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Impact of Pre-Existing Prosthesis-Patient Mismatch on Survival Following Aortic Valve-in-Valve Procedures

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ABSTRACT

OBJECTIVES The aim of this study was to determine whether the association of small label size of the surgical valve with increased mortality after transcatheter valve-in-valve (ViV) implantation is, at least in part, related to pre-existing prosthesis-patient mismatch (PPM) (i.e., a bioprosthesis that is too small in relation to body size).

BACKGROUND Transcatheter ViV implantation is an alternative for the treatment of patients with degenerated bioprostheses. Small label size of the surgical valve has been associated with increased mortality after ViV implantation.

METHODS Data from 1,168 patients included in the VIVID (Valve-in-Valve International Data) registry were analyzed. Pre-existing PPM of the surgical valve was determined using a reference value of effective orifice area for each given model and size of implanted prosthetic valve indexed for body surface area. Severe PPM was defined according to the criteria proposed by the Valve Academic Research Consortium 2: indexed effective orifice area <0.65 cm^2/m^2 if body mass index is <30 kg/m^2 and <0.6 cm^2/m^2 if BMI is ≥ 30 kg/m^2. The primary study endpoint was 1-year mortality.

RESULTS Among the 1,168 patients included in the registry, 89 (7.6%) had pre-existing severe PPM. Patients with severe PPM had higher 30-day (10.3%, $p = 0.01$) and 1-year (unadjusted: 28.6%, $p < 0.001$; adjusted: 19.3%, $p = 0.03$) mortality rates compared with patients with no severe PPM (4.3%, 11.9%, and 10.9%, respectively). After adjusting for surgical valve label size, Society of Thoracic Surgeons score, renal failure, diabetes, and stentless surgical valves, presence of pre-existing severe PPM was associated with increased risk for 1-year mortality (odds ratio: 1.88; 95% confidence interval: 1.07 to 3.28; $p = 0.03$). Patients with severe PPM also more frequently harbored high post-procedural gradients (mean gradient ≥ 20 mm Hg).

CONCLUSIONS Pre-existing PPM of the failed surgical valve is strongly and independently associated with increased risk for mortality following ViV implantation. (J Am Coll Cardiol Intv 2018;11:133–41) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

CI = confidence interval

EOA = effective orifice area

HR = hazard ratio

PPM = prosthesis-patient mismatch

STS = Society of Thoracic Surgeons

THV = transcatheter heart valve

ViV = valve-in-valve

Currently, the vast majority of surgical aortic valve replacements (AVRs) are performed with bioprosthetic valves, essentially because these valve substitutes are associated with less thrombotic and bleeding complications compared with mechanical valves (1). However, the main limitation of bioprosthetic valves is that they have limited durability and commonly fail within 10 to 15 years (2,3). Patients with failing surgical bioprosthetic valves are frequently at high surgical risk because of old age, comorbidities, and the need for repeat cardiac surgery (4,5). Transcatheter heart valve (THV) implantation within the failed aortic surgical bioprostheses (valve-in-valve [ViV] implantation) represents a valuable, less invasive alternative to surgery for patients considered to be at high risk for reoperation (6).

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Surgical bioprostheses often have a small internal orifice diameter and a nonelastic stent, which predispose to THV underexpansion at the time of ViV implantation (7). As a result, elevated postprocedural gradients are common following aortic ViV implantation and have been associated with increased mortality (8,9). In the VIVID (Valve-in-Valve International Data) registry, small label size of the surgical valve was found to be associated with increased mortality after ViV implantation (9). However, it is unknown whether that association is, at least in part, related to pre-existing prosthesis-patient mismatch (PPM) (i.e., PPM of the surgical bioprosthetic valve). PPM refers to a prosthetic valve with normal function that is too small in relation to body size and thus for the cardiac output requirements of the patient. PPM is therefore defined as the prosthetic valve effective orifice area (EOA) divided by the patient's body surface area. The objective of this study was thus to examine the association between pre-existing PPM and the occurrence of high residual gradients and mortality after ViV implantation.

