Supplementary Online Content

Pibarot P, Hahn RT, Weissman NJ, et al. Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve . *JAMA Cardiol*. Published online September 27, 2017. doi:10.1001/jamacardio.2017.3425

This supplementary material has been provided by the authors to give readers additional information about their work.

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ADDITIONAL CONTENT - METHODS

Pre-procedural THV sizing

Pre-procedural sizing was performed on the basis of measurements of annular area from multi-slice computed tomography or 3D transesophageal echocardiography with the optimal oversizing being 5-10% by area. This measurement was assessed by the core laboratories only for the intermediate-risk cohort; the percentage of valve oversizing is thus reported only for this group.

Multi-Parameter Approach to Grade PVR severity

In the multi-parameter integrative approach to grade PVR severity, we relied more heavily on the width at the origin, the circumferential extent, the features, and the number of PVR jet(s), assessed visually in multiple views ***(Online Table 1)***. The other parameters including jet deceleration time, diastolic flow reversal in descending aorta and regurgitant volume and fraction estimated from the difference of left ventricular minus right ventricular stroke volumes, were used to corroborate the PVR grading or to discriminate cases that were borderline between 2 classes.

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eTable 1: Parameters and Criteria for Grading the Severity of Paravalvular Regurgitation

3-CLASS GRADING SCHEME	**TRACE**	**MILD**		**MODERATE**		**SEVERE**
5-CLASS GRADING SCHEME	**TRACE**	**MILD**	**MILD-TO-MODERATE**	**MODERATE**	**MODERATE-TO-SEVERE**	**SEVERE**
Structural Parameters ● Valve stent	Usually normal	Usually normal	Normal/ abnormal†	Normal/ abnormal†	Usually abnormal†	Usually abnormal†
Doppler parameters (qualitative or semi-quantitative)						
● Jet features Extensive/wide jet origin Multiple jets Jet path visible along the stent Proximal Flow convergence visible	 Absent Possible Absent Absent	 Absent Possible Absent Absent	 Absent Often present Possible Absent	 Present Often present Often present Possible	 Present Usually present Usually present Often present	 Present Usually present Present Often present
● Jet width at its origin (%LVOT diameter): color Doppler	Narrow (<5)	Narrow (5-15)	Intermediate (15-30)	Intermediate (30-45)	Large (45-60)	Large (>60)
○ Jet deceleration rate (PHT, ms): CW Doppler	Slow (>500)	Slow (>500)	Slow (>500)	Variable (200-500)	Variable (200-500)	Steep (<200)
○ Diastolic flow reversal in the descending aorta: PW Doppler	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (EVD>20 cm/s)	Holodiastolic (EDV>25 cm/s)
● Circumferential extent of PVR (%): color Doppler	<10	<10	10-20	20-30	>30	>30
Doppler parameters (quantitative)						
○ Regurgitant fraction (%)	<15	<15	15-30	30-40	40-50	>50

Legend: Th 5-class scheme divides mild PVR (in 3-class) into 2 separate grades of mild and mild-to-moderate, and divides moderate PVR (in 3-class)into 2 separate grades of moderate and moderate-to-severe. The visual assessment of: i) the width of the PVR jet(s) at its origin in multiple views and multiple planes, ii) the circumferencial extent the PVR jet(s) in multiple planes of the parasternal short-axis views, ii) the identification of features of significant PVR (presence of multiple jets or jets with a path clearly visiblealong the stent, or the presence of a proximal flow convergence remains the most important and also the most often applicable parameters to grade PVR. The other parameters including the pressure half time, the flow reversal in the descending aorta, the regurgitant fraction (estimated from the difference of LV outflow and RV outflow stroke volumes) are additional parameters that may be useful to corroborate PVR severity.

● Parameters that are most frequently applicable and used to grade PVR severity by echocardiography. ○ Parameters that are less often applicable due to pitfalls in the feasibility/accuracy of the measurements and/or to the interaction with other factors. † Abnormalities of stent position (too low or too high),

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deployment, and/or circularity. CW denotes continuous wave, EDV, end-diastolic velocity, LVOT: left ventricular outflow tract, PHT, pressure half time, PVR: paravalvular regurgitation, PW: pulsed wave.

