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Pulmonary Hypertension in Patients With Severe Aortic Stenosis: Prognostic Impact After Transcatheter Aortic Valve Replacement

Pulmonary Hypertension in Patients Undergoing TAVR

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ABSTRACT

OBJECTIVES The authors investigated the development of pulmonary hypertension (PH), predictors of PH regression, and its prognostic impact on short, mid-, and long-term outcomes in patients undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS).

BACKGROUND PH represents a common finding in patients with AS. Although TAVR is frequently associated with regression of PH, the predictors of reversible PH and its prognostic significance remain uncertain.

METHODS In this study, 617 consecutive patients undergoing TAVR between 2009 and 2015 were stratified per baseline tertiles of pulmonary artery systolic pressure (PASP) as follows: normal (PASP <34 mm Hg), mild-to-moderate (34 mm Hg ≤ PASP <46 mm Hg), and severe PASP elevation (PASP ≥46 mm Hg). After TAVR, 520 patients with PH at discharge were stratified according to the presence or absence of PASP reduction. Primary outcome was all-cause mortality at 30 days, 1 year, and long-term follow-up at a maximum of 5.9 years.

RESULTS In patients with both mild-to-moderate and severe PH at baseline, PASP decreased significantly at discharge (ΔPASP 3.0 ± 9.3 mm Hg and 12.0 ± 10.0 mm Hg, respectively) and 1 year (ΔPASP 5.0 ± 9.7 mm Hg and 18.0 ± 14.0 mm Hg, respectively). At a median follow-up of 370 days (interquartile range [IQR]: 84 to 500 days), the risk of all-cause mortality was similar among baseline PASP groups at all time intervals evaluated. After TAVR, a significant regression of PH was observed in 46% of patients. Contrarily, patients with residual PH had a higher risk of all-cause mortality at 30 days (hazard ratio [HR]: 3.49, 95% confidence interval [CI]: 1.74 to 6.99; $p < 0.001$), 1 year (HR: 3.12, 95% CI: 2.06 to 4.72; $p < 0.001$), and long-term (HR: 2.47, 95% CI: 1.74 to 3.49; $p < 0.001$). Left ventricular ejection fraction (LVEF) >40% (odds ratio [OR]: 3.56, 95% CI: 2.24 to 5.65; $p < 0.001$), baseline PASP ≥46 mm Hg (OR: 3.26, 95% CI: 2.07 to 5.12; $p < 0.001$), absence of concomitant tricuspid regurgitation (TR) ≥ moderate (OR: 0.53, 95% CI: 0.34 to 0.84; $p < 0.001$), and logistic EuroSCORE <25% (OR: 1.59, 95% CI: 1.04 to 2.45; $p = 0.03$) were independent predictors of PASP reduction.

CONCLUSIONS In most patients with PH and AS, TAVR is associated with a significant early and late reduction of PASP. Patients with reversible PH after TAVR are at lower risk of all-cause mortality at early, mid-, and long-term follow-up. Therefore, the presence of PH should not preclude treatment with TAVR. (J Am Coll Cardiol Img 2018;■:■–■)
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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MR = mitral regurgitation

PASP = pulmonary artery systolic pressure

PH = pulmonary hypertension

TAPSE = tricuspid annular plane systolic excursion

TAVR = transcatheter aortic valve replacement

TR = tricuspid regurgitation

SAVR = surgical aortic valve replacement

Pulmonary hypertension (PH) is a common finding in patients with aortic stenosis (AS) and has been associated with increased mortality and morbidity following both transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) (1-4). Post-capillary PH secondary to the left-sided heart diseases is the most common type of PH, which can be found in up to 75% of patients with symptomatic AS (5-7). In these patients, PH is often caused by a chronic elevation of left ventricular (LV) end-diastolic pressure, concomitant presence of mitral regurgitation (MR), and/or impaired left ventricular ejection fraction (LVEF). Further, persistent PH after SAVR has been associated with modest clinical improvement and quality-of-life gain (8,9). Although right-heart catheterization (RHC) is the best method to measure the pulmonary artery pressure (PAP), echocardiographic estimation of pulmonary artery systolic pressure (PASP) correlates well with RHC measurements (10) and is widely used in the clinical routine.

