0.041). Most patients (n = 1,850 [76.7%]) underwent TAVR via the transfemoral approach, and the preferred device was the balloon-expandable prosthesis (SAPIEN valve) in 1,100 patients (51.8%) (Edwards Lifesciences, Irvine, California), followed by the self-expandable CoreValve system in 42.2% (Medtronic, Minneapolis, Minnesota). Other valves included the Lotus (Boston Scientific, Natick, Massachusetts) in 3 patients and the Direct Flow (Direct Flow Medical, Santa Rosa, California), Portico (St. Jude Medical, St. Paul, Minnesota), and Accurate TF Neo (Symetis SA, Eclubens, Switzerland) in 1 patient each. The procedure was successful in 94.7% of the global population, and the in-hospital mortality rate was 7.2% (n = 142).

No significant differences in device success rate were found irrespective of the presence of a PMV. However, interaction between the TAVR prosthesis and the mitral prosthesis leading to TAVR device embolization occurred in 6 patients (6.7%), with 5 (5.5%) requiring second valve implantation. In all patients with device embolization, the distance from the aortic annulus to the PMV, as determined by multidetector computed tomography (Figure 1), was <7 mm, but no impact of the angle between the PMV and the aortic root was found (68 ± 11.1° in patients with no embolization vs. 70.1 ± 2.1°; p = 0.308). Other factors, such as type of PMV (mechanical or biological) and type of TAVR prosthesis (balloon- or self-expandable), did not show differences in the rate of embolization. In addition, analysis for the subgroup of patients treated via the transfemoral approach did not show relevant differences in the comparison of main outcomes according to the presence of a PMV (Online Table 1).

TABLE 2 Procedural, In-Hospital, and Follow-Up Outcomes in the Global Population and According to the Presence of Prior Mitral Prostheses

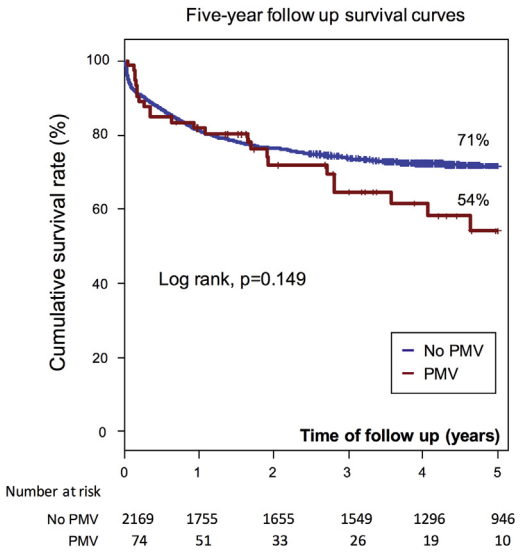
		Entire Cohort		
	Total (n = 2,414 [100%])	Non-PMV Group (n = 2,323 [96.2%])	PMV Group (n = 91 [3.8%])	p Value*
Procedural outcomes				
Transfemoral approach	1,850 (76.7%)	1,778 (76.6%)	72 (79.1%)	0.578
Balloon-expandable valve	1,100 (51.8%)	1,049 (51.6%)	51 (56.0%)	0.152
TAVR device embolization	81 (3.4%)	75 (3.3%)	6 (6.7%)	0.127
Need second valve	71 (3.3%)	66 (3.2%)	5 (5.6%)	0.221
Orotracheal intubation	1,201 (49.8%)	1,177 (50.7%)	24 (26.4%)	**<0.001**
In-hospital outcomes				
Permanent pacemaker	346 (14.5%)	334 (14.5%)	12 (14.8%)	0.944
New LBBB	126 (31.0%)	100 (30.4%)	26 (33.3%)	0.614
Myocardial infarction	12 (0.5%)	12 (0.5%)	0 (0.0%)	0.999
Stroke/TIA	90 (3.8%)	88 (3.8%)	2 (2.5%)	0.768
Bleeding complication	360 (16.4%)	338 (16.1%)	22 (24.2%)	**0.041**
Life-threatening bleeding	93 (5.5%)	87 (5.5%)	6 (6.6%)	0.654
Major bleeding	136 (8.2%)	122 (7.8%)	14 (15.4%)	**0.010**
Minor bleeding	40 (8.7%)	27 (7.3%)	13 (14.3%)	**0.034**
Sepsis	48 (3.0%)	41 (2.7%)	7 (7.7%)	**0.017**
Mean aortic gradient post	11.28 ± 6.2	11.23 ± 6.0	12.86 ± 9.1	0.144
SPAP post (mm Hg)	44.00 ± 13.1	44.50 ± 14.5	53.20 ± 16.0	**<0.001**
Aortic regurgitation 3 or 4 post	77 (4.1%)	75 (4.2%)	2 (2.9%)	0.999
Mitral regurgitation 3 or 4 post	203 (10.1%)	200 (10.3%)	3 (4.3%)	0.107
Length of stay (days)	9.24 ± 11.2	9.13 ± 11.2	11.73 ± 9.5	**<0.001**
In-hospital death	142 (7.2%)	137 (7.3%)	5 (5.5%)	0.514
Device success VARC-2	1,296 (75.7%)	1,244 (75.9%)	52 (72.2%)	0.476
Procedural success VARC-2	1,104 (94.7%)	1,032 (94.4%)	72 (98.6%)	0.174
Follow-up outcomes				
Mean aortic gradient, 6 months	10.28 ± 6.2	10.53 ± 5.2	13.54 ± .10.7	0.062
SPAP, 6 months	40.90 ± 12.7	40.61 ± 12.6	43.79 ± 13.7	0.103
Aortic regurgitation 3 or 4, 6 months	3 (1.1%)	2 (0.9%)	1 (1.9%)	0.495
Mitral regurgitation 3 or 4, 6 months	115 (9.2%)	113 (9.5%)	2 (3.7%)	**0.043**
Mean aortic gradient, 1 yr	11.26 ± 5.6	10.96 ± 4.7	13.53 ± 10.0	0.059
SPAP, 1 yr	42.65 ± 14.6	40.99 ± 13.7	48.39 ± 16.5	**0.001**
Aortic regurgitation 3 or 4, 1 yr	13 (3.2%)	12 (3.5%)	1 (1.7%)	0.702
Mitral regurgitation 3 or 4, 1 yr	117 (9.4%)	113 (9.5%)	4 (6.7%)	0.484
NYHA functional class III or IV, 1 yr	147 (11.2%)	136 (10.8%)	11 (20.8%)	**0.024**
Dead at follow-up	795 (33.1%)	767 (33.1%)	28 (31.1%)	0.636

