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Impact of Mild Paravalvular Regurgitation on Long-Term Clinical Outcomes After Transcatheter Aortic Valve Implantation

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The impact of mild paravalvular regurgitation (PVR) after transcatheter aortic valve implantation (TAVI) remains controversial. We evaluated the impact of mild PVR after TAVI on long-term clinical outcomes. We included patients who underwent TAVI for severe symptomatic aortic stenosis between December 2008 and June 2019 at 2 international centers and compared all-cause death between the group with mild PVR (group 1) and the group with none or trace PVR (group 2). PVR was categorized using a 3-class grading scheme, and patients with PVR ≧ moderate and those who were lost to follow-up were excluded. This retrospective analysis included 1,404 patients (mean age 81.7 ± 6.5 years, 58.0% women). Three hundred fifty eight patients (25.5%) were classified into group 1 and 1,046 patients (74.5%) into group 2. At baseline, group 1 was older and had a lower body mass index, worse co-morbidities, and more severe aortic stenosis. To account for these differences, propensity score matching was performed, resulting in 332 matched pairs. Within these matched groups, during a mean follow-up of 3.2 years, group 1 had a significantly lower survival rate at 5 years (group 1: 62.0% vs group 2: 68.0%, log-rank p = 0.029, hazard ratio: 1.41 [95% confidence interval: 1.04 to 1.91]). In the matched cohort, patients with mild PVR had a significant 1.4-fold increased risk of mortality at 5 years after TAVI compared with those with none or trace PVR. Further studies with more patients are needed to evaluate the impact of longer-term outcomes. **© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)** **(Am J Cardiol 2023;191:14−22)**

Abbreviations: AS, Aortic stenosis; PVR, paravalvular regurgitation; TAVI, Transcatheter aortic valve implantation

Postoperative paravalvular regurgitation (PVR) is an important complication after transcatheter aortic valve implantation (TAVI) and is associated with increased mortality.[1,2] The impact of PVR ≧ moderate after TAVI on clinical outcomes has been debated. PVR ≧ moderate occurs in 5% to 25% of patients after TAVI and is associated with a twofold to threefold increased risk of mortality.[3−5] However, at present, PVR ≧ moderate rarely occurs after this procedure along with the improvements in valve design, for example, external sealing skirts and repositionability, and increasing operator experience.[6] Although the prevalence of mild PVR ranges from 30% to 41% after TAVI using current generation valves and implantation techniques,[7−9] it is still markedly higher than that after surgical aortic valve replacement (SAVR) reported in some clinical trials (3% to 20%).[10,11] The application of TAVI has been expanded to a younger population as a first-line therapeutic approach for patients with severe aortic stenosis (AS)[12]; therefore, it is important to clarify the long-term effect of mild PVR in a clinical setting. Studies in the short-term effect of mild PVR have presented conflicting results,[1−3,13,14] and long-term data related to mild PVR remain scarce. Some reports have shown that mild PVR is associated with an increased risk of mortality at 5 years after the procedure.[6,15] In this study, we aimed to assess the effect of mild PVR after TAVI on 5-year mortality using an international TAVI registry with a propensity-score matching method.

Methods

The international TAVI registry (UMIN-CTR, Identifier: UMIN000040413, https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000046115) includes retro- and prospectively collected data from patients who were consecutive and unselected and who underwent TAVI for severe AS or degenerated surgical aortic valves at 2 centers: Shonan Kamakura General Hospital in Japan and Helsinki University Central Hospital in Finland. The study cohort for this retrospective analysis comprised patients with

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severe AS who underwent TAVI between December 2008 and June 2019. Patients with PVR ≧ moderate were excluded from the analysis, as were those without information regarding PVR or follow-up.

Data were retro- and prospectively collected using a dedicated electronic case report form by cardiologists, cardiac surgeons, and trained research nurses. The data were checked for completeness and quality. The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the institutional clinical research and ethics committee.

Preprocedural planning was based on multidetector computed tomography. A local heart team evaluated all patients for eligibility for TAVI according to the recommendations.[16] During the study period at both centers, the TAVI procedure was mainly performed using a transfemoral approach with general or conscious sedation at the discretion of the operators, using either a self-expanding transcatheter heart valve (THV) (Corevalve, Evolut R, and Evolut Pro; Medtronic Inc.; ACURATE neo; Boston Scientific, Marlborough, Massachusetts; Allegra; Biosensors, Singapore and New Valve Technology, Hechingen, Germany, Portico; Abbott Vascular, Santa Clara, California), balloon-expanding THV (Sapien, Sapien XT, Sapien 3, and SAPIEN 3 ultra; Edwards Lifesciences, Irvine, California), or mechanically expanding THV (Lotus; Boston Scientific).

All echocardiographic assessments were performed on the basis of standard practice and were site reported. We collected transthoracic echocardiographic (TTE) measurements at baseline, after the procedure before discharge, and at 1 or 3 months and 1 year after the procedure. Independent echocardiographers assessed PVR according to the Valve Academic Research Consortium−2 criteria[17]; therefore, PVR was categorized as none/trace, mild, moderate, or severe (3-class grading scheme).