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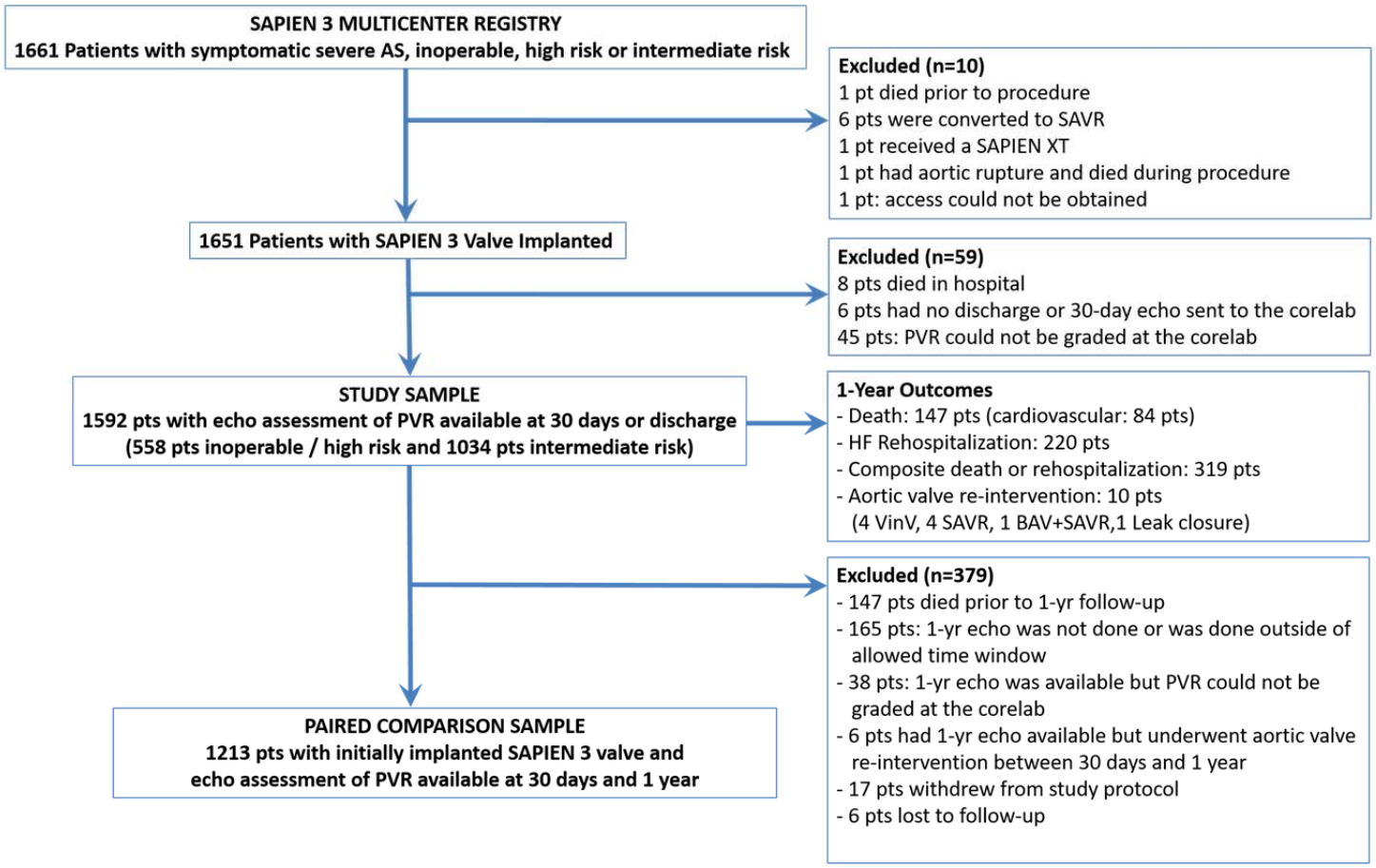
eFigure 1: Study Flow Chart



Legend: AS: aortic stenosis; BAV: balloon aortic valvuloplasty; HF: heart failure; Pt / Pts: patient / patients; PVR: paravalvular regurgitation; SAVR: surgical aortic valve replacement; VinV: valve-in-valve.