Values are n (%) or mean ± SD. Device success VARC-2: not dead in hospital, no need for second prostheses, mean aortic gradient at 30 days <20 mm Hg. *Significant p values (<0.05) are in **bold**.

LBBB = left bundle brunch block; post = after transcatheter aortic valve replacement; VARC-2 = Valve Academic Research Consortium 2; other abbreviations as in Table 1.

FOLLOW-UP OUTCOMES AND PREDICTORS OF MORTALITY. A total of 639 patients (26.5%) had died after a median follow-up period of 5 years. No differences in cumulative mortality rate were found according to the presence of a PMV (31.1% vs. 33.1%, p = 0.636) (Figure 3), but patients with PMV remained more often in New York Heart Association functional class III or IV at 1-year follow-up (20.8% vs. 10.8%; p = 0.024). Main predictors of 5-year cumulative mortality are summarized in Table 3. After propensity score analysis, similar predictors of mortality were confirmed (Table 4). Bleeding complications were associated with higher mortality (hazard ratio: 2.278; 95% confidence interval: 1.753 to 2.961;

FIGURE 3 Survival Curves



Survival curves for the global transcatheter aortic valve replacement population according to the presence or absence of a prosthetic mitral valve (PMV).

$p < 0.001$). Other predictors of mortality were atrial fibrillation, chronic obstructive pulmonary disease, higher Society of Thoracic Surgeons score, and worse New York Heart Association functional class.

In the cohort of patients with PMVs, higher Society of Thoracic Surgeons score but also the use of self-expandable devices (hazard ratio: 2.695; 95% confidence interval: 1.133 to 6.412; $p = 0.025$) were associated with greater mortality, as shown in Online Table 2. A comparison of self- versus balloon-expandable recipients in the PMV cohort is depicted in Online Table 3.

DISCUSSION

Patients with PMVs could undergo TAVR with risk for early and long-term mortality comparable with that of patients without PMVs. Several medical and technical factors contributed to the prognosis in this scenario. First, a more common use of long-term anticoagulation and highly variable periprocedural management with antithrombotic agents increased the risk for bleeding events, which were a factor independently associated with higher mortality. Second, from a technical perspective, TAVR recipients with PMVs presented an elevated risk for device embolization (6.7%), with a distance from the aortic annulus to the PMV <7 mm in all embolized valves. Finally, a controversial association of self-expandable devices (presenting a deeper landing zone within the ventricle) with higher mortality was found in patients with PMVs. Hence, in patients with PMVs, TAVR can be safely performed, but pharmacological, imaging, and technical factors are critical to achieve optimized outcomes.