The outcomes of this study were 1- and 5-year mortality rates in the overall cohort and in the matched cohort, comparing patients with mild PVR at discharge with those with none or trace PVR at discharge. As a subanalysis, 5-year mortality was also evaluated according to the THV generation and THV type in the unmatched population.

Data on the date and cause of death were obtained from the National Registry Statistics Finland, which is based on death certificates reviewed by local and central authorities. All data were retrospectively collected by reviewing medical records and by means of telephone calls in Japan.

All adverse events were based on the Valve Academic Research Consortium−2 criteria.[17]

All the data were collected from a collaborative registry database. Continuous variables are presented as mean ± SD. The Shapiro−Wilk test was used to assess data normality. Categorical variables are presented as numbers and percentages, and Fisher's exact test was used to compare the data between the groups. For continuous variables, differences between groups were assessed using the Mann−Whitney *U* test. Kaplan−Meier analysis was performed using the log-rank test to compare the end points between the groups, and landmark analysis at 1 year was also done. A propensity score was calculated for each patient to estimate their tendency to belong to a PVR grade (mild vs none or trace). This was done by means of multivariable logistic regression including the following covariates: demographics (age, gender, body mass index, New York Heart Association functional class III or IV, Society of Thoracic Surgeons score, treatment in Japan), co-morbidities (hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, peripheral artery disease, previous percutaneous coronary intervention, previous coronary artery bypass graft, previous stroke, right bundle branch block, left bundle branch block, atrial fibrillation, previous pacemaker implantation), and laboratory data (estimated glomerular filtration rate, hemoglobin concentration, platelet count, left ventricular ejection fraction, aortic valve area, peak aortic valve velocity, mean aortic valve pressure gradient). Patients were matched on the logit of the propensity score using 1:1 optimal matching with a caliper width of 0.2 of

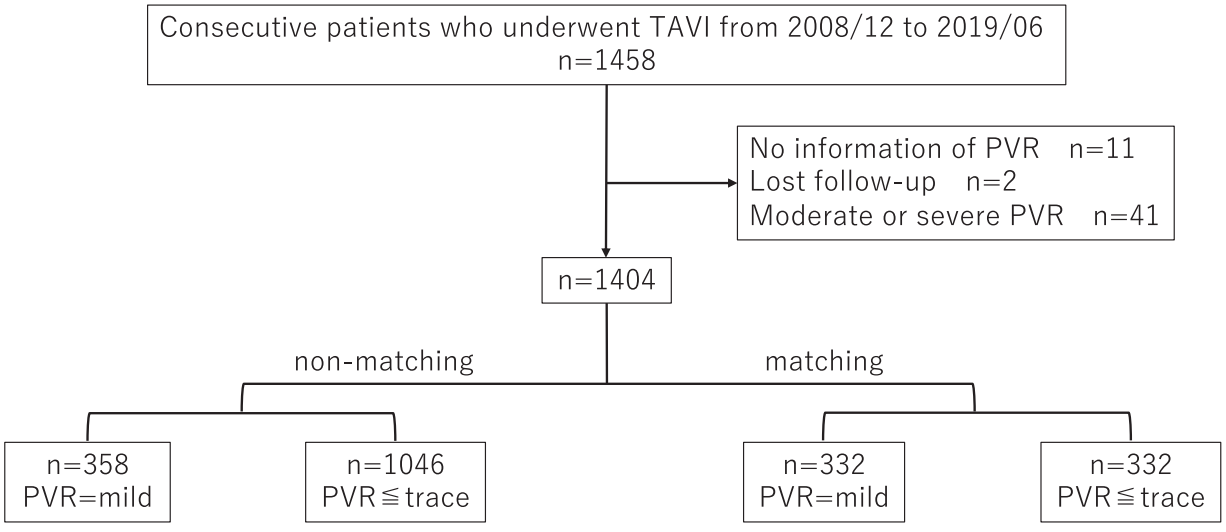

Figure 1. Flowchart of the study population.

the SD of the logit. An absolute standardized difference <0.2 was accepted as reflective of adequate matching between the comparator groups. To evaluate the serial change in PVR grade along with the progression of TAVI devices, we divided the study period into quartiles and investigated the severity of PVR. To analyze hazard estimates of mortality, we used Cox proportionate hazard models. The first generation of THV was defined as Sapien, Sapien XT, CoreValve, and ACURATE neo, whereas the subsequent generation of THV was defined as other THVs. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using EZR version 1.55 (Jichi Medical University, Saitama, Japan).

Results

Of 1,458 consecutive patients with AS who underwent TAVI between December 2008 and June 2019, 11, 2, and 41 patients were excluded because they lacked information on PVR (0.25%), were lost to follow-up (0.14%), and had PVR ≧ moderate (2.8%), respectively. Therefore, the data of 1,404 patients (mean age 81.7 ± 6.5 years, 58.0% women), including 1,046 (74.5%) with none or trace PVR and 358 (25.5%) with mild PVR, were analyzed (Figure 1).