METHODS

REGISTRY DESIGN. The VIVID registry is a multicenter international registry of ViV procedures, which includes different THV devices and valve positions (10). Since 2010, the registry has prospectively collected data using a dedicated case report form from centers in Europe, North America, South America, Africa, Oceania, and the Middle East. Inconsistencies were resolved directly with local investigators and on-site data monitoring. All patients gave written informed consent for a transcatheter ViV procedure. A local ethics committee approved the inclusion of patients at each center. In the present analysis, only cases performed in the aortic position were included.

DEFINITIONS. Conventional scores (Society of Thoracic Surgeons [STS] and European System for Cardiac Operative Risk Evaluation [EuroSCORE] score) were calculated to estimate operative mortality risk for surgical valve replacement. The mechanism of bioprosthetic valve failure (i.e., regurgitation, stenosis, or mixed) was assessed using criteria proposed by the American Society of Echocardiography (11). Patients with at least a moderate degree of both stenosis and regurgitation were included in the mixed dysfunction group. Other patients were categorized according to the primary mechanism of failure, either stenosis or regurgitation. Body surface area was calculated using the Mosteller formula using the patient's height and weight measured at the time of ViV implantation.

Pre-existing PPM of the surgical valve was determined using the predicted EOA (i.e., the published normal reference value of EOA for each given model and size of implanted bioprosthesis, divided by the patient's body surface area [12]). Severe PPM was defined according to the to the Valve Academic Research Consortium 2 criteria (13): indexed EOA $\leq$0.65 cm^2/m^2 for nonobese patients (body mass index $<$30 kg/m^2) and indexed EOA $\leq$0.60 cm^2/m^2 for obese patients (body mass index $\geq$30 kg/m^2).

The primary endpoint for this study was 1-year all-cause mortality. The secondary endpoints were: 1)

for echocardiography core laboratory analyses in transcatheter heart valves. Dr. Dvir is a consultant for Edwards Lifesciences, Medtronic, and St. Jude Medical. Dr. Moat has received consulting and speaking fees from Abbott, Edwards Lifesciences, and Medtronic. Dr. Latib is a consultant for Medtronic; has received speaking honoraria from Abbott Vascular; and research grants from Medtronic and Edwards Lifesciences. Dr. Kim is a proctor for Symetis and St. Jude Medical. Dr. Linke is a consultant for Medtronic, St. Jude Medical, Claret Medical, Boston Scientific, Edwards Lifesciences, Symetis, and Bard; and owns stock options in Claret Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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30-day mortality; and 2) the presence of elevated post-procedural gradient, which was defined as a mean transvalvular gradient ≥20 mm Hg at either intra-procedural or first post-procedural echocardiographic examination (13). Major clinical endpoints were assessed according to the Valve Academic Research Consortium 2 criteria (13).

STATISTICAL ANALYSIS. Results are presented as mean ± SD for continuous variables with normal distribution, median (interquartile range) for continuous variables without normal distribution, and number (percentage) for categorical data. The Student *t*-test was used to compare normally distributed continuous variables between the pre-existing severe PPM group and the group with no or moderate PPM. The Mann-Whitney *U* test was used for variables not normally distributed. Chi-square and Fisher exact tests were used to compare categorical variables. A Cox proportional hazards analysis was used for univariate and multivariate analyses of factors associated with 1-year mortality. The variables entered in the multivariable model were those with p values <0.10 in the univariate analysis. A variable could also be included in the model if it was considered important for outcomes on the basis of prior clinical knowledge. The results of the multivariate analysis are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Survival curves derived from the Cox proportional hazards analysis were used to display adjusted cumulative hazard of death from any cause according to the presence or absence of pre-existing severe PPM. A 2-tailed p value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS version 22 (IBM, Armonk, New York).