BASELINE RISK AND ANTITHROMBOTIC MANAGEMENT. Redo surgical procedures are a well-known factor increasing the risk for death in cardiac surgery (1,2). More than 70% of patients who undergo mitral surgery develop aortic valve disease during follow-up, with 5% of them requiring new intervention (13). In this scenario, TAVR may minimize the risk compared with repeat surgery. Moreover, our findings suggest that TAVR did not increase mortality compared with patients without PMV, which may be of great clinical relevance, and that some risk assessment tools (as the European System for Cardiac Operative Risk Evaluation score) may be poor choices for the evaluation of procedural risk in TAVR candidates with PMVs. Nevertheless, bleeding complications were clearly more frequent in subjects with PMVs. The need for more aggressive antithrombotic therapy because of a higher rate of atrial fibrillation and the presence of mechanical PMV can partially explain this fact (14). About two-thirds of the patients with PMVs in this study followed current recommendations for antithrombotic bridging therapy (10,15), most with LMWH, which was recently suggested to be a safe alternative to prevent thrombotic events (16). However, this strategy has been associated with higher bleeding risk (17,18), especially when patients taking LMWH receive UFH for the procedure, as is actually done at most centers (19).

TECHNICAL ASPECTS AND PROGNOSIS. The transfemoral approach for TAVR presents better outcomes than most alternative approaches (20). However, some investigators have suggested that longer distance from the PMV to the aortic annulus when transfemoral and not transapical TAVR is performed may be required (9). Computed tomographic analysis demonstrated that a distance of at least 7 mm from the mitral prosthesis to the aortic annulus was safe for transfemoral implantation of both self- and balloon-expandable devices. The TAVR procedure is probably also safe in most patients with distances <7 mm, but additional security measures should be taken, including the use of fully or partially repositionable devices and avoidance of deep implantation in the outflow tract. Evidence is still scarce to support the use of newer resheathable