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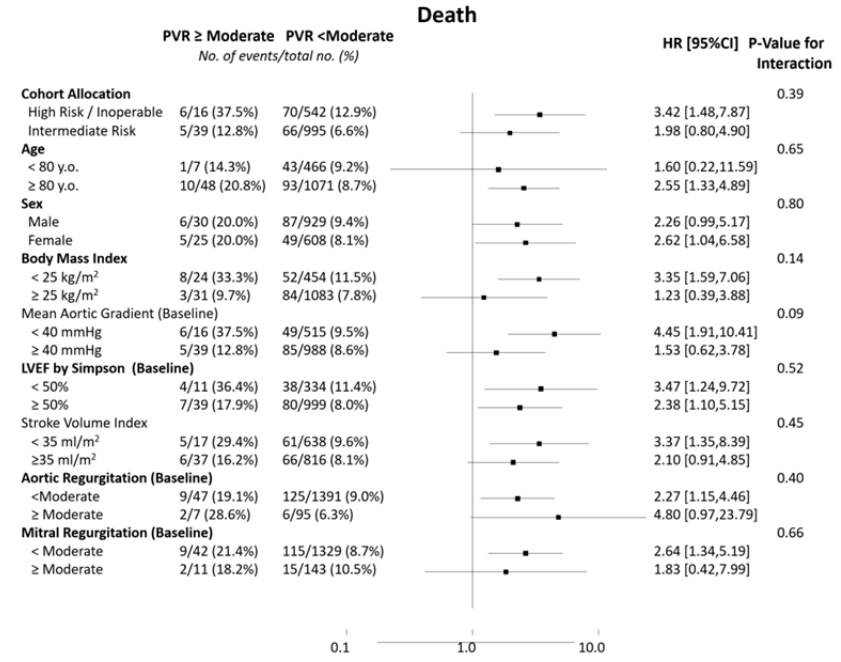
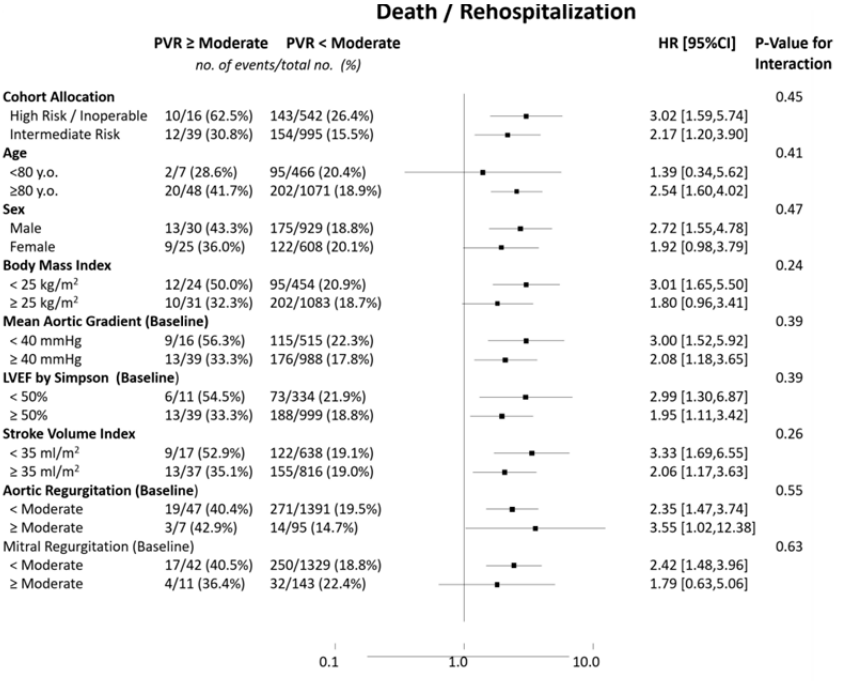
eFigure 2: Subgroup analyses of the effect of ≥ moderate PVR at 30 days on 1-year outcomes