Table 1 shows the baseline patient characteristics. Patients with mild PVR were older than those with none or trace PVR, had a lower body mass index, and had a higher prevalence of previous coronary artery bypass graft and left bundle branch block ($p = 0.032$, $p = 0.023$, $p = 0.03$, and $p = 0.016$, respectively). Moreover, patients with mild PVR had more severe AS on baseline TTE (aortic valve area: 0.64 ± 0.18 cm^2 vs 0.67 ± 0.19 cm^2, $p = 0.006$; peak aortic valve velocity: 4.43 ± 0.75 m/s vs 4.29 ± 0.72 m/s, $p = 0.002$; mean aortic valve pressure gradient: 47.8 ± 16.5 mm Hg vs 45.7 ± 15.2 mm Hg, $p = 0.025$).

In the matched cohort, the data of 664 patients (mean age 82.4 ± 6.5 years, 57.4% women, 332 pairs) were analyzed (Figure 1). There were no significant differences

Table 1
Baseline characteristics

	Unmatched				Matched				
	Overall	PVR≦Trace	PVR=Mild	p Value	Overall	PVR≦Trace	PVR=Mild	p Value	SD
Number	1404	1,046	358		664	332	332		
Demographics									
Age, years	81.7±6.5	81.4±6.5	82.3±6.7	0.032	82.4±6.5	82.5±6.1	82.3±6.8	0.568	0.045
Sex (female), n (%)	815 (58.0)	613 (58.6)	202 (56.4)	0.495	381 (57.4)	188 (56.6)	193 (58.1)	0.754	0.030
Body mass index, kg/m^2	25.3±5.2	25.5±5.1	24.8±5.3	0.023	24.9±5.2	25.2±5.0	24.7±5.4	0.273	0.087
NYHA functional class III or IV, n (%)	940 (67.0)	691 (66.1)	249 (69.6)	0.242	442 (66.6)	218 (65.7)	224 (67.5)	0.681	0.038
STS score, %	5.0±3.7	5.0±3.7	5.3±3.8	0.27	5.3±3.8	5.3±3.9	5.2±3.6	0.764	0.024
Treatment in Japanese hospital, n (%)	405 (28.8)	297 (28.4)	108 (30.2)	0.543	210 (31.6)	102 (30.7)	108 (32.5)	0.677	0.039
Co-morbidities									
Hypertension, n (%)	1,237 (88.1)	921 (88.0)	316 (88.3)	>0.99	584 (88.0)	292 (88.0)	292 (88.0)	>0.99	0
Dyslipidemia, n (%)	932 (66.4)	700 (66.9)	232 (64.8)	0.476	421 (63.4)	206 (62.0)	215 (64.8)	0.519	0.058
Diabetes mellitus, n (%)	388 (27.6)	296 (28.3)	92 (25.7)	0.374	178 (26.8)	91 (27.4)	87 (26.2)	0.793	0.027
Chronic kidney disease, n (%)	636 (45.3)	473 (45.2)	163 (45.5)	0.951	296 (44.6)	142 (42.8)	154 (46.4)	0.39	0.072
COPD, n (%)	300 (21.4)	235 (22.5)	65 (18.2)	0.1	117 (17.6)	56 (16.9)	61 (18.4)	0.684	0.039
Peripheral artery disease, n (%)	218 (15.5)	157 (15.0)	61 (17.0)	0.354	99 (14.9)	49 (14.8)	50 (15.1)	>0.99	0.008
Prior PCI, n (%)	335 (23.9)	262 (25.0)	73 (20.4)	0.085	142 (21.4)	72 (21.7)	70 (21.1)	0.925	0.015
Prior CABG, n (%)	152 (10.8)	102 (9.8)	50 (14.0)	0.03	88 (13.3)	48 (14.5)	40 (12.0)	0.423	0.074
Prior stroke, n (%)	171 (12.2)	121 (11.6)	50 (14.0)	0.261	81 (12.2)	40 (12.0)	41 (12.3)	>0.99	0.009
Right bundle branch block, n (%) (n = 1,403)	154 (11.0)	107 (10.2)	47 (13.1)	0.142	73 (11.0)	32 (9.6)	41 (12.3)	0.321	0.087
Left bundle branch block, n (%) (n = 1,403)	79 (5.6)	68 (6.5)	11 (3.1)	0.016	19 (2.9)	10 (3.0)	9 (2.7)	>0.99	0.018
Atrial fibrillation, n (%)	514 (36.6)	377 (36.0)	137 (38.3)	0.485	221 (33.3)	101 (30.4)	120 (36.1)	0.138	0.121
Prior pacemaker implantation, n (%)	141 (10.0)	103 (9.8)	38 (10.6)	0.684	71 (10.7)	38 (11.4)	33 (9.9)	0.616	0.049
Laboratory data									
eGFR, ml/min/1.73 m^2	61.2±20.2	61.0±20.1	61.7±20.8	0.594	62.0±20.4	62.6±19.9	61.4±21.0	0.462	0.057
Hemoglobin, g/L	123.2±16.5	123.4±16.6	122.7±16.4	0.506	122.7±16.6	122.7±16.7	122.7±16.5	0.989	0
Platelet,10^9/L (n = 1,403)	160.6±108.4	161.3±108.7	158.3±107.5	0.652	153.9±108.4	153.1±108.3	154.6±108.7	0.859	0.014
Echocardiographic findings									
LVEF, %	57.9±11.8	58.0±11.6	57.6±12.3	0.535	58.2±11.9	58.1±11.8	58.3±12.1	0.874	0.013
Aortic valve area, cm^2 (n = 1,388)	0.66±0.19	0.67±0.19	0.64±0.18	0.006	0.65±0.19	0.65±0.20	0.64±0.18	0.479	0.053
AVmax, m/s (n = 1,298)	4.32±0.73	4.29±0.72	4.43±0.75	0.002	4.42±0.71	4.44±0.69	4.41±0.73	0.631	0.042
Mean APG, mm Hg (n = 1,399)	46.2±15.5	45.7±15.2	47.8±16.5	0.025	47.8±15.9	48.2±15.6	47.5±16.2	0.554	0.046

Values are presented as number (%) or mean±SD. In unmatched population, if the value of the index is not completed, (n =) is shown as the number next to the index.