Although TAVR is frequently associated with a reduction of PASP, only limited data from small studies are available on the impact of post-TAVR changes of PASP on mid- and long-term clinical outcomes (11-13). To date, the prognostic significance of reversible PH and the predictors of PH regression remain uncertain (14,15).

The purpose of this study was to investigate the natural course and prognostic impact of elevated PASP following TAVR and identify predictors of PASP reduction in patients with severe AS.

METHODS

STUDY DESIGN AND DATA COLLECTION. This is a multicenter study comprising consecutive patients with severe AS referred for TAVR at 4 European tertiary cardiovascular (CV) centers from March 2009 to January 2015. The study complies with the Declaration of Helsinki and was approved by the locally appointed ethics committees. The indication to TAVR was appraised upon consensus of the multidisciplinary heart team. At each site, data were collected at discharge and scheduled follow-up. Following TAVR and up to discharge, at least 1 echocardiographic examination was obtained for each patient. When more than 1 echocardiographic control was performed during the hospital stay, the last one prior to discharge was included in the study. Long-term follow-up was obtained based on either medical records or physician and patient interviews.

Based on current local guidelines recommendation (16) patients were stratified into 3 groups according to their baseline PASP: normal (PASP <34 mm Hg), low-to-moderate (≥34 PASP <46 mm Hg), and severe (PASP ≥46 mm Hg). After TAVR, patients with PH were stratified in 2 groups according to the presence or absence of reduction of PASP at discharge. This was defined as a change of PASP group at discharge by at least 1 category as compared with baseline: namely, from severe to mild-to-moderate or normal (**Figure 1**).

INTERVENTIONAL TREATMENT. The least invasive vascular access was selected (transfemoral, transsubclavian, or transapical) based on the heart-team decision. According to the center expertise and device availability at different time points, commercially available valves (CoreValve [Medtronic, Minneapolis, Minnesota], Edwards Sapien [Edwards Lifesciences, Irvine, California], JenaValve [JenaValve Technology Inc., Irvine, California], LotusEdge Valve [Boston Scientific, Marlborough, Massachusetts], and Portico [Abbott, Abbott Park, Illinois]), were implanted.

ECHOCARDIOGRAPHIC ASSESSMENT OF PASP. Transthoracic echocardiography was used for the assessment of PASP as indicated in current guidelines. The estimation of PASP is based on the sum of the right atrial pressure (RAP) and the peak tricuspid regurgitation (TR) velocity, as described by the modified Bernoulli equation. Echocardiographic RAP estimation is based on the diameter and respiratory excursions of the inferior vena cava, as previously described (16).

OUTCOMES. Clinical outcomes were defined according to the criteria of the Valve Academic Research Consortium-2 consensus document (17). The primary outcome was all-cause mortality at 30 days, 1 year, and maximal follow-up. Secondary outcomes included major adverse cardiovascular (CV) and cerebrovascular events (all-cause mortality, CV mortality, myocardial infarction [MI], and stroke) at 30

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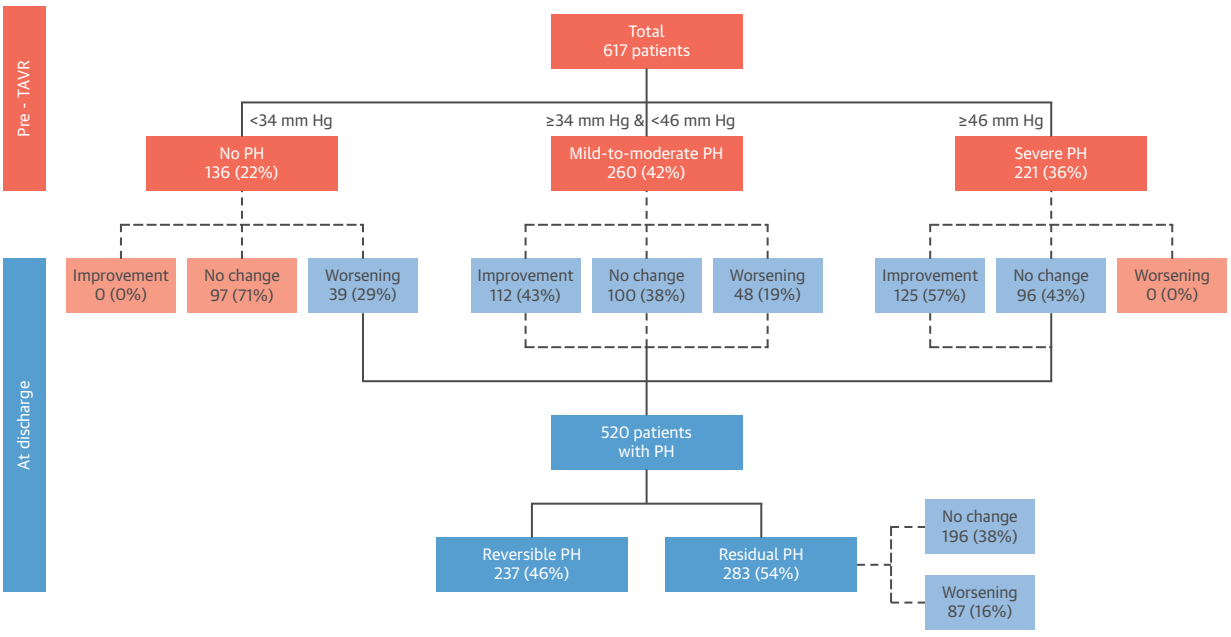
FIGURE 1 Flow Chart of Patient Stratification According to Groups of PASP