A



B



Legend: Hazard ratios and 95% confidence intervals are shown for all-cause death (Panel A) and composite of death and re-hospitalization (Panel B) at 1 year according to presence of absence of

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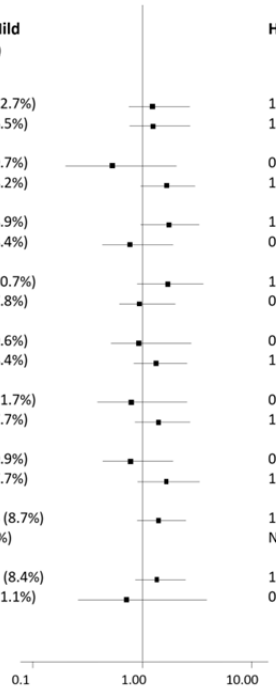
≥ moderate PVR at 30 days. The P value for interaction represents the likelihood of an interaction between the variable and the effect of ≥ moderate PVR.

eFigure 3: Subgroup analyses of the effect of mild and mild-to-moderate PVR at 30 days on 1-year outcomes

A

Death

	PVR Mild-Mod	PVR ≤ Mild	HR [95%CI]	P-Value for Interaction
	No. of events/total no. (%)			
Cohort Allocation				0.98
High Risk / Inoperable	7/45 (15.6%)	63/497 (12.7%)	1.24 [0.57,2.70]	
Intermediate Risk	7/86 (8.1%)	59/909 (6.5%)	1.25 [0.57,2.74]	
Age				0.09
< 80 y.o.	1/35 (2.9%)	42/431 (9.7%)	0.28 [0.04,2.06]	
≥ 80 y.o.	13/96 (13.5%)	80/975 (8.2%)	1.67 [0.93,3.00]	
Sex				0.11
Male	11/71 (15.5%)	76/858 (8.9%)	1.75 [0.93,3.30]	
Female	3/60 (5.0%)	46/548 (8.4%)	0.59 [0.18,1.91]	
Body Mass Index				0.25
< 25 kg/m^2	8/44 (18.2%)	44/410 (10.7%)	1.70 [0.80,3.61]	
≥ 25 kg/m^2	6/87 (6.9%)	78/996 (7.8%)	0.88 [0.38,2.01]	
Mean Aortic Gradient (Baseline)				0.53
< 40 mmHg	3/35 (8.6%)	46/480 (9.6%)	0.87 [0.27,2.79]	
≥ 40 mmHg	10/91 (11.0%)	75/897 (8.4%)	1.33 [0.69,2.57]	
LVEF by Simpson (Baseline)				0.30
< 50%	2/27 (7.4%)	36/307 (11.7%)	0.62 [0.15,2.57]	
≥ 50%	10/93 (10.8%)	70/906 (7.7%)	1.41 [0.72,2.73]	
Stroke Volume Index				0.14
< 35 ml/m^2	3/50 (6.0%)	58/588 (9.9%)	0.60 [0.19,1.92]	
≥ 35 ml/m^2	9/72 (12.5%)	57/744 (7.7%)	1.65 [0.82,3.34]	
Aortic Regurgitation (Baseline)				0.98
< Moderate	13/107 (12.1%)	112/1284 (8.7%)	1.41 [0.79,2.50]	
≥ Moderate	0/19 (0.0%)	6/76 (7.9%)	N/A	
Mitral Regurgitation (Baseline)				0.36
< Moderate	12/106 (11.3%)	103/1223 (8.4%)	1.36 [0.75,2.46]	
≥ Moderate	1/17 (5.9%)	14/126 (11.1%)	0.51 [0.07,3.88]	



