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ORIGINAL RESEARCH

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ABSTRACT

Background: To evaluate the impact of various measurements of paravalvular regurgitation (PVR) on survival after transcatheter aortic valve replacement (TAVR). PVR can be difficult to grade and both its incidence and impact on survival may be decreasing as TAVR evolves.

Methods: This retrospective study included 911 patients undergoing TAVR in two institutions. PVR was graded according to the 3-grade scheme proposed by the guidelines (PVR grade), and subsequently grade 2 and 3, and grade 0 and 1 were lumped together. PVR was also graded as a composite score (PVR score), based on 6 commonly used metrics. PVR grade, PVR score and its six individual components were tested against the risk of both 1-year and longer term mortality after TAVR.

Results: Patients with moderate/severe PVR had a higher Society of Thoracic Sugeons (STS) score, higher levels of serum creatinine and larger left atria compared to patients with none/mild PVR. Moderate/severe PVR was more frequent with self-expandable and larger valves. After adjusting for American College of Cardiology (ACC) TAVR risk score, neither PVR grade, PVR score nor its six components were associated with an increased risk of mortality at 1-year (severe PVR adjusted HR: 0.75, 95% Confidence Interval [CI]: 0.19, 3.01, $p = 0.50$). However, intervention for clinically severe PVR increased the risk of mortality by more than 7-fold (adjusted hazard ratio [HR]: 7.6, 95% CI: 2.4, 23.5, $p < 0.0001$).

Conclusions: In the contemporary era, moderate-severe PVR is uncommon. However, re-intervention for PVR portends a poor prognosis. This highlights the crucial importance of clinical judgment over imaging alone.

Introduction

Transcatheter aortic valve replacement (TAVR) is now considered the standard of care for high-risk and inoperable patients with severe aortic stenosis (AS), and a valid option also for intermediate risk patients since studies comparing TAVR to surgery have demonstrated similar results in this group of patients.[1–3] Many of the feared complications that used to undermine the efficacy of this procedure have been significantly overcome by advances in valve sizing, valve design, smaller delivery systems and greater expertise of the "heart team." Among these, paravalvular regurgitation (PVR) has been shown to be an important complication of TAVR, associated with a 2- to 3-fold increase in mortality when judged severe.[4–6] However, a great variability in its incidence has been reported so far, varying from 0% to 24% for moderate/severe PVR and from 7% to 70% for mild PVR.[7,8] Such wide ranges could be due to: (1) the baseline risk profile of the populations, 2) the type of transcatheter heart valve (THV) used (first vs. second generation prostheses), (3) the method of assessment of PVR, (4) the parameters and criteria relied upon to grade PVR, (5) the type of grading (i.e. 3- vs. 4-class) scheme used to classify PVR severity,

and (6) the standardization of the assessment of PVR (i.e. site vs. core lab reported). Clinically, the echocardiographic assessment of PVR severity can be very challenging. Although cine magnetic resonance (CMR) imaging can be used to quantify PVR in situations where echocardiography is uncertain or conflicting, we sought to compare different echo parameters and grading schemes against outcomes instead. Thus, we tested both the guideline-recommended 3-class grading scheme (none/mild, moderate, and severe) and a composite PVR score and its individual components on the prediction of the survival of consecutive patients undergoing TAVR in our institutions.[9,10] The purpose of this retrospective study was, therefore, to evaluate the occurrence of PVR (both grade, score and its components) and analyze its role on 1-year and long-term survival after TAVR.

Materials and methods

Study design

We retrospectively examined 911 patients with severe symptomatic AS undergoing TAVR at Baylor Heart and Vascular

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🛈 Supplemental data for this article can be accessed here.