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS ACCORDING TO PRE-EXISTING PPM. Among the 1,168 patients included in the registry, 89 (7.6%) had pre-existing severe PPM. Patients with severe PPM had significantly larger body surface areas and body mass index values; higher prevalence rates of obesity, diabetes, renal failure, and prior cerebrovascular events; and higher STS scores (Table 1). All patients in the severe PPM group received stented bioprosthetic valves at the time of the index surgical AVR, whereas among those with no or moderate PPM, 10.1% received stentless bioprostheses. The average size of the surgical bioprosthesis was smaller and the proportion of small (≤21-mm) valves was much larger in the severe PPM group than in the group with no or moderate PPM (Table 1). As expected, predicted EOA and indexed EOA were significantly smaller in the severe PPM group. There was no significant difference between the 2 groups with regard to the distribution of the mode of surgical valve failure. However, patients with severe PPM had smaller aortic valve areas and indexed aortic valve areas and a lower

TABLE 1 Baseline Characteristics According to Pre-Existing Prosthesis-Patient Mismatch

	Severe PPM (n = 89)	No or Moderate PPM (n = 1,079)	p Value
Age, yrs	78 ± 7.6	78.6 ± 8.5	0.48
Male	51 (57.3)	604 (56.1)	0.82
Height, cm	171.3 ± 9.4	166.8 ± 9.5	<0.001
Weight, kg	87.7 ± 16.5	73.9 ± 15.5	<0.001
Body surface area, m^2	2.00 ± 0.20	1.84 ± 0.20	<0.001
Body mass index, kg/m^2	30 ± 5.7	26.6 ± 5.6	<0.001
Obesity	28 (31.5)	230 (21.3)	0.03
NYHA functional class			0.15
I	0 (0)	9 (0.9)	
II	5 (5.8)	106 (10.1)	
III	51 (59.3)	674 (63.9)	
IV	30 (34.9)	265 (25.1)	
STS score, %	9.9 (5–16.1)	7.3 (4.6–11.5)	0.002
Diabetes mellitus	38 (42.7)	267 (24.8)	<0.001
Peripheral vascular disease	16 (18.4)	232 (21.7)	0.47
Renal failure	53 (60.2)	528 (49.3)	0.049
Prior cerebrovascular event	19 (21.3)	145 (13.5)	0.04
Chronic lung disease	10 (16.9)	168 (22.9)	0.29
Previous permanent pacemaker	10 (12.7)	129 (13.7)	0.8
>1 cardiac surgical procedure	15 (17.6)	128 (12.3)	0.15
Label size of surgical valve, mm	21 ± 1.5	23.3 ± 2	<0.001
Label size of surgical valve (mm)			<0.001
≤21 mm	69 (77.5)	287 (26.6)	
>21 and <25	18 (20.2)	429 (39.8)	
≥25	2 (2.2)	363 (33.6)	
Predicted EOA, cm^2	1.22 ± 0.11	1.51 ± 0.26	<0.001
Predicted indexed EOA, cm^2/m^2	0.60 ± 0.04	0.83 ± 0.14	—
Time to surgical valve failure, yrs	7 (5–9)	9 (6.25–12)	<0.001
Mechanism of surgical valve failure			0.14
Regurgitation	15 (17.9)	247 (24.2)	
Stenosis	44 (52.4)	423 (41.4)	
Mixed	25 (29.8)	351 (34.4)	
Aortic valve area, cm^2	0.78 ± 0.28	0.91 ± 0.46	<0.001
Indexed aortic valve area, cm^2/m^2	0.38 ± 0.14	0.5 ± 0.25	<0.001
Peak gradient, mm Hg	66.5 ± 23.9	62.6 ± 27.2	0.21
Mean gradient, mm Hg	40.2 ± 15.1	36.7 ± 17.6	0.09
Aortic regurgitation			<0.001
None	25 (30.5)	159 (15.4)	
Mild	19 (23.2)	250 (24.2)	
Moderate	10 (12.2)	149 (14.4)	
Moderately severe	20 (24.4)	224 (21.6)	
Severe	8 (9.8)	253 (24.4)	
LVEF, %	51.6 ± 12.7	52.4 ± 13	0.61

Values are mean ± SD, n (%), or median (interquartile range).

EOA = effective orifice area; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons.