At baseline, patients were stratified into 3 PASP groups. At discharge, patients were stratified according to the presence or absence of PASP-reduction post-TAVR. Depicted are counts (%).

days, 1 year, and maximal follow-up of 5.9 years. Furthermore, vascular complications (major and minor), bleeding (life threatening, major, and minor), and rates of pacemaker implantation were assessed at 30 days. New York Heart Association (NYHA) functional class was assessed at baseline, discharge, and 1 year.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD, median (interquartile range [IQR]), or frequencies and percentages. All variables were tested for normal distribution with the Shapiro-Wilk test. Discrete variables were compared using the Fisher exact test and continuous ones using the Student's *t*-test. Analysis of variance (ANOVA) or Kruskal-Wallis tests were used for comparing more than 2 groups for normally distributed and skewed variables, respectively. The changes from baseline values of PASP and other echocardiographic and functional parameters at discharge and 12 months were analyzed overall and within each group using a linear mixed model considering the within-patient correlation. This analysis included only patients with available echocardiographic follow-up at each analyzed time point. Subgroups of PASP reduction at discharge were compared for their baseline characteristics and clinical outcomes. Multivariable logistic regression was used to identify predictors of reversible PH at discharge. The model included baseline variables significantly different at the univariate analysis ($p < 0.05$). Hosmer-Lemeshow statistics were used to assess the goodness of fit of the model. Kaplan-Meier analysis was used to estimate the incidence of clinical outcomes at 30 days, 1 year, and maximal follow-up of 5.9 years. Adjusted hazard ratios (HRs) were calculated in multivariable Cox-regressions including baseline, clinical, echocardiographic, and periprocedural characteristics known to affect patient outcomes after TAVR (age >85 years, sex, body mass index, diabetes mellitus, coronary artery disease, previous MI or coronary artery bypass, peripheral artery disease, chronic obstructive pulmonary disease [COPD] stage >II, logistic EuroSCORE, atrial fibrillation, LVEF <35%, NYHA functional class >II at discharge). Proportional assumptions hazard was tested based on Schoenfeld residuals.

All probability values were 2-tailed and considered significant when $p < 0.05$. Data analysis was performed using STATA version 14.0 (StataCorp, College Station, Texas).