Hospital (Dallas, TX, USA) and The Heart Hospital Baylor Plano (Plano, TX, USA) from January 2012 to July 2016. Baseline demographics, echocardiographic and procedural data were retrospectively collected and analyzed. For the purpose of this analysis, data from both medical centers were pooled and a joint database was created. Only patients with complete echocardiographic information at baseline and post-TAVR were considered for this analysis. The severity of PVR was assessed before discharge. Echocardiographic adjudication of PVR severity was done by two imaging experts (P. G. and A.S.) who read all the echocardiographic exams from both centers. Primary outcome was all-cause mortality at 1-year follow-up, which was obtained through querying the National Death Index. As a secondary endpoint of interest, long–term mortality was also investigated. The study was approved by the Baylor Institutional Review Board.

Two-dimensional echocardiography

Transthoracic echocardiography was performed using a commercially available system (iE33 or Epiq, Koninklijke Philips Electronics N.V., Amsterdam, the Netherlands). Images of the standard parasternal and apical views were obtained with the patient in the left lateral decubitus position. Left ventricular (LV) dimensions and function, left atrium diameters were measured according to the current guidelines.[11] Aortic, mitral and tricuspid regurgitation were quantified according to the most recent guidelines.[12]

Using parasternal long- and short-axis, apical and three chamber views, the severity of PVR was graded according to a 6-metric system, derived from the one proposed by Pibarot et al in 2015.[9] The metrics included were: (1) number of jet(s), (2) jet path visible along the stent, (3) circumferential extension of PVR, (4) aortic regurgitation index (measured by echocardiography), (5) jet density at CW Doppler, (6) pressure half-time (PHT) (Figure 1 and Supplemental Table 1). All these metrics were derived from echocardiography. The aortic regurgitation index was derived according to the

following formula: [(DPB-LVEDP)/SBP] * 100, where DBP is the diastolic blood pressure, LVEDP is the left ventricle end-diastolic pressure obtained from the end-diastolic velocity of the CW Doppler through the PVR, applying the modified Bernoulli equation ($4v^2$) and SBP is the systolic blood pressure (Figure 2). Based on the characteristics of these six metrics, the PVR severity was graded as none/mild, moderate and severe (PVR grade), as suggested by the guidelines.[10] Additionally, by giving at each metric a specific numeric value, increasing with the severity of the PVR as reported in Supplemental Table 1, we were able to obtain a numerical score (PVR score). The PVR grade and score, as well as each of the six metrics were evaluated for their ability to predict the risk of 1-year and long-term mortality.

Statistical analysis

For simplicity, PVR severity was dichotomized (None+Mild vs. Moderate+Severe) to compare patient preoperative characteristics (Table 1) and procedural characteristics (Table 2). Within this dichotomy, unadjusted baseline data were reported and compared using mean(SD) and Wilcoxon rank sum tests (which are generally more conservative than t-tests for continuous variables) or frequency (%) and exact chi-squared tests. This dichotomization also helped avoid the loss of statistical power due to the low number of patients with severe PVR. To test differences in characteristics by dichotomized PVR severity, t-tests were conducted for continuous covariates, and chi-squared tests were conducted for categorical covariates.