TABLE 2 Valve-in-Valve Procedural Characteristics According to Pre-Existing Prosthesis-Patient Mismatch

	Severe PPM (n = 89)	No or Moderate PPM (n = 1,079)	p Value
THV type			<0.001
CoreValve/Evolut	63 (70.8)	516 (47.8)	
SAPIEN/SAPIEN XT/SAPIEN 3	25 (28.1)	507 (47)	
Other	1 (1.1)	56 (5.2)	
THV size, mm	24.0 ± 1.6	24.4 ± 1.9	0.04
THV size, mm			0.15
20	3 (3.4)	13 (1.2)	
23	53 (59.6)	587 (55.6)	
25	0 (0)	9 (0.9)	
26	33 (37.1)	377 (35.7)	
27	0 (0)	2 (0.2)	
29	0 (0)	65 (6.2)	
31	0 (0)	2 (0.2)	
Access			0.02
Transfemoral	75 (84.3)	768 (71.2)	
Transapical	10 (11.2)	266 (24.7)	
Other	4 (4.5)	45 (4.2)	
General anesthesia	44 (49.4)	704 (65.4)	0.003
Transesophageal echocardiography	32 (36.4)	628 (58.5)	<0.001
Initial device malposition	9 (10.7)	70 (6.8)	0.18
Need for a second THV	6 (6.7)	40 (3.7)	0.16

Values are n (%) or mean ± SD.
PPM = prosthesis-patient mismatch; THV = transcatheter heart valve.

TABLE 3 30-Day Hemodynamic and Clinical Outcomes According to Pre-Existing Prosthesis-Patient Mismatch

	Severe PPM (n = 89)	No or Moderate PPM (n = 1,079)	p Value
Duration of hospital stay, days	7 (5-10)	7 (5-11)	0.59
Vascular complications			0.65
Minor	8 (9)	73 (6.8)	
Major	2 (2.2)	35 (3.2)	
Major bleeding	2 (2.4)	62 (5.9)	0.17
Major stroke	1 (1.2)	14 (1.3)	0.92
Acute kidney injury	6 (7.1)	65 (6.1)	0.74
Coronary obstruction	1 (1.1)	21 (2)	0.58
Pacemaker need	4 (5.1)	60 (6.4)	0.66
Death	9 (10.3)	45 (4.3)	0.01
Aortic valve area, cm^2	1.47 ± 0.54	1.43 ± 0.44	0.43
Indexed aortic valve area, cm^2/m^2	0.72 ± 0.26	0.78 ± 0.25	0.07
Peak gradient, mm Hg	34.4 ± 16.7	29.3 ± 14.3	0.003
Mean gradient, mm Hg	19.5 ± 10	16.2 ± 8.7	0.001
Elevated (≥20 mm Hg) post-procedural gradient	38 (47.5)	293 (29.6)	0.001
Aortic regurgitation			0.80
None	55 (69.6)	649 (64.6)	
Mild	20 (25.3)	307 (30.6)	
Moderate	4 (5.1)	41 (4.1)	
Moderately severe	0 (0)	5 (0.5)	
Severe	0 (0)	2 (0.2)	
LVEF, %	53.9 ± 10.4	51.4 ± 12.1	0.049

Values are median (interquartile range), n (%), or mean ± SD.
Abbreviations as in Tables 1 and 2.

prevalence of significant aortic regurgitation before the ViV procedure. The time from AVR to ViV implantation was significantly shorter in the severe PPM group compared with the group with no or moderate PPM (Table 1).

With regard to ViV procedural characteristics (Table 2), CoreValve or Evolut THV (Medtronic, Fridley, Minnesota), transfemoral access, and conscious sedation were more frequently used in the group with pre-existing severe PPM than in that with no or moderate PPM. The average size of the THV was smaller in the pre-existing severe PPM group.

ASSOCIATION BETWEEN PRE-EXISTING PPM AND 30-DAY OUTCOMES. Patients with pre-existing severe PPM harbored significantly higher early post-procedural gradients than those with no or moderate PPM (Table 3). The proportion of patients with high post-procedural gradients (mean gradient ≥20 mm Hg) was greater in the severe PPM group: 47.6% versus 29.5% (p = 0.001) (Table 3, Figure 1). Patients with pre-existing severe PPM had 2.4-fold higher 30-day mortality (10.3%) compared with those with no or moderate PPM (4.3%) (p = 0.01) (Figure 1). The rates of other 30-day morbidities were not statistically different between the 2 groups (Table 3).