APG = pressure gradient of aortic valve; AVmax = peak aortic valve velocity; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SD = standardized difference; STS = Society of Thoracic Surgeons.

Table 2
Aortic valve anatomy and procedure characteristics

	Unmatched				Matched			
	Overall	PVR≦Trace	PVR=Mild	p Value	Overall	PVR≦Trace	PVR=Mild	p Value
No.	1404	1,046	358		664	332	332	
Valve anatomy								
Bicuspid, n (%) (n = 1,119, 543)	150 (13.4)	122 (14.2)	28 (10.9)	0.177	67 (12.3)	41 (14.2)	26 (10.2)	0.191
Annular Perimeter, mm (n = 1,061, 526)	76.7±8.2	76.6±8.5	77.0±6.9	0.465	77.0±7.6	77.0±8.3	76.9±6.8	0.882
Annulus area, mm^2 (n = 1,062, 526)	457.2±87.4	456.9±89.0	457.8±82.5	0.886	458.1±86.3	459.7±91.0	456.4±81.0	0.659
Area-derived diameter, mm (n = 1,062, 526)	24.1±2.8	24.1±2.9	24.1±2.2	0.896	24.1±2.3	24.1±2.4	24.0±2.1	0.711
Procedure characteristics								
Access site				0.39				0.551
Transfemoral, n (%)	1,322 (94.2)	991 (94.7)	331 (92.5)		619 (93.2)	313 (94.3)	306 (92.2)	
Transaortic, n (%)	21 (1.5)	14 (1.3)	7 (2.0)		13 (2.0)	7 (2.1)	6 (1.8)	
Transapical, n (%)	44 (3.1)	30 (2.9)	14 (3.9)		22 (3.3)	8 (2.4)	14 (4.2)	
Transsubclavian, n (%)	17 (1.2)	11 (1.1)	6 (1.7)		10 (1.5)	4 (1.2)	6 (1.8)	
Predilatation, n (%)	856 (61.1)	605 (58.0)	251 (70.1)	<0.001	437 (65.8)	206 (62.0)	231 (69.6)	0.049
Postdilatation, n (%)	167 (11.9)	108 (10.3)	59 (16.5)	0.003	67 (10.1)	22 (6.6)	45 (13.6)	0.004
Valve-in-valve, n (%)	46 (3.3)	42 (4.0)	4 (1.1)	0.006	13 (2.0)	9 (2.7)	4 (1.2)	0.262
THV (n = 1,402, 633)				<0.001				0.01
Balloon-expanding, n (%)	818 (58.3)	617 (59.1)	201 (56.1)		386 (58.2)	205 (61.9)	181 (54.5)	
Self-expanding, n (%)	489 (34.9)	343 (32.9)	146 (40.8)		252 (38.0)	109 (32.9)	143 (43.1)	
Mechanical-expanding, n (%)	95 (6.8)	84 (8.0)	11 (3.1)		25 (3.8)	17 (5.1)	8 (2.4)	

Values are presented as number (%) or mean±SD. If the value of the index is not completed, (n = unmatched cohort, matched cohort) is shown as the number next to the index.

THV = transcatheter heart valve.

between the groups for any indexes of the baseline characteristics, and the standardized differences of all indexes were within ±0.2 (Table 1).

Compared with patients with none or trace PVR, patients with mild PVR showed no significant difference in aortic valve anatomy, including the rate of bicuspid, annulus perimeter, annulus area, and area-derived diameter using multidetector computed tomography, both in the overall and matched cohorts (Table 2). Regarding procedural characteristics, in the overall cohort, there was a significant difference in the prevalence of predilatation, postdilatation, valve-in-valve, and THV types (Table 2). In contrast, in the matched cohort, a significant difference was detected in the predilatation and postdilatation rates, and in the THV type (p = 0.049, p = 0.004, and p = 0.01, respectively) (Table 2).

With respect to PVR grade, none or trace, and mild grades were observed in 74.5% and 25.5% of the overall cohort, respectively. In the matched cohort, none or trace, and mild grades were observed in 50.0% and 50.0% of the patients, respectively. Regarding procedural outcomes of the patients, in the overall cohort, patients with mild PVR had a significantly higher ratio of major and minor bleeding (major bleeding, p = 0.003; minor bleeding, p <0.001) (Table 3). Postprocedural TTE showed that there was a significant difference in peak aortic valve velocity between the groups (1.97 ± 0.46 m/s [mild PVR] vs 2.06 ± 0.48 m/s [none or trace PVR], p = 0.006) (Table 3). In the matched cohort, a significant difference was observed in minor bleeding and acute kidney injury (p = 0.005 and p = 0.03, respectively) (Table 3). Postprocedural aortic valve velocity was significantly different between the groups (1.99 ± 0.46 m/s [mild PVR] vs 2.07 ± 0.49 m/s [none or trace PVR], p = 0.023) (Table 3).