For the primary analysis, we pre-specified five logistic regression models using 1-year mortality as the dependent (outcome) variable. We specified these five separate models in order to determine whether PVR grade, its six individual components, and/or PVR score played a significant role in predicting 1-year mortality after TAVR. The five models tested were: Model 1. Six metrics: The six separate PVR score metrics adjusted for TAVR risk score + any subsequent re-intervention /closure. Model 2. PVR score: PVR score adjusted for TAVR
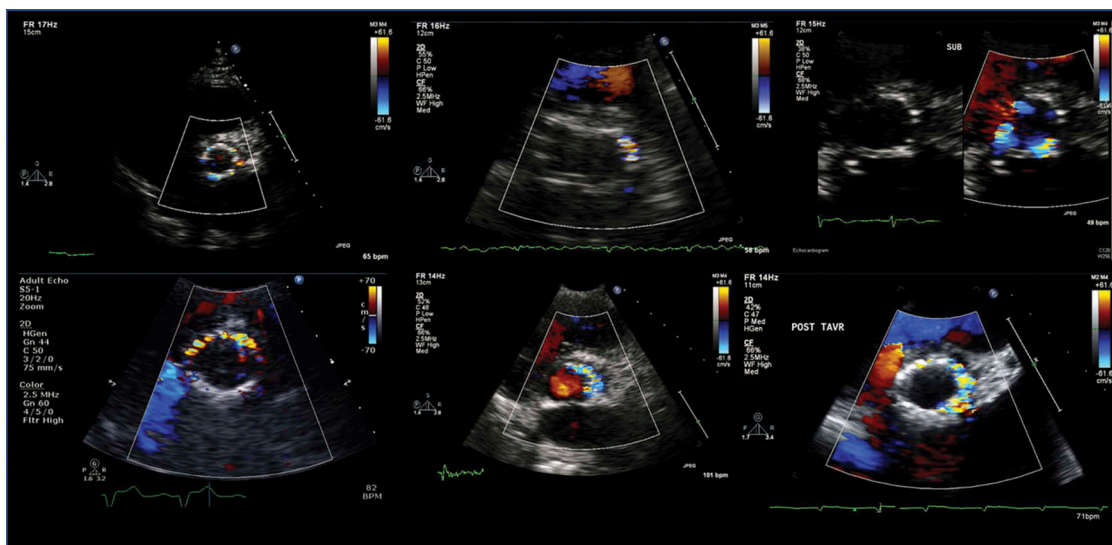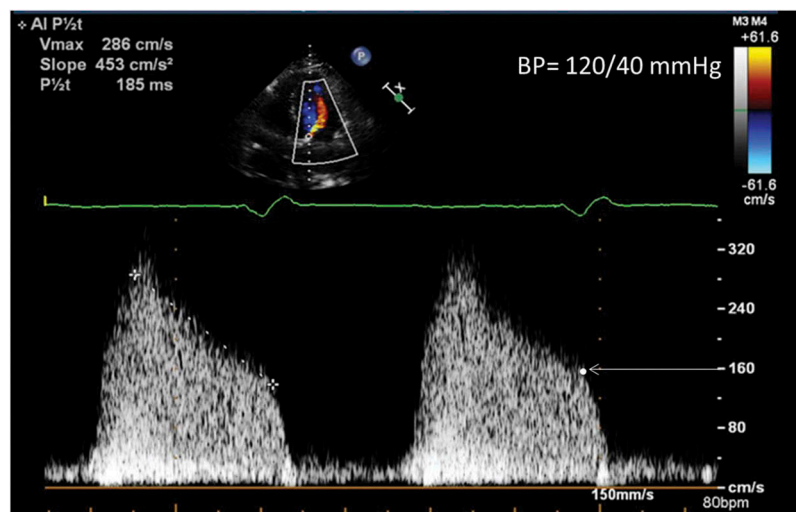

Figure 1. Circumferential extension of PVR. Examples of progressively higher circumferential extensions of the PVR.

Figure 2. Continuous-wave Doppler of PVR. Example of a continuous-wave Doppler through PVR and assessment of aortic regurgitation index.

risk score + any subsequent re-intervention/closure. Model 3. PVR grade: Traditional PVR grade adjusted for TAVR risk score + any subsequent re-intervention/closure. Model 4. 6 + PVR grade: The six separate PVR score metrics and traditional PVR grade adjusted for TAVR risk score + any subsequent re-intervention/closure. Model 5. TAVR: TAVR risk score only. Receiver Operating Characteristic (ROC) curves for each model were generated and compared using Model 5 as the reference and a significance level of $p < 0.05$. A ROC of 1 indicates a model that perfectly predicts 1-year mortality; whereas a ROC of 0.5 indicates a model with no predictive ability (i.e. the model does not predict 1-year mortality any better than a simple coin-flip). In all models, we treated the six PVR score metrics as continuous variables. Re-intervention /closure was dichotomized (yes/no), and PVR grade was categorized as None, Mild, Moderate, or Severe. In post-hoc sensitivity analyses, PVR grade dichotomization as none+mild versus moderate+severe (rather than four distinct categories) did not meaningfully change model results or interpretations.