B

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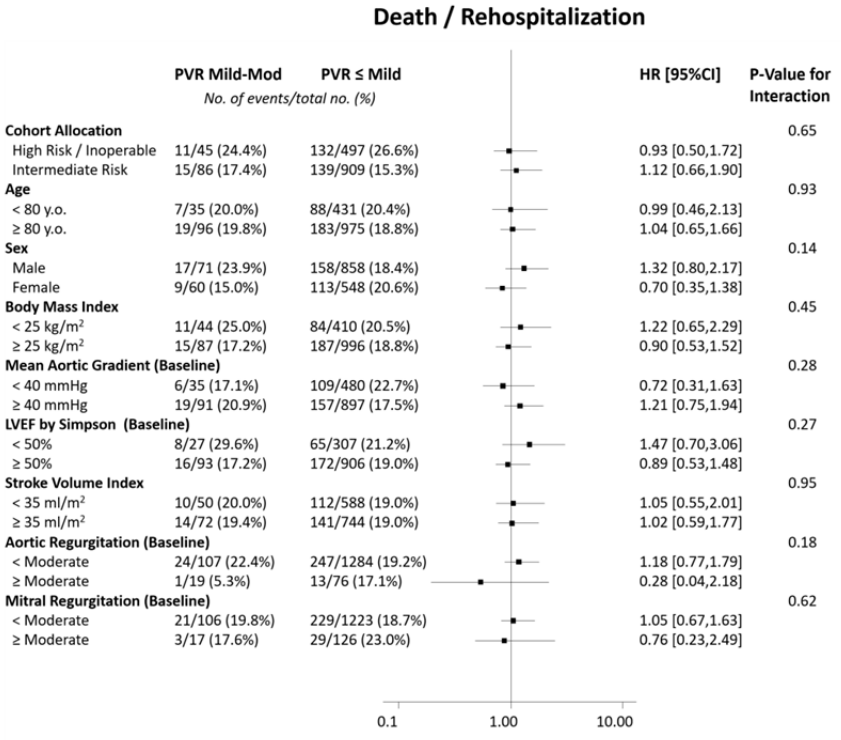

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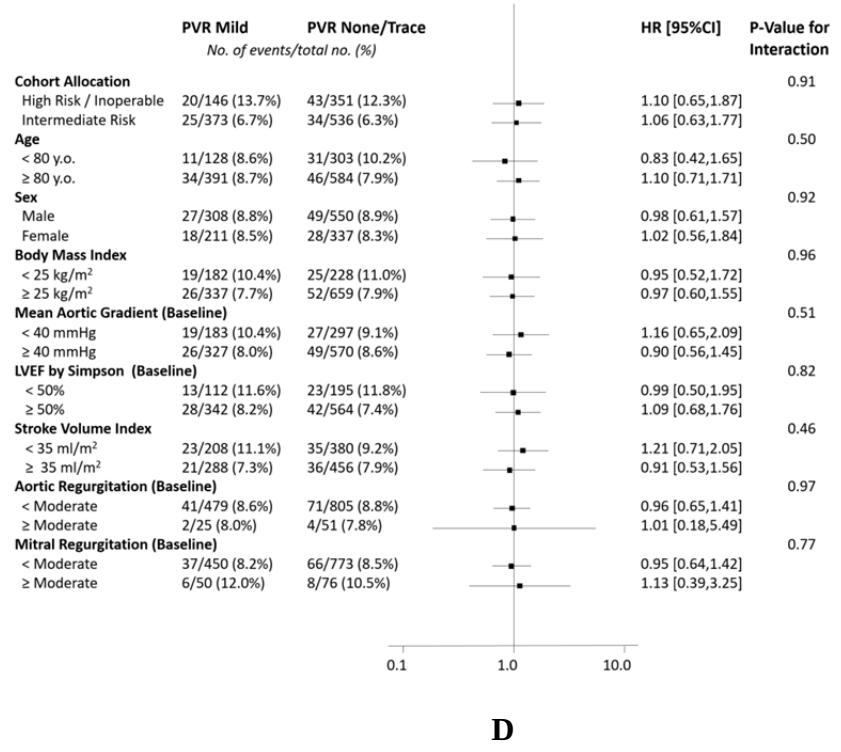