In this cohort, the rate of mild PVR evaluated using TTE gradually decreased from 25.5% before discharge (n = 1,404) to 22.0% at 3 months (n = 762) and 17.0% at 1 year (n = 295), and some patients with moderate PVR were observed (at 3 months, 2.2% and at 1 year, 1.7%) (Supplementary Figure 1). Moreover, the rate of mild PVR decreased from 66.7% in quartile 1 and 41.0% in quartile 2 to 20.3% in quartile 3 and 23.4% in quartile 4. There was a significant difference in PVR grade in quartile 4 compared with quartiles 1, 2, and 3 (all p <0.001) (Supplementary Figure 2).

Regarding the survival rate, there was no significant difference in 30-day mortality because of any cause and because of cardiovascular disease between the groups, in both the overall and matched cohorts (overall cohort: all-cause p = 0.817, cardiovascular death p >0.99; matched cohort: all-cause p >0.99, cardiovascular death p = 0.772) (Table 3). During a mean follow-up of 1,184.7 ± 733.9 days in the overall cohort, patients with mild PVR had significantly lower 1- and 5-year survival rates than did those with none or trace PVR (1-year survival rate: 89.1% [mild PVR] vs 92.3% [none or trace PVR], log-rank p = 0.048, hazard ratio [HR]: 1.47 [95% confidence interval (CI) 1.00 to 2.15]; 5-year survival rate: 59.7% [mild PVR] vs 69.9% [none or trace PVR], log-rank p <0.001, HR: 1.55 [95% CI 1.24 to 1.94]) (Figure 2). Conversely, during a mean follow-up of 1,168.0 ± 766.7 days in the matched cohort, the difference in 1-year survival rate did not appear significant (89.4% [mild PVR] vs 91.2% [none or trace PVR], log-rank p = 0.415, HR: 1.23 [95% CI 0.75 to 2.01]); however, there was a significant difference in 5-year survival rate between the groups (62.0% [mild PVR] vs 68.0% [none or trace PVR], log-rank p = 0.029, HR: 1.41 [95% CI

Table 3
Outcomes after TAVI

	Unmatched				Matched			
	Overall	PVR ≦ Trace	PVR=Mild	p Value	Overall	PVR ≦ Trace	PVR=Mild	p Value
Number	1404	1,046	358		664	332	332	
Device success, n (%)	1,302 (92.9)	965 (92.4)	337 (94.1)	0.341	617 (92.9)	306 (92.2)	311 (93.7)	0.545
In-hospital death, n (%)	28 (2.0)	18 (1.7)	10 (2.8)	0.271	18 (2.7)	8 (2.4)	10 (3.0)	0.812
Hospital stay, days	8.3±14.1	8.3±15.5	8.4±8.9	0.922	9.0±17.6	9.7±23.2	8.3±8.9	0.334
Hospital stay after procedure, days	6.1±8.6	6.0±9.3	6.4±6.5	0.459	6.6±9.6	6.7±11.9	6.4±6.7	0.717
Complications								
Bleeding								
Life-threatening bleeding, n (%)	58 (4.1)	42 (4.0)	16 (4.5)	0.758	27 (4.1)	11 (3.3)	16 (4.8)	0.432
Major bleeding, n (%)	151 (10.8)	97 (9.3)	54 (15.1)	0.003	88 (13.3)	38 (11.4)	50 (15.1)	0.208
Minor bleeding, n (%)	123 (8.8)	74 (7.1)	49 (13.7)	<0.001	71 (10.7)	24 (7.2)	47 (14.2)	0.005
RBC transfusion, n (%)	149 (10.6)	104 (9.9)	45 (12.6)	0.165	81 (12.2)	38 (11.4)	43 (13.0)	0.635
Major vascular complication, n (%)	111 (7.9)	75 (7.2)	36 (10.1)	0.089	57 (8.6)	22 (6.6)	35 (10.5)	0.096
Minor vascular complication, n (%)	87 (6.2)	63 (6.0)	24 (6.7)	0.614	41 (6.2)	18 (5.4)	23 (6.9)	0.519
Stroke or transient ischemic attack, n (%)	39 (2.8)	26 (2.5)	13 (3.6)	0.265	16 (2.4)	7 (2.1)	9 (2.7)	0.801
Post pacemaker implantation, n (%)	117 (8.3)	84 (8.0)	33 (9.2)	0.506	60 (9.0)	31 (9.3)	29 (8.7)	0.892
Acute kidney injury				0.105				0.03
None, n (%)	973 (94.6)	735 (95.6)	238 (91.9)		442 (93.8)	230 (96.6)	212 (91.0)	
Stage 1, n (%)	29 (2.8)	19 (2.5)	10 (3.9)		16 (3.4)	6 (2.5)	10 (4.3)	
Stage 2, n (%)	11 (1.1)	6 (0.8)	5 (1.9)		5 (1.1)	0 (0.0)	5 (2.1)	
Stage 3, n (%)	15 (1.5)	9 (1.2)	6 (2.3)		8 (1.7)	2 (0.8)	6 (2.6)	
Postprocedural echocardiography								
LVEF, % (n = 528, 250)	58.8±12.3	58.7±12.2	59.1±12.5	0.743	59.3±12.5	59.4±12.5	59.2±12.6	0.901
EOA, cm^2 (n = 418, 216)	1.84±0.52	1.85±0.52	1.81±0.52	0.438	1.81±0.49	1.80±0.47	1.82±0.52	0.841
AVmax, m/s (n = 1,379, 657)	2.04±0.48	2.06±0.48	1.97±0.46	0.006	2.03±0.48	2.07±0.49	1.99±0.46	0.023
Mean APG, mm Hg (n = 1,394, 659)	9.68±4.93	9.81±5.08	9.29±4.46	0.086	9.79±5.01	10.10±5.43	9.48±4.54	0.11
Clinical outcomes								
30-d all-cause death, n (%)	25 (1.8)	18 (1.7)	7 (2.0)	0.817	14 (2.1)	7 (2.1)	7 (2.1)	>0.99
30-d cardiovascular death, n (%)	19 (1.4)	14 (1.3)	5 (1.4)	>0.99	12 (1.8)	7 (2.1)	5 (1.5)	0.772
All-cause death during follow-up, n (%)	386 (27.5)	251 (24.0)	135 (37.7)	<0.001	195 (29.4)	77 (23.2)	118 (35.5)	0.001
Follow-up duration, days	1,184.7±733.9	1,170.1±688.6	1,227.4±852.3	0.202	1,168.0±766.7	1,106.4±666.9	1,229.6±851.5	0.038