We also conducted a secondary analysis using two separate Cox Regression models with time-to-death as the outcome to determine whether, after adjusting for TAVR score, either 1) PVR score, or 2) PVR grade were independent predictors of long-term mortality. Again, PVR score was treated as a continuous variable and PVR grade was used as a four-category variable. In order to avoid the introduction of "immortal-time" bias, patients who died prior to discharge were excluded from these analyses.

Results

Study population

A total of 911 patients undergoing TAVR between January 2012 and July 2016 had complete echocardiographic and survival data and were therefore included in this study. Table 1 displays the

baseline characteristics for the study population according to the post-TAVR PVR grade. Due to the extremely low incidence of severe PVR, grade 2 (moderate) and grade 3 (severe) were lumped together. Similarly, grade 0 (none) and grade 1 (Mild) were lumped together as there were no differences between them in baseline characteristics or outcomes. Therefore, the study population was stratified in two categories: None/Mild (n = 875, 96.1%) and Moderate/Severe (n = 36, 3.9%). The two groups were similar for baseline characteristics, although the group of patients with moderate/severe PVR displayed a higher Society of Thoracic Surgeons (STS) score and a higher serum creatinine level at baseline. Mean follow-up duration was 40.8 ± 13.9 months.

Baseline echocardiography

Patients with moderate/severe PVR had larger left atria at baseline echocardiography. The two groups were otherwise similar for the other echocardiographic characteristics. Figure 3 shows the incidence of moderate and severe PVR over the years and with the use of different prosthesis types.

Procedural characteristics

The occurrence of moderate/severe PVR was more frequent with self-expandable valves (Table 2 and Figure 3B) and with larger prostheses (Table 2). No differences in the incidence of PVR were found regarding the prostheses generation or the type of approach.

PVR and survival

As shown in Table 3, none of the five logistic regression models for prediction of 1-year mortality after TAVR (n = 71/911, 7.8%) was statistically significant. Although the

Table 1. Characteristics of the study population according to paravalvular regurgitation severity at discharge.

	Paravalvular regurgitation		
	None/mild (n = 875, 96.1%)	Moderate/ severe (n = 36, 3.9%)	p
Demographics			
Age, yrs	81.3 ± 8.0	82.6 ± 8.0	0.325
Female	410 (46.9)	14 (38.9)	0.348
Body mass index, kg/m^2	27.8 ± 6.7	26.8 ± 6.3	0.373
Body surface area, m^2	1.9 ± 0.25	1.9 ± 0.24	0.494
STS score, %	7.7 ± 4.3	9.6 ± 4.8	0.010
ACC TAVR risk score, %	4.8 ± 2.2	4.7 ± 1.6	0.744
Cardiac comorbidities			
Hypertension	757 (86.5)	29 (80.6)	0.309
Hyperlipidemia	657 (75.1)	26 (72.2)	0.697
Diabetes	347 (39.6)	12 (33.3)	0.738
Coronary artery disease	627 (71.7)	26 (72.2)	0.941
Peripheral artery disease	287 (32.8)	7 (19.4)	0.093
Atrial fibrillation	272 (31.1)	12 (33.3)	0.193
Previous CABG/PCI	424 (48.5)	19 (52.8)	0.611
Previous CVA	177 (20.2)	7 (19.4)	0.909
Permanent pacemaker	176 (20.3)	7 (20.6)	0.962
Non-cardiac comorbidities			
Chronic kidney disease	657 (75.1)	30 (83.3)	0.260
End stage renal disease	27 (3.1)	3 (8.3)	0.084
Serum creatinine, ml/L	1.34 ± 0.7	1.63 ± 0.8	0.026
COPD	198 (22.6)	4 (11.1)	0.103
On home oxygen	53 (6.1)	1 (2.8)	0.414
Myelodysplastic disease	26 (3.0)	1 (2.8)	0.946
Liver disease	15 (1.7)	1 (2.8)	0.634
Baseline echocardiographic findings			
LVEF, %	54.7 ± 13.0	52.8 ± 12.9	0.404
Stroke volume indexed, ml/beat/m^2	37.6 ± 12.0	36.1 ± 9.7	0.456
Aortic valve mean gradient, mmHg	44.5 ± 13.7	46.3 ± 14.5	0.444
Aortic valve area, cm^2	0.68 ± 0.18	0.65 ± 0.22	0.402
Bicuspid aortic valve, %	99/847 (11.3)	4/36 (11.1)	0.989
Aortic peak velocity, m/sec	4.3 ± 0.61	4.3 ± 0.69	0.725
Mitral valve mean gradient, mmHg	3.1 ± 2.1	3.4 ± 2.6	0.448
Mitral regurgitation ≥2+	153 (17.5)	7 (19.4)	0.762
Aortic regurgitation ≥2+	94 (10.7)	5 (13.9)	0.552
Tricuspid regurgitation ≥2+	104 (11.9)	8 (22.2)	0.064
Systolic pulmonary arterial pressure, mmHg	42.7 ± 14.5	43.6 ± 18.3	0.761
Left atrial volume, ml	82.7 ± 30.3	109.2 ± 47.9	<0.0001