Compared with balloon-expandable THVs (SAPIEN, SAPIEN XT, or SAPIEN 3, Edwards Lifesciences, Irvine, California), the self-expanding THVs (CoreValve and Evolut) were associated with lower rates of high residual gradients early after ViV implantation in the whole cohort as well as in the groups with no or moderate PPM and with severe PPM (Figure 2). This difference in the proportion of high gradients between self-expanding and balloon-expandable THVs was particularly striking in the subset of patients with pre-existing severe PPM (34% vs. 78%; p < 0.001).

ASSOCIATION BETWEEN PRE-EXISTING PPM AND 1-YEAR MORTALITY. Patients with pre-existing severe PPM had a 1.88-fold higher adjusted 1-year mortality rate compared with patients without severe PPM (unadjusted: 28.6% vs. 11.9%; p < 0.001, Figure 1; adjusted: 19.3% vs. 10.9%; p = 0.03, Figure 3). The other factors associated with 1-year mortality in univariate analysis were higher STS score (HR: 1.05; 95% CI: 1.04 to 1.06; p < 0.001), diabetes (HR: 1.54; 95% CI: 1.05 to 2.26; p = 0.026), renal failure (HR: 1.71; 95% CI: 1.17 to 2.51; p = 0.005), and smaller label size of the surgical valve (HR: 0.86; 95% CI: 0.78 to 0.94; p = 0.001). The mode of failure of the surgical valve as well as the other pre-procedural and procedural factors were not associated with mortality. Stentless surgical valves were not associated with mortality in univariate analysis (HR: 1.39; 95% CI:

0.79 to 2.42; p = 0.25), but we decided to force this variable into the model because of its potential importance in terms of likelihood of complications. Therefore, after adjusting for label valve size, STS score, renal failure, diabetes, and stentless surgical valves, presence of pre-existing severe PPM was independently associated with increased risk for 1-year mortality (HR: 1.88; 95% CI: 1.07 to 3.28; p = 0.03) (**Figure 4**).

DISCUSSION

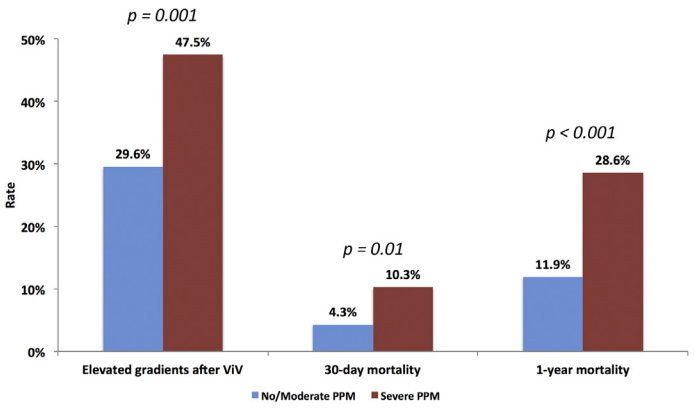
The main finding of this study is that pre-existing severe PPM of the surgical bioprosthesis is associated with higher prevalence of elevated transaortic gradient after the ViV procedure, with 2.4- and 1.8-fold higher rates of 30-day and 1-year mortality, respectively. This is the first study to report an independent association between pre-existing PPM and mortality after ViV implantation.

Most previous studies of ViV implantation (8,9,14) did not assess the presence and impact on outcomes of pre-existing PPM of the surgical bioprosthesis. However, in the recent report from the CoreValve US Expanded Use Study including 233 patients (15), 13% had pre-existing severe PPM, and of these patients, 77% had high residual gradients after ViV implantation. In the present study, 7.6% of the patients had pre-existing severe PPM, which appears lower that the prevalence in the CoreValve US registry (15). This difference may, at least in part, be related to the fact that, as recommended by Valve Academic Research Consortium 2 (13), we used lower cutoff values of indexed EOA to define PPM in obese patients. The use of EOA indexed to body surface area may indeed result in an overestimation of the prevalence and severity of PPM in obese patients. The prevalence of pre-existing PPM in the present study is, however, consistent with the data reported in contemporary surgical AVR series (15–17). In a recent analysis of the STS database using similar PPM definition as used in our study (15), the prevalence of severe PPM was 15% in 2004 and dropped to 6% in 2014.