Values are presented as number (%) or mean±SD. If the value of the index is not completed, (n = unmatched cohort, matched cohort) is shown as the number next to the index.

APG = aortic valve pressure gradient; AVmax = peak aortic valve velocity; EOA = effective orifice area; LVEF = left ventricular ejection fraction; RBC = red blood cell; TAVI = transcatheter aortic valve implantation.

1.04 to 1.91]) (Figure 3). Regarding landmark analysis at 1 year, there was still a significant difference between the groups (log-rank p <0.001) (Supplementary Figure 3).

According to the THV generation, in the unmatched cohort, in patients implanted with first-generation THV (274 of 1,402), there was no significant difference in 5-year survival rate compared with patients with mild PVR and those with none or trace PVR (log-rank p = 0.117) (Supplementary Figure 4). In contrast, in those with subsequent-generation THV (1,128 of 1,402), patients with mild PVR had significantly lower 5-year survival rates than did those with none or trace PVR (log-rank p <0.001) (Supplementary Figure 4). In unmatched cohorts, after excluding 95 patients treated using mechanically expanding THV, we evaluated the difference of mortality between patients with none or trace PVR and those with mild PVR according to THV type, and there was a significant difference (log-rank p <0.001) (Supplementary Figure 5). Moreover, in the unmatched cohort, no significant difference was observed in 5-year survival rate in overall patients and in patients with mild PVR between first-generation THV and subsequent-generation THV (log-rank p = 0.116, log-rank p = 0.79) (Supplementary Figure 6).

Discussion

The findings of this study show that, in the matched cohort, mild PVR after TAVI is associated with a 1.4-fold increased risk of mortality compared with none or trace PVR at 5 years, whereas there was no significant difference in mortality at 1 year between the groups.

PVR is a known complication of TAVI, and according to previous publications, PVR ≧ moderate can lead to higher mortality rates.[3–5] Regarding the impact of mild PVR on outcomes, results are inconsistent at short-term follow-up.[1–3,13,14] Owing to the progression of TAVI devices, PVR can now be controlled and maintained at a lower grade; however, the potential long-term effect of mild PVR on outcomes should be evaluated because the application of the TAVI procedure has been expanded to younger patients with low surgical risk according to the current guidelines.[12,15] Recently, some studies on the long-term impact of mild PVR have been published—similarly to the short-term data, the results are inconsistent. Okuno et al[15] reported that both mild PVR using the 3-class grading scheme and mild-to-moderate PVR using the 5-class grading scheme are associated with an increased risk of 5-year