TABLE 3 Main Predictors of 5-Year Follow-Up Mortality in Global Population

	Total (n = 2,396 [100%])	Dead at FU (n = 707 [29.7%])	Alive at FU (n = 1,674 [70.3%])	Univariate Analysis		Multivariate Analysis		
				HR	95% CI	HR	95% CI	p Value
Baseline characteristics								
Weight (kg)	71.32 ± 15.0	70.51 ± 14.89	71.69 ± 15.1	0.995	0.990–1.001	–	–	–
COPD	**706 (29.8%)**	**270 (34.2%)**	**436 (27.6%)**	**1.277**	**1.083–1.505**	**1.205**	**1.011–1.436**	**0.0369**
Prior AF	**754 (31.9%)**	**307 (39.3%)**	**447 (28.3%)**	**1.663**	**1.420–1.949**	**1.531**	**1.296–1.808**	**<0.0001**
Stroke/TIA BL	256 (16.8%)	108 (18.9%)	148 (15.5%)	1.289	1.032–1.609	–	–	–
PMV	73 (3.1%)	26 (3.3%)	47 (2.9%)	1.349	0.897–2.028	–	–	–
STS score	**7.55 ± 5.4**	**8.72 ± 6.4**	**6.89 ± 4.7**	**1.048**	**1.036–1.060**	**1.041**	**1.029–1.054**	**<0.0001**
Logistic EuroSCORE	20.57 ± 13.5	23.21 ± 14.4	19.20 ± 12.9	1.016	1.011–1.021	-	-	-
NYHA functional class III or IV BL	**1,383 (66.9%)**	**450 (71.3%)**	**933 (65%)**	**1.258**	**1.059–1.495**	**1.260**	**1.053–1.507**	**0.0115**
Echocardiographic characteristics								
Mean aortic gradient BL (mm Hg)	45.78 ± 16.9	43.61 ± 16.3	46.95 ± 17.0	0.992	0.987–0.997	–	–	–
LVEF BL (%)	54.09 ± 14.2	52.63 ± 14.5	54.80 ± 14.0	0.994	0.988–0.999	–	–	–
Mitral regurgitation 3 or 4 BL	405 (17.4%)	158 (20.5%)	247 (15.8%)	1.319	1.089–1.587	–	–	–
SPAP BL (mm Hg)	44.90 ± 14.7	46.29 ± 15.5	44.29 ± 14.3	1.010	1,004–1.016	–	–	–
Procedural characteristics								
Transfemoral approach	1,838 (77.1%)	577 (72.9%)	1,261 (79.1%)	0.682	0.575–0.808	–	–	–
Self-expandable valve	1,018 (48.4%)	315 (43.6%)	703 (50.9%)	0.648	0.551–0.762	–	–	–
Device embolization	79 (3.4%)	42 (5.4%)	37 (2.4%)	1.637	1.135–2.363	–	–	–
Need second valve	70 (3.3%)	31 (4.6%)	39 (2.7%)	1.414	0.932–2.147	–	–	–
Orotracheal intubation	**1,175 (49.2%)**	**480 (60.5%)**	**695 (43.6%)**	**2.126**	**1.805–2.505**	**2.019**	**1.680–2.427**	**<0.0001**
Post-procedural events								
Days of admission	9.24 ± 11.2	11.01 ± 12.55	8.33 ± 11.3	1.010	1.006–1.013	–	–	–
Sepsis post	48 (3.1%)	29 (5.5%)	19 (1.8%)	2.533	1.716–3.748	–	–	–
Myocardial infarction post	27 (1.4%)	13 (2.1%)	14 (1.0%)	1.652	0.909–3.002	–	–	–
Stroke/TIA post	88 (3.8%)	42 (5.4%)	46 (3.0%)	1.683	1.197–2.367	–	–	–
Bleeding complications	**353 (16.2%)**	**198 (26.5%)**	**155 (10.9%)**	**2.260**	**1.896–2.692**	**2.278**	**1.753–2.961**	**<0.0001**
Major bleeding	131 (8.0%)	57 (11.2%)	74 (6.6%)	1.891	1.403–2.548	–	–	–
Life-threatening bleeding	90 (5.5%)	61 (11.9%)	29 (2.6%)	3.163	2.308–4.336	–	–	–
SPAP post	44.0 ± 13.1	46.13 ± 13.8	43.3 ± 12.7	1.014	1.005–1.023	–	–	–
Mitral regurgitation 3 or 4, 6 months	113 (9.2%)	38 (12.5%)	75 (8.1%)	1.616	1.138–2.296	–	–	–
Mitral regurgitation, 3 or 4 post	201 (10.1%)	77 (12.2%)	124 (9.1%)	1.354	1.049–1.746	–	–	–
NYHA functional class III or IV, 6 months	177 (12.9%)	68 (17.6%)	109 (11.0%)	1.563	1.188–2.055	–	–	–
NYHA functional class III or IV, 1 yr	144 (11.1%)	64 (18.6%)	80 (8.4%)	2.087	1.572–2.771	–	–	–

Values are mean ± SD or n (%). Variables included in multivariable analysis model are in **bold**.
AF = atrial fibrillation; CI = confidence interval; FU = follow-up; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

devices in this scenario, but future research in patients with PMVs is warranted (21,22). The fact that self-expandable devices were associated with higher mortality in the PMV cohort should be interpreted with caution, as it may be random given the presence of numerous baseline differences, as summarized in Online Table 1. Prosthesis deformation leading to moderate to severe paravalvular regurgitation occurred in some of the self-expandable cases because of interaction with the PMV, but the difference in the rate of this complication was not statistically significant (6.1% vs. 0%; p = 0.219).

Finally, although several studies have explored the impact of TAVR in native mitral valve function (23), the hemodynamic effect in patients with PMVs has been barely described. Mitral effective area should not be used for mitral prostheses, and the continuity equation is not valid when there is concomitant aortic valve disease. The mean transmitral gradient is the best parameter to evaluate correct function and did not vary significantly in our study population (12,24). However, about one-third of the patients had an increase in that gradient that was associated with worse functional recovery. This is an intriguing finding that may have prognostic implications and needs to be further explored.