In the present study, the time from initial surgical AVR to bioprosthetic valve failure was substantially shorter in patients with pre-existing severe PPM compared with those with no or moderate PPM. These findings may be, at least in part, explained by the fact that PPM may accelerate the structural degeneration of bioprostheses (18,19). Indeed, PPM increases the flow turbulence through the prosthetic valve orifice as well as the mechanical stress on the valve leaflets (18,19). In turn, leaflet mechanical stress is an important factor contributing to the structural degeneration of bioprostheses (20). Furthermore, patients with pre-existing severe PPM already have significantly increased LV afterload at the outset of the index AVR, and they may thus be less likely to tolerate the additional hemodynamic burden caused by a significant acquired dysfunction (stenosis and/or regurgitation).

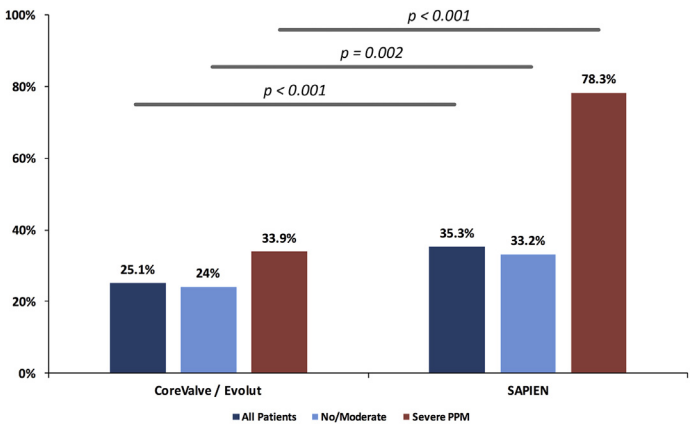
In this study, patients with pre-existing severe PPM had worse hemodynamic and clinical outcomes

FIGURE 1 Rates of Elevated Post-Procedural Transvalvular Gradients and 30-Day and 1-Year Mortality According to Pre-Existing Severe Prosthesis-Patient Mismatch



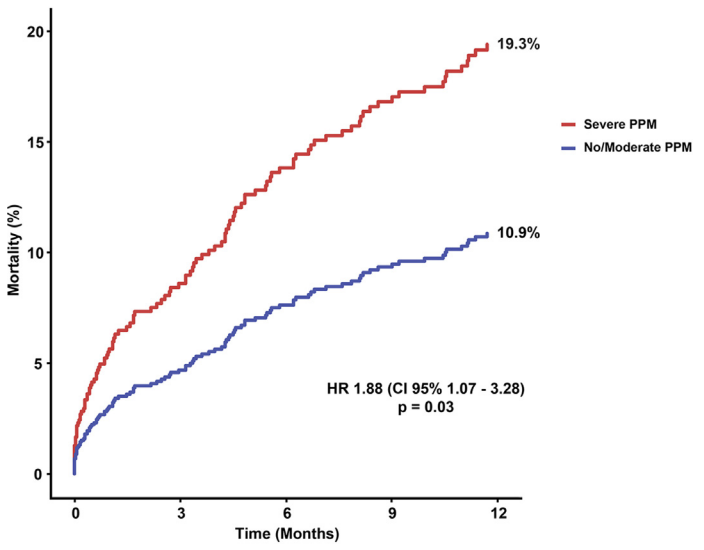
Rates of elevated (≥20 mm Hg) post-procedural gradients, 30-day mortality, and unadjusted 1-year mortality according to presence or absence of pre-existing severe prosthesis-patient mismatch (PPM).

FIGURE 2 Rates of Elevated Post-Procedural Transvalvular Gradient According to Pre-Existing Severe Prosthesis-Patient Mismatch and Type of Transcatheter Heart Valve Used for Valve-in-Valve Implantation



Rates of elevated (≥20 mm Hg) post-procedural gradients, 30-day mortality, and 1-year mortality according to presence or absence of pre-existing severe prosthesis-patient mismatch (PPM) and to the type of transcatheter heart valve (i.e., self-expanding CoreValve or Evolut vs. balloon-expandable SAPIEN) used for valve-in-valve implantation.

FIGURE 3 Adjusted 1-Year Mortality Rate According to Pre-Existing Severe Prosthesis-Patient Mismatch



Cox proportional hazards regression curves showing the adjusted cumulative hazard of death from any cause according to the presence or absence of pre-existing severe prosthesis-patient mismatch (PPM).