Notes. Values are mean±SD, n (%).
CABG, coronary artery by-pass graft; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 2. Procedural characteristics.

	Paravalvular regurgitation		
	None/mild (n = 875, 96.1%)	Moderate/severe (n = 36, 3.9%)	p
Type of valve			<0.0001
Self-expandable	342 (39.1)	25 (69.4)	
Balloon –expandable	533 (60.9)	11 (30.6)	
Valve generation			0.657
First	590 (67.4)	23 (63.9)	
Second	285 (32.6)	13 (36.1)	
Valve size (mm)			<0.0001
20	13 (1.5)	0 (0)	
23	191 (21.9)	3 (8.3)	
25	12 (1.4)	2 (5.6)	
26	315 (36.1)	8 (22.2)	
27	12 (1.4)	0 (0)	
29	263 (30.2)	12 (33.3)	
31	62 (7.1)	11 (30.6)	
34	3 (0.3)	0 (0)	
Balloon pre-dilatation	599 (68.5)	20 (55.6)	0.102
Balloon post-dilatation	419 (47.9)	21 (58.3)	0.219
approach			0.177
Trans-femoral	769 (87.9)	36 (100)	
Trans-apical	69 (7.9)	0 (0)	
Trans-aortic	7 (0.8)	0 (0)	
Subclavian	30 (3.4)	0 (0)	

prediction of 1-year mortality. In all models, having a re-intervention/closure increased the risk of mortality by more than 7-fold over baseline risk (Table 3). We additionally tested the predictive role of PVR score and grade on long-term mortality (Table 4). As shown in Table 4, neither PVR grade nor PVR score were significant predictors of long-term mortality. Supplemental Table 4 reports detailed data about re-intervention in the 15 patients that required it.

Discussion

This large retrospective study demonstrated that in the current era, with the advances in valve sizing, implant techniques, prosthesis design and experience, the incidence of moderate/severe PVR is low (3.9%). Probably due to this low occurrence, our study did not find a link between significant PVR and 1-year or longer-term survival after TAVR. However, re-intervention for PVR closure, though uncommon (1.8%), significantly influences mortality.

PVR has been one of the most feared complications since the early phases of TAVR use. Over the years, a large body of literature has been published on this topic, showing somewhat different results. Early reports showed a prevalence of significant PVR in the range of 20%, with a 2- to 3-fold increase in mortality for severe PVR.[4,6,8,13,14] Differences in the grading of the PVR, as well as the high risk profile of earlier TAVR populations and in the type of transcatheter heart valve (THV) used might be responsible for the observed discrepancies in the incidence and impact on survival of PVR in the various studies.[4,8] In addition, early TAVR experiences were based on