STUDY LIMITATIONS. The main limitations of the present study include its retrospective nature, that may have led to the exclusion of patients deemed

TABLE 4 Main Baseline and Procedural Predictors of 5-Year Mortality After Matching

	Available Data/ Total Patients	Dead at FU (n = 55)	Alive at FU (n = 105)	p Value*
Baseline characteristics				
Age (yrs)	160/160	75.5 ± 8.2	72.5 ± 10.4	0.065
BMI (kg/m^2)	156/160	26.1 ± 5.3	28 ± 6.2	0.065
Female	160/160	34 (61.8)	62 (59.0)	0.734
COPD	159/160	20 (37.0)	17 (16.2)	**0.003**
Prior AF	159/160	47 (87.0)	68 (64.8)	**0.003**
Stroke/TIA BL	131/160	5 (10.6)	13 (15.5)	0.440
Prior cardiac surgery	159/160	40 (74.1)	72 (68.6)	0.471
PMV	160/160	26 (48.1)	53 (50.5)	0.781
STS score (%)	137/160	10.2 ± 8.3	7.1 ± 5	**0.018**
Logistic EuroSCORE (%)	159/160	30.8 ± 17	23.4 ± 14.8	**0.005**
NYHA functional class III or IV BL	155/160	47 (87.0)	74 (73.3)	**0.048**
Echocardiographic characteristics				
Mean aortic gradient BL	159/160	42.4 ± 14	43.9 ± 16.5	0.563
LVEF BL	159/160	54.7 ± 14.7	54.2 ± 14.1	0.829
Mitral regurgitation 3 or 4 BL	155/160	9 (17.6)	15 (14.4)	0.602
SPAP BL	139/160	49.8 ± 16	50.6 ± 16.1	0.797
Procedural characteristics				
Transfemoral approach	159/160	35 (66.7)	75 (71.4)	0.536
Self-expandable valve	155/160	24 (44.4)	33 (32.7)	0.148
Valve embolization	157/160	3 (5.7)	3 (2.9)	0.406
Need second valve	155/160	4 (7.8)	3 (2.9)	0.219
Orotracheal intubation	159/160	26 (48.1)	44 (41.9)	0.453
Post-procedural events				
Permanent pacemaker	159/160	7 (13.0)	12 (11.4)	0.778
Sepsis	142/160	5 (9.8)	3 (3.3)	0.136
Myocardial infarction	138/160	2 (4.3)	4 (4.4)	0.999
Stroke/TIA	159/169	2 (3.7)	5 (4.8)	0.999
Procedural success	148/160	42 (80.8)	86 (89.6)	0.134
Bleeding complications	155/160	16 (29.6)	14 (13.9)	**0.018**
Life-threatening bleeding	134/160	5 (11.1)	3 (3.4)	0.118
Major bleeding	134/160	7 (15.6)	8 (9.0)	0.225
Minor bleeding	134/160	7 (19.4)	8 (12.1)	0.318
Length of stay (days)	153/160	10 (7–14)	8 (6–11.5)	**0.004**
Time of follow-up (yrs)	159/160	0.5 (0.1–1.8)	5.1 (3.5–5.9)	**<0.001**

Values are n, mean ± SD or n (%). or median (interquartile range). Matched variables: age, logistic EuroSCORE, diabetes mellitus, COPD, prior AF, and LVEF. *Significant p values (<0.05) are in **bold**.
Abbreviations as in Tables 1 to 3.

surgical or inoperable who did not undergo TAVR, and the relatively small proportion of patients with PMVs precludes deeper insights into the impact of antithrombotic strategies. The function and changes of tricuspid regurgitation may have played a role in the functional outcomes of these patients but were not explored in the present study. Finally, evaluation of mitral regurgitation in a PMV using transthoracic echocardiography has limited accuracy, and therefore our findings regarding mitral regurgitation should be interpreted with caution.

CONCLUSIONS

TAVR presents comparable in-hospital and follow-up mortality irrespective of the presence of a PMV. However, patients with PMVs had a higher bleeding risk that was itself independently associated with higher mortality. Risk for TAVR device embolization in patients with PMVs was relatively high but occurred only in those with PMV-to-aortic annulus distances <7 mm.

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PERSPECTIVES

WHAT IS KNOWN? TAVR is performed relatively often in patients with PMVs, but specific risks in this unique population are not well described.

WHAT IS NEW? TAVR presents comparable mortality irrespective of the presence of a PMV but a relatively high risk for TAVR device embolization, which in all cases occurred when the PMV-to-aortic annulus distance was <7 mm. In addition, patients with PMVs presented a higher bleeding risk that was itself independently associated with higher mortality.

WHAT IS NEXT? TAVR is a safe option in patients with PMVs, but improved outcomes will be obtained through the use of fully repositionable newer devices and optimized antithrombotic management. Hence, TAVR is likely to become in the near future the gold-standard therapy in patients with PMVs.

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APPENDIX For a supplemental figure and tables, please see the online version of this article.