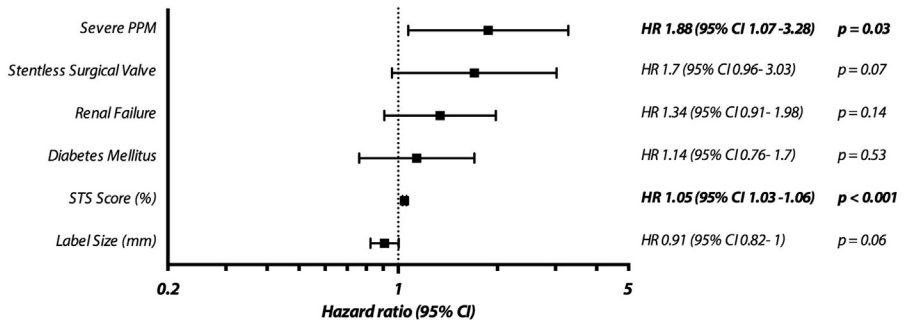
following ViV implantation. The ViV procedure generally improves the hemodynamic and clinical status of patients who have acquired dysfunction resulting from structural valve degeneration. However, PPM is a nonstructural "iatrogenic" complication that is characterized by a prosthetic valve with normal function but that is too small in relation to the body size and thus to the cardiac output requirements of the patient. Hence, given that the stent and internal orifice diameter of surgical bioprosthetic valves are generally not expansible, the ViV procedure cannot correct pre-existing PPM, and in fact, this procedure may even worsen the PPM. Indeed, the implantation of a THV within a severely mismatched bioprosthetic valve may further reduce the already limited valve orifice area available for flow.

Patients with small surgical bioprostheses harbor a higher prevalence of severe PPM (17,21). Hence, the association that was previously reported between small (≤21 mm) surgical valve label size and mortality after ViV implantation may, at least in part, be related to the presence of unidentified pre-existing severe PPM (8,9). As a matter of fact, in the present study, smaller label size was strongly associated with increased 1-year mortality in univariate analysis. However, this association was no longer significant in the multivariate model that also included pre-existing severe PPM (**Figure 4**).

Similarly, the previously reported association between stenosis as the failure mode of the surgical valve and mortality following ViV implantation could be related to pre-existing PPM (9). Indeed, patients with high transprosthetic gradients before ViV implantation were generally considered to have severe acquired prosthetic valve stenosis due to calcific degeneration of valve leaflets. However, it is likely that in a high proportion of these patients, the elevated gradient observed before ViV implantation was, in large part, due to pre-existing PPM. In such patients, a ViV procedure would result in minimal to no reduction, or even an increase in gradient.

CLINICAL IMPLICATIONS. The findings of this study provide a strong argument for the prevention of PPM

FIGURE 4 Multivariate Cox Regression Demonstrating Variables Associated With 1-Year Mortality



Multivariate regression demonstrates an independent association between pre-existing severe prosthesis-patient mismatch (PPM) of the surgical valve and increased 1-year mortality after aortic valve-in-valve implantation. CI = confidence interval; STS = Society of Thoracic Surgeons.

at the time of initial surgical AVR. First, according to meta-analyses (16,17), severe PPM is associated with a 1.8-fold increase in mortality and 1.6-fold increase in heart failure rehospitalization after AVR. Second, severe PPM may increase the valve leaflet mechanical stress and flow turbulence, which may in turn accelerate the structural degeneration of bioprosthetic valves (18,19,22).

Hence, patients with severe PPM may require a ViV procedure earlier after the initial AVR. Furthermore, as demonstrated in the present study and in the previous CoreValve registry (15), the presence of pre-existing severe PPM negatively affects hemodynamic, functional, and clinical outcomes after ViV. Surgeons should thus make a particular effort to implant a bioprosthetic valve with the largest possible EOA in relation to patient's body size to avoid PPM at the time of initial AVR. This goal may be achieved by using: 1) new generations of stented bioprosthetic valves implanted in a supra-annular position; 2) stentless or sutureless bioprostheses; and 3) aortic root enlargement to accommodate a larger bioprosthetic valve size. Given that transcatheter AVR is associated with less PPM compared with surgical AVR, especially in patients with small native aortic annuli (23,24), one may also consider performing transcatheter rather than surgical AVR at the time of initial AVR. Furthermore, ViV implantation in a failed THV is generally associated with lower residual gradients compared with ViV implantation in a failed surgical bioprosthesis.