model including the six metrics +PVR grade (Model 4) had a higher ROC (0.69 vs. 0.62) than case mix adjustment alone, it, nor any of the other models, was able to add significant predictive utility at the $p < 0.05$ significance level for 1-year mortality versus simple TAVR risk score alone (Figure 4 and Supplemental Table 3). However, PVR characteristics and grading exhibited a non-significant trend ($p = 0.06$) for
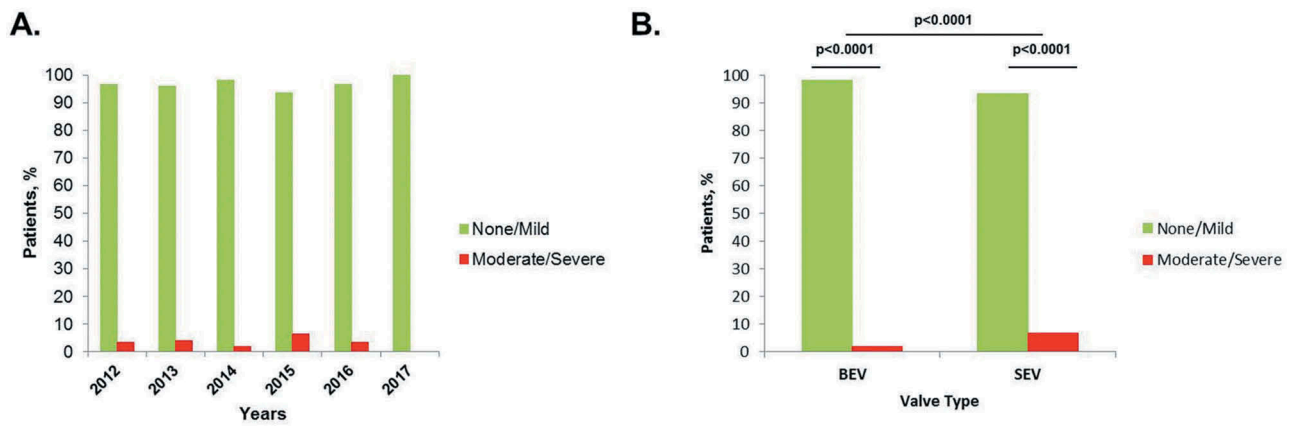
Figure 3. PVR characteristics. (A) PVR incidence over the years. (B) Differential incidence of PVR according to the device type.

Table 3. Logistic Regression models for the prediction of 1-year mortality.

Characteristic at discharge:	Odds Ratio (95% CI)	p-value
Model 1		
N regurg jet S	0.53 (0.25, 1.13)*	0.10
Jet visible	1.62 (0.48, 5.44)*	0.44
Circumferential extension	1.40 (0.73, 2.68)*	0.31
Aortic regurg index score	1.18 (0.72, 1.92)*	0.51
Jet density	0.52 (0.23, 1.21)*	0.13
PHT score	1.12 (0.44, 1.86)*	0.81
Reintervention/closure	11.9 (3.6, 39.5)	<0.0001
Model 2		
PVR score	1.00 (0.93, 1.08)	0.97
Reintervention/closure	7.6 (2.4, 23.5)	<0.0001
Model 3		
PVR grade		0.50
None	Reference	<0.0001
Mild	0.72 (0.30, 1.72)	
Moderate	1.32 (0.77, 2.27)	
Severe	0.75 (0.19, 3.01)	
Reintervention/closure	8.3 (2.5, 27.8)	
Model 4		
N regurg jet S	0.52 (0.24, 1.11)*	0.09
Jet visible	1.28 (0.35, 4.67)*	0.71
Circumferential extension	1.27 (0.53, 2.56)*	0.50
Aortic regurg index score	1.20 (0.82, 1.75)*	0.35
Jet density	0.49 (0.21, 1.12)*	0.09
PHT score	1.11 (0.44, 1.83)*	0.83
PVR grade		0.60
None	Reference**	<0.0001
Mild	<0.01 (<0.01, >99.9)**	
Moderate	<0.01 (<0.01, >99.9)**	
Severe	<0.01 (<0.01, >99.9)**	
Reintervention/closure	10.9 (3.2, 37.6)	