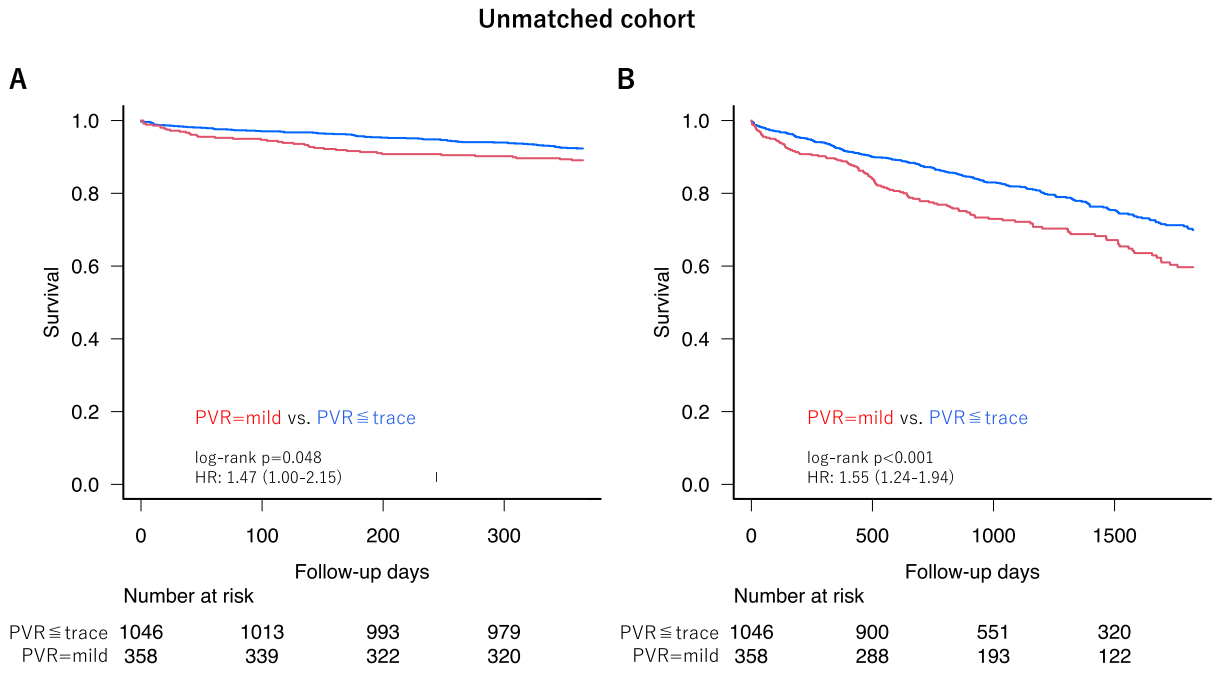

Figure 2. Kaplan−Meier curves for mortality before propensity score matching Kaplan−Meier curves at 1 year (*A*) and 5 years (*B*) after TAVI comparing patients with mild PVR and those with none or trace PVR.

mortality. Moreover, Schoechlin et al[6] reported that mild PVR using the 3-class grading scheme is an independent predictor of 5−year mortality. In terms of randomized trials, in the PARTNER-1 trial and in the trial including a high-risk population treated with self-expanding valves, mild PVR was associated with a higher 5-year mortality rate.[18,19] In contrast, in the PARTNER-2 trial, mild PVR was not associated with an increased risk of 5-year mortality.[20] One of the several potential reasons for this discordance is the PVR assessment quality. TTE is the tool most commonly used to assess PVR; however, it is often disturbed by acoustic artifacts generated by the prosthetic valve itself or severe calcification in the aortic or mitral valve, leading to missed diagnoses or misrepresentation of

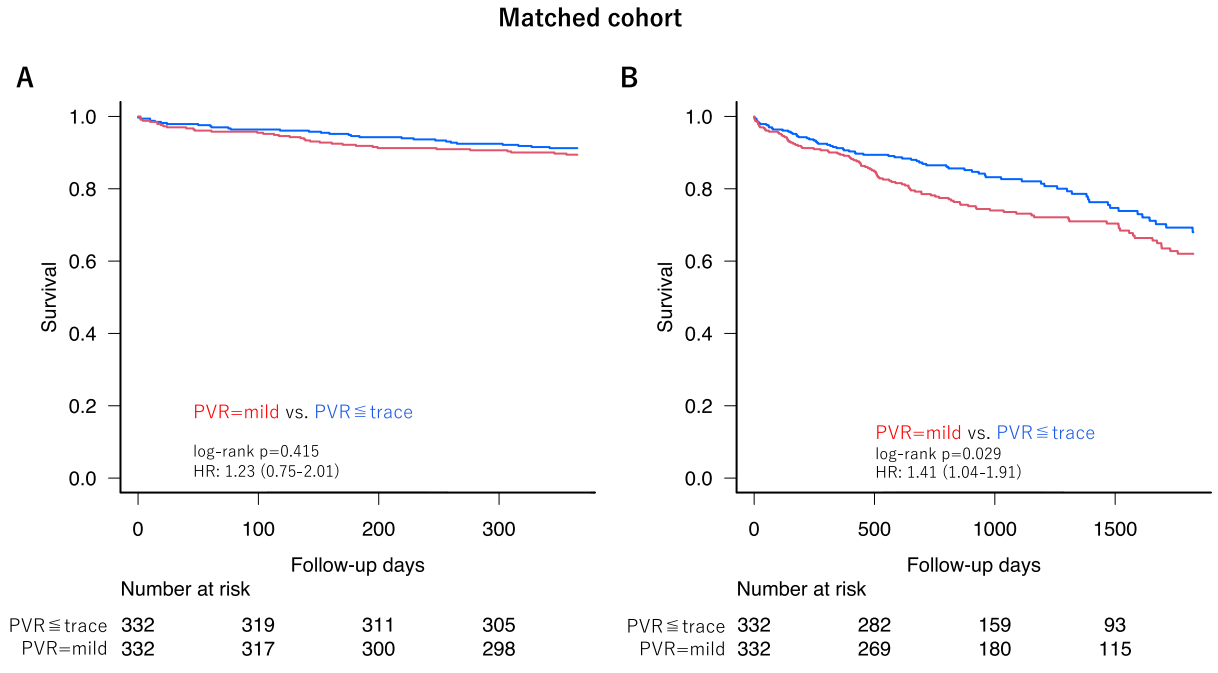

Figure 3. Kaplan−Meier curves for mortality after propensity score matching Kaplan−Meier curves at 1 year (*A*) and 5 years (*B*) after TAVI comparing patients with mild PVR and those with none or trace PVR.