RESULTS

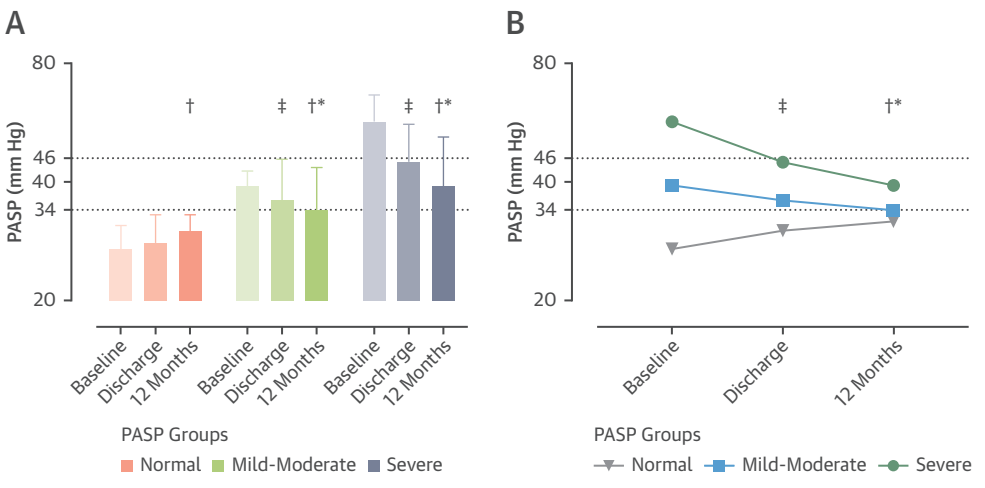
BASELINE AND PERI-PROCEDURAL CHARACTERISTICS. A total of 617 patients (n = 303 men, 49%) with severe

AS undergoing TAVR were included in the study. Demographic, clinical, echocardiographic, and peri-procedural characteristics according to PASP tertiles at baseline are outlined in Online Tables 1 and 2. Of these patients, 136 (22%) had normal PASP values, whereas 260 (42%) and 221 (36%) presented with mild-to-moderate and severe PASP values, respectively. Patients were severely symptomatic and at high risk for SAVR, as reflected by advanced age (81 ± 7 years), high logistic EuroSCORE (24 ± 16%), reduced NYHA functional class, and elevated PASP values (43 ± 13 mm Hg). Figure 1 depicts the flow chart of patient stratification according to the different PASP groups pre-TAVR and at discharge. Patients with severe PH had significantly higher prevalence of atrial fibrillation (24% vs. 19% vs. 16%; $p = 0.02$), lower prevalence of peripheral artery disease (21% vs. 32% vs. 29%; $p = 0.02$), and significantly higher logistic EuroSCORE (28 ± 17 vs. 23 ± 15, vs. 21 ± 12). The other comorbidities did not differ among the groups. There were no cases with concomitant mitral stenosis or undergoing specific pharmacological treatment for PH.

Compared with patients with mild-to moderate and no PH, those with severe PH had significantly smaller aortic valve area (AVA) (0.66 ± 0.19 vs. 0.67 ± 0.20 vs. 0.73 ± 0.21, respectively; $p < 0.01$), higher prevalence of moderate-to-severe MR (40% vs. 26% vs. 14%; $p < 0.01$), TR (43% vs. 21% vs. 16%; $p < 0.01$) and AR (18% vs. 10% vs. 14%; $p = 0.04$), higher left atrial volume (93 ± 29 ml vs. 78 ± 27 ml vs. 66 ± 19 ml; $p < 0.01$), and end diastolic filling index (18 ± 5 vs. 16 ± 5 vs. 13 ± 5; $p < 0.01$). Furthermore, a reduced RV-function (tricuspid annular plane systolic excursion [TAPSE] <17 mm) was observed more frequently in the severe PH compared with the groups with mild-to-moderate and no PH (11% vs. 6% vs. 1%; $p < 0.01$). The most frequent access route was transfemoral (81%), and the most frequently implanted valve was Edwards SAPIEN XT and 3 (60%). Device success was achieved in 99% of cases. Nineteen percent (118) of patients required new pacemakers. Peri-procedural complications included stroke (0.8%), transient ischemic attack (0.5%), and MI (1.6%). No difference in peri-procedural characteristics and complications was observed.