D

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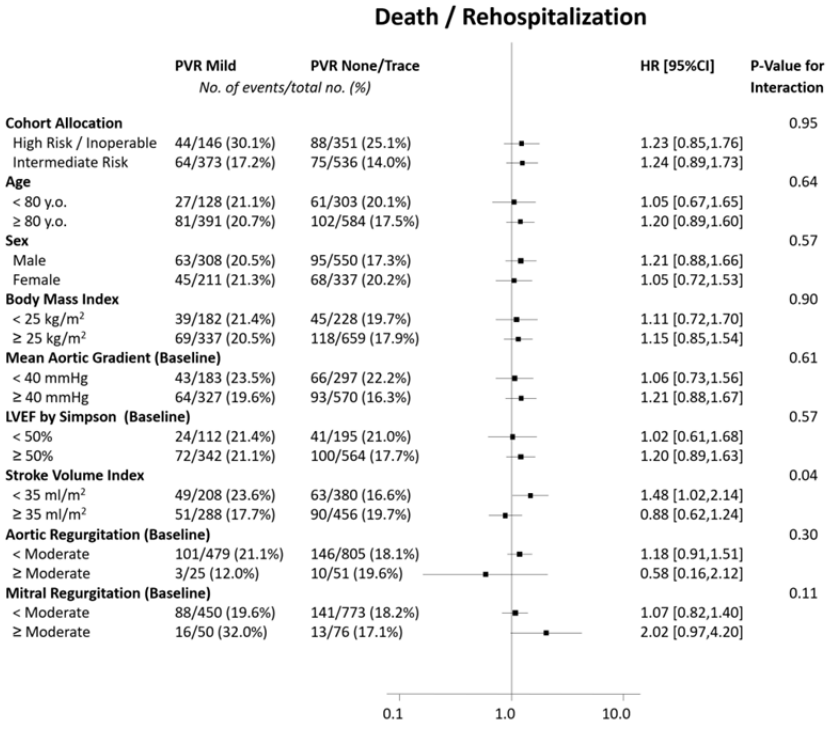

Legend: Hazard ratios and 95% confidence intervals are shown for mild-to-moderate vs. ≤ mild PVR (Panels A and B) and for mild vs. none/trace PVR (Panels C and D). Panels A and C present all-cause death and B and D present composite of death and re-hospitalization.

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ADDITIONAL CONTENT - RESULTS

Inter-Core Laboratory Variability Analysis

In the inter-core laboratory variability analysis that included 64 echocardiograms, the percentage of agreement for PVR grading in the 5-class scheme was 88% between Laboratories A and B, 75% between Laboratories A and C, and 75% between Laboratories B and C. When collapsed into the 3-class scheme, the percentage of agreement was: 91%, 78%, and 81%, respectively. The vast majority of the disagreement in PVR grading were between trace, mild, and mild-to-moderate classes and were generally of one-class difference. One patient was graded >moderate by one laboratory but <moderate by the 2 other laboratories.

Association Between Changes in PVR and Changes in Heart rate, Blood pressure, and Medications

There was no significant difference in 30-day, 1-year, or 30 days to 1 year changes in blood pressure or medications between the patients (n=24) with ≥ moderate PVR at 30 days who decreased to < moderate PVR at 1 year versus those (n=9) who remained moderate at 1 year. Heart rate, however, decreased significantly in patients who experienced a reduction in PVR, (p=0.04) whereas it remained stable in those who had no change in PVR. These results thus do not support the fact that changes in hemodynamics or loading conditions were the main factors responsible for the change in PVR severity in this subset of 24 patients. These results are based on a small number of patients and should thus be interpreted cautiously.

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