PVR severity.[21,22] Hahn et al[23] reported that, in the PARTNER-2 trial cohort, low reproducibility was observed between the measurement of multiple parameters performed by a core laboratory and those performed by a consortium of echocardiographers. Moreover, in a clinical setting, PVR tends to be more eccentric and has a noncylindrical jet morphology[24]; hence, the accurate determination of PVR severity often requires the integration of clinical, laboratory, and other imaging-based findings in addition to TTE, and is even more challenging.[25]

Our findings indicate the prognostic impact of mild PVR on mortality in the late phase after TAVI. Several potential reasons for the adverse effect of mild PVR have been proposed. First, patients with severe AS typically have a much thicker and less compliant left ventricle (LV). Therefore, a possible mechanism may be that after the strong afterload through the aortic valve is relieved by TAVI, even mild PVR can produce an increased preload and hemodynamic wall stress that the LV cannot endure, gradually leading to LV heart failure, especially in patients who have no aortic regurgitation before the procedure.[24,26] Second, the occurrence of critical bleeding can be speculated. According to a previous study, patients with mild PVR have higher rates of major or life-threatening bleeding than do those with none or trace PVR at 5 years.[15] One of the underlying mechanisms is that PVR can cause high shear stress and flow turbulence, resulting in loss of high-molecular-weight von Willebrand factor.[15,27] This phenomenon was identified in patients with more-than-mild PVR,[27] and this may be the reason for the gradually decreasing rate of survival in these patients. Third, there might be some patients who gradually progress from having mild PVR before discharge to moderate PVR over time, which could lead to increased mortality.[22] The progression of PVR has been reported in some publications[26,28]; however, it may simply be related to variability, which is dependent on image quality.[22] These proposals are speculative because this study includes little data or information on them. This registry database did not include any adverse events, except for mortality during follow-up; therefore, the reasons for this result should be clarified in further studies.

The findings of this study provide clinical suggestions for the management of severe AS in the current TAVI era, in which the target population has been expanded to younger patients. Although TAVI devices are progressing, mild PVR before discharge was observed in 26% of patients in this cohort, which is markedly higher than that after SAVR. Considering the long-term impact of mild PVR on mortality as presented in this and previous studies, SAVR may be considered as an optional therapeutic approach in patients with a longer life expectancy and a few predictors of mild PVR, for example, the annular eccentricity or moderate-to-severe LV outflow tract calcification.[29]

This study has several limitations; therefore, the results should be interpreted with caution. First, this was a retrospective study, and the inclusion of patients started in December 2008. Thus, some early-generation valves were implanted, which might have affected the results. Second, the evaluation of PVR was performed by experienced cardiologists or technicians at each center using TTE, and there was no centralized laboratory analysis. Third, in this database, postdischarge follow-up TTE was documented until 1 year; however, we had a relatively low amount of data on serial PVR grade. Previous studies have reported changes in PVR during follow-up,[5,26,30,31] which might affect the long-term clinical course. Fourth, the information of aortic regurgitation at baseline is lacking. Therefore, the first speculation that is mentioned above cannot be investigated. Fifth, the postprocedural complications, for example bleeding, acute kidney injury, or stroke, were not matched. Hence, they might influence the long-term mortality. Sixth, we did not have detailed information on the analysis and calcification of the aortic valve. Thus, the predictors of PVR could not be evaluated. Finally, the outcome of this study was mortality, and the rates of rehospitalization, valve performance, aortic valve reintervention, and stroke were not considered. Moreover, the change in functional status—measured using, for example, the NYHA Functional Classification—was also unknown. These points are major limitations of this study. However, we believe that this study can provide valuable contributions because the sample population was enrolled from an international registry including people from mainly 2 races, and we considered a relatively long-term follow-up period, performing evaluations using the propensity score matching method.

In conclusions, this study indicates that patients with mild PVR have a 1.4-fold increase in mortality risk at 5 years after TAVI compared with those with none or trace PVR; however, this increased risk was not found at the 1-year follow-up. Further studies with more patients and regular echocardiographic follow-up are required to investigate the impact of mild PVR on longer-term clinical outcomes in depth.

Disclosures

Dr. Vähäsilta is a clinical proctor of Edwards Lifesciences (Sapien). Dr. Saito is a clinical proctor of Edwards Lifesciences (SAPIEN), Medtronic (Minneapolis, Minnesota, United States) (CoreValve). Dr. Laine reports receiving nonregulatory research grants from Teleflex and consultant fees from Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Moriyama is a clinical proctor of Edwards Lifesciences (SAPIEN) and Boston Scientific (ACURATE neo) and received a research grant from the Japanese Circulation Society. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.12.002.

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