The presence of pre-existing severe PPM should be systematically integrated in the pre-ViV implantation risk stratification process. Knowing the exact model and size of surgical bioprosthesis, one can easily obtain the normal reference value of EOA (12) and calculate the predicted indexed EOA to determine the presence and severity of pre-existing PPM. The results of our study suggest that it is preferable to use self-expanding THVs with supra-annular design rather than balloon-expandable THVs for ViV procedures in patients with pre-existing severe PPM (**Figure 2**). The development of new surgical bioprosthesis designs with an expandable stent may also help improve outcomes following ViV in the future, especially in patients with pre-existing severe PPM. For example, the INSPIRIS valve (Edwards Lifesciences), recently approved by the U.S. Food and Drug Administration, has an expandable stent frame, as well as fluoroscopically visible size markers, which may facilitate and optimize a future ViV procedure. Pending the introduction of these new valves specifically adapted for ViV implantation, an alternative in these patients would be to fracture the stent of the bioprosthesis by pre-dilation with an oversized noncompliant balloon. The procedure can be performed in small surgical bioprostheses to facilitate ViV implantation with either balloon-expandable or self-expanding THVs, potentially resulting in reduced residual transvalvular gradients (25). The risk-to-benefit ratio of this procedure should, however, be carefully assessed.

STUDY LIMITATIONS. We did not have systematic access to data after the initial surgical AVR that was performed at a median of almost a decade before ViV implantation. Therefore, to define PPM, we used the predicted indexed EOA (i.e., the normal reference value of EOA for the model and size of implanted bioprosthesis divided by the patient's body surface area [12,21]), as commonly performed. Several studies and meta-analyses have shown that predicted indexed EOA is a valid parameter to identify and quantify PPM and predict outcomes after AVR (16,17,26). In a recent study from the STS registry including >59,000 patients who underwent isolated surgical AVR, PPM defined on the basis of predicted indexed EOA was found to be a powerful independent predictor of mortality and cardiac rehospitalization (15). There were also several differences in the baseline characteristics between patients with versus without pre-existing severe PPM. We used height and weight measured at the time of the ViV procedure. Weight may have changed between the initial surgical AVR and the ViV procedure. However, this limitation is in part overcome by the fact that we used a definition of PPM that was adjusted for body mass index.

CONCLUSIONS

Pre-existing severe PPM of the failed surgical valve is strongly and independently associated with increased risk for 1-year mortality following aortic ViV implantation. Furthermore, it is associated with high rates of 30-day mortality and of elevated post-procedural transaortic gradients. The findings of this study further emphasize the extreme importance of avoiding severe PPM at the time of the index surgical AVR. These findings also support the systematic integration of the assessment of pre-existing PPM in the risk stratification and decision-making processes before ViV implantation. This can easily be achieved by calculating the predicted indexed EOA.

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PERSPECTIVES

WHAT IS KNOWN? The presence of severe PPM of the surgical valve (i.e., pre-existing PPM) is associated with worse outcomes after surgical AVR, including increased mortality. It may also accelerate the structural degeneration of bioprosthetic valves.

WHAT IS NEW? Patients with pre-existing severe PPM of the surgical bioprosthesis have higher occurrence of high residual transaortic gradients and increased risk for mortality after aortic ViV procedure.

WHAT IS NEXT? Pre-existing PPM of the surgical valve may compromise both hemodynamic and clinical outcomes after ViV implantation. Particular attention should be paid to the prevention of PPM at the time of the index surgical AVR. We suggest the systematic inclusion of severe pre-existing PPM assessment in ViV implantation risk stratification and decision making. Further research is needed to develop and validate new designs of surgical bioprosthetic valves with expansible or adjustable stents to optimize the hemodynamic and clinical outcomes of potential future ViV procedures.

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KEY WORDS **prosthesis-patient-mismatch, transcatheter aortic valve replacement, valve-in-valve**