Notes. *Odds Ratio and 95% Confidence Interval for each 1-point increase in each metric: (i.e. OR for 1 vs. 0; 2 vs. 1; 3 vs. 2).
**Due to high correlation between covariates, model estimates for PVR grade are extremely wide.
PHT, pressure half-time; PVR, paravalular regurgitation.

echocardiographic sizing of the prosthesis, which could have increased the incidence of significant PVR compared to the current standard of MDCT sizing.[1] Indeed, a huge effort has been put in the development of a unifying
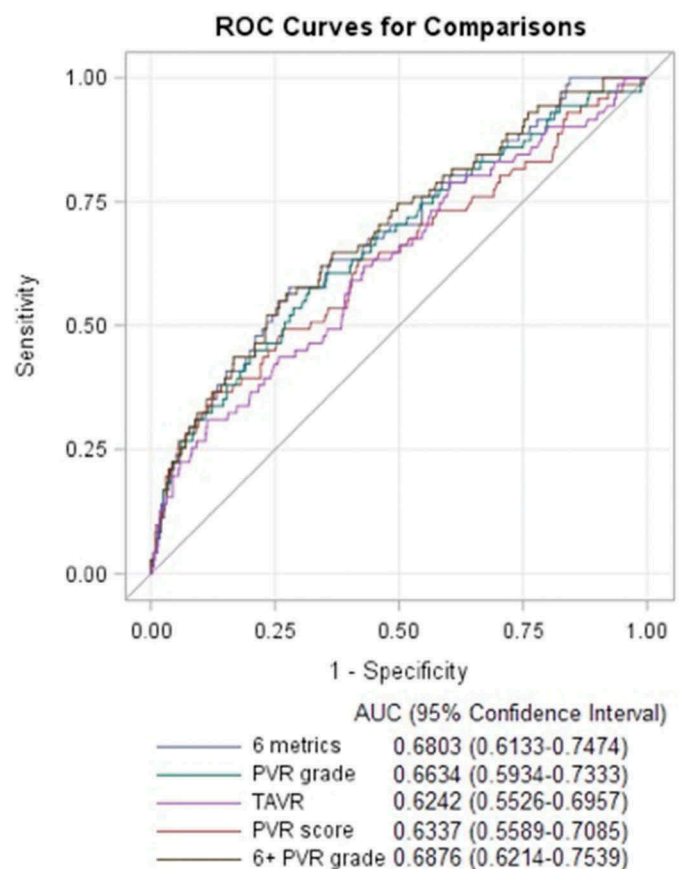

Figure 4. ROC curves comparison. ROC curves comparison relative to the five models tested for the prediction of 1-year mortality.

Table 4. TAVR risk-adjusted long-term mortality.

Characteristic at discharge:	Hazard Ratio (95% CI)	p-value
PVR score*	0.99 (0.93, 1.05)	0.70
PVR grade*		0.81
None	Reference	
Mild	0.83 (0.43, 1.60)	
Moderate	0.95 (0.62, 1.47)	
Severe	1.40 (0.56, 3.51)	

Notes. *Adjusted for TAVR risk score.
TAVR, transcatheter aortic valve replacement; PVR, paravalvular regurgitation.