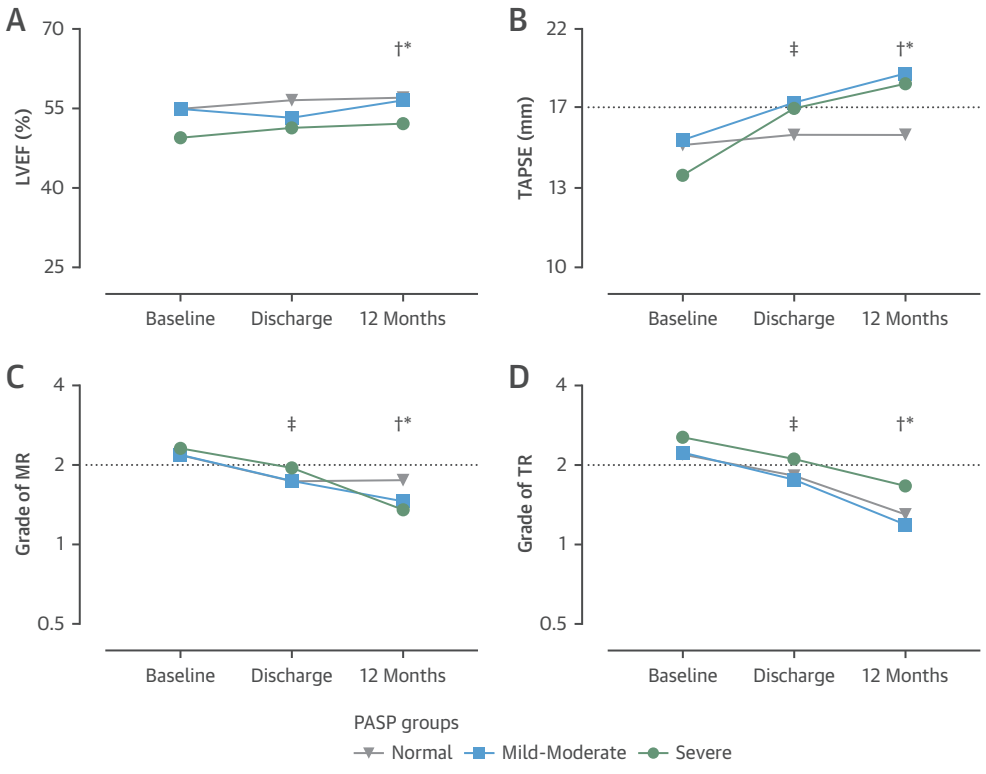
ECHOCARDIOGRAPHIC PARAMETERS. As shown in Figure 1, of patients with baseline PH (78% [468 of 617]), a significant regression of PH was observed in 49% (237 of 481) at discharge and in 59% (99 of 169) at 1 year after TAVR. Of patients with severe baseline PH, 57% (125 of 221) experienced reductions of their baseline PASPs with an overall mean reduction of 12 ± 10 mm Hg (57.0 ± 9.5 mm Hg vs. 45 ± 11 mm Hg; $p < 0.001$) at discharge and 18 ± 14 mm Hg (57.0 ± 9.5 mm Hg vs. 39 ± 13 mm Hg; $p < 0.001$) and at 1 year. In the group with mild-to-moderate PH, 43% (112 of 260) of patients had a mean PASP reduction of 3 ± 9.3 mm Hg (39.0 ± 3.6 mm Hg vs. 36 ± 9.7 mm Hg; $p < 0.001$) at discharge and 5.0 ± 9.7 mm Hg (39.0 ± 3.6 mm Hg vs.

FIGURE 2 Reduction of PASP Values From Baseline at Discharge and 12 Months



Depicted are mean changes of PAPS-values between and within PAPS-stratification groups at each time point. **(A) Bars** represent mean ± SD, p values are from paired *t*-tests. **(B) Symbols** represent means of PASP. The analysis considers the between and within-patient correlation, p values are from a linear mixed model. *$p < 0.05$, values at 12 months versus discharge; †$p < 0.05$, values at 12 months versus baseline; ‡$p < 0.05$, values at discharge versus baseline.

FIGURE 3 **Changes in Echocardiographic Parameters at Discharge and 12 Months**



Improvement of **(A)** LVEF, **(B)** previously impaired RV-function (TAPSE <17 mm), baseline moderate-to-severe **(C)** MR, and **(D)** TR at discharge and 12 months post-TAVR per each baseline PASP-group is shown. **Symbols** represent means. The analysis considers the between- and within-patient correlation, (p values are from a linear mixed model). *p < 0.05, values at 12 months versus discharge; †p < 0.05, values at 12 months versus baseline; ‡p < 0.05, values at discharge versus baseline.

34.0 ± 9.5 mm Hg; p < 0.001) at 1 year. Significant differences were observed in both within- and between-group comparisons (Figures 2A and 2B).