grading system for PVR. Unlike native aortic regurgitation, the quantification of PVR is notably challenging. Shadowing artifact from the prosthesis together with an off-axis cut plane of the ultrasound beam might influence significantly how PVR is graded.[9] In this study we sought to investigate the role of PVR on 1-year and long-term survival after TAVR, by using two methods of PVR grading; the first, PVR grade, based on the 3-grade scheme suggested by the actual guidelines, and a second, PVR score, based on an adapted version of the scoring system proposed by Pibarot et al in 2015.[9] Moderate and severe PVR were subsequently lumped together given the paucity of patients in the severe group (n = 2). PVR was also graded based on six individual metrics, all of which are derived non-invasively through echocardiography (Supplemental Table 1). The results of this study show that, in the current era, the cumulative incidence of significant (moderate/severe) PVR is low and that none of the PVR parameters, nor the grade nor the score exerted a statistically significant impact on survival. However, our results might have been masked by some factors, notably limited statistical power; only two patients out of 911 had severe PVR. While this reflects excellent results in the current era, it is too small a sample size to exclude the possibility that severe, but not moderate PVR is a predictor of outcomes. In this regard, it is worth mentioning that, in our centers, valve sizing is based on MDCT which could account for a better sizing algorithm compared to echocardiography, and in turn could have led to a lower incidence of significant PVR. Second, when the PVR was judged as clinically severe after the implant, our heart team tended toward prompt intervention. Therefore, such patients would not be classified as severe PVR on a discharge echocardiogram because it had already been alleviated. Indeed, as demonstrated in Table 3, patients undergoing a re-intervention or closure of a leak experienced a 7-fold higher mortality at 1-year after TAVR. As to why these patients had a bad prognosis, despite early correction of severe PVR remains an open question. It is tempting to speculate that their baseline risk profile was higher or the post-TAVR hemodynamic deterioration that prompted intervention resulted in poor long-term outcomes. However, given the low number of patients undergoing re-intervention for severe PVR, it was not possible to perform any meaningful statistical analysis. Secondly, it has to be acknowledged that echocardiography is limited in assessing PVR, due to the frequent observation of the multiple, irregular, and eccentric paravalvular jets and to the difficulties in measuring or unreliability of the quantitative and semiquantitative parameters proposed in the American Society of Echocardiography/European Association of Echocardiography guidelines (vena contracta width, jet width to LVOT diameter ratio, pressure half-time of the continuous wave Doppler aortic regurgitant envelope) post-TAVR. This is mainly due to the acute nature of the regurgitation and the reduced compliance of the LV. As demonstrated by cardiac magnetic resonance (CMR) studies, there is indeed, a great discrepancy between various echocardiographic grading parameters and the regurgitant

fraction as measured by CMR.[15–17] For this reason, we chose to compare various PVR grading parameters to outcomes rather than to an independent quantitative reference standard. Finally, we did not include holodiastolic flow reversal in the descending aorta because it was rarely seen in our population and has been shown to occur even in the absence of aortic regurgitation.[18,19] This parameter is, indeed, influenced by LV and aortic compliance. In particular, low transvalvular end-diastolic aorta to LV pressure gradient that is due to concomitant moderate/severe LV diastolic dysfunction may lead to false-positive results. The high dependency of aortic flow reversal on aortic compliance considerably limits the utility of this parameter in the elderly population undergoing TAVR.[9,18]

The very low incidence of PVR in our study might be the result of the improvement in TAVR valve-sizing and the technical experience of the heart team, which, in turn could explain why we did not find any impact of PVR on 1-year survival. Consistently, even when looking at longer-term survival, PVR was not found to be a predictor of mortality when adjusted for TAVR risk score. In conclusion, this study shows the occurrence and the prognostic role of PVR in a real world scenario. Independently of how PVR is graded, it does not seem to be linked to long-term survival after TAVR. However, it has to be acknowledged that the extremely low incidence of significant PVR in our population might have masked its own impact on survival. Our results are, indeed, in contrast with previous studies showing that PVR was linked to a 2- to 3-fold increase in mortality at 1-year after TAVR and this could be explained by the fact that we registered only a 4% incidence in significant PVR.

Finally, when the heart team performs an early re-intervention for PVR, it portends a bad prognosis.

Conclusion

Clinical competencies

This study might have important implications for current clinical practice. The assessment of PVR on echocardiography might be misleading whereas clinical judgment needs to be advocated when considering the severity of PVR. In the current era, the occurrence of significant PVR is extremely rare and so is the mortality risk connected to this problem.

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Disclosure statement

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