In patients with mild-to-moderate or severe PH and concomitant left- and right-ventricular functional impairment (TAPSE <17 mm), a significant improvement of LVEF and TAPSE at discharge and 1 year were observed (Figures 3A and 3B). Further, a significant reduction of moderate-to-severe MR and TR was observed after TAVR at discharge and 1 year, with the regression of both valvular regurgitations being more prominent in the group with severe PH (Figures 3B and 3C). Changes in echocardiographic parameters at discharge and 1 year are outlined in the Online Table 3.

OUTCOMES AT 30 DAYS, 1-YEAR, AND MAXIMAL FOLLOW-UP. Among all 617 patients, rates of all-cause mortality, CV mortality, MI, and stroke at 30 days were 11% (n = 67), 5% (n = 32), 0.5% (n = 3) and 4% (n = 23), respectively. At 1 year, all-cause and CV mortality occurred in 27% (n = 164) and 8.4% (n = 52) of patients, respectively. MI and stroke were observed in 0.001% (n = 1) and 2.9% (n = 18) of patients. At a maximal follow-up of 5.9 years, all-cause and CV mortality occurred in 33% (n = 205) and 9.4% (n = 58) patients, respectively. At each time point, no significant difference between baseline PASP groups regarding the outcomes was observed (Table 1). Interestingly, PASP values at baseline and at discharge, as continuous variables, were not independent predictors of mortality at all evaluated time points (Online Tables 4 and 5).

DEVELOPMENT OF PH POST-TAVR. As depicted in Figure 1, in 97 (16%) patients without PH at baseline, PASP remained unchanged. In the remaining 520 (84%) patients, a reversible PH was observed in 237 patients (46%), with a change of PASP category of ≥1, from severe to mild-to-moderate or normal, whereas in 283 (54%) patients, no change was observed. These 520 patients were further explored and stratified according to the presence or absence of PASP reduction

TABLE 1 Clinical Outcomes at 30-Day, 1-Year, and Long-Term Follow-Up According to PASP Groups at Baseline

		Baseline PASP Groups			Moderate Versus Normal		Severe Versus Normal		Severe Versus Low Moderate	
	Total (n = 617)	Normal (n = 136)	Mild-to Moderate (n = 260)	Severe (n = 221)	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
30 days										
All-cause mortality	67 (11.0)	12 (9.0)	26 (10.0)	29 (13.0)	1.13 (0.57-2.24)	0.72	1.49 (0.76-2.93)	0.24	1.32 (0.78-2.22)	0.30
CV mortality	32 (5.0)	5 (4.0)	15 (6.0)	12 (5.0)	1.56 (0.57-4.31)	0.38	1.48 (0.52-4.21)	0.47	0.94 (0.44-2.01)	0.88
Stroke	23 (4.0)	4 (3.0)	8 (3.0)	11 (5.0)	1.05 (0.32-3.51)	0.93	1.74 (0.56-5.49)	0.33	1.65 (0.66-4.11)	0.27
MI	3 (0.5)	0 (0.0)	3 (1.0)	0 (0.0)	-		-		-	
1 year										
All-cause mortality	164 (27.0)	34 (25.0)	67 (26.0)	63 (29.0)	1.05 (0.69-1.59)	0.80	1.19 (0.78-1.80)	0.41	1.12 (0.80-1.59)	0.48
CV mortality	52 (8.4)	8 (5.9)	26 (10.0)	18 (8.0)	1.72 (0.78-3.81)	0.17	1.42 (0.62-3.28)	0.40	0.82 (0.45-1.50)	0.53
Stroke	18 (2.9)	5 (3.7)	6 (2.3)	7 (3.2)	0.65 (0.19-2.12)	0.47	0.91 (0.29-2.89)	0.88	1.14 (0.47-4.20)	0.53
MI	1 (0.001)	0 (0)	1 (0.4)	0 (0)	-		-		-	
Long term (5.9 years)										
All-cause mortality	205 (33.0)	43 (32.0)	81 (31.0)	81 (37.0)	0.98 (0.68-1.42)	0.93	1.26 (0.87-1.82)	0.22	1.28 (0.94-1.74)	0.11
CV mortality	58 (9.4)	10 (7.0)	27 (10.0)	21 (9.6)	1.43 (0.69-2.96)	0.33	1.36 (0.64-2.89)	0.42	0.95 (0.54-1.68)	0.86

Values are n (%) unless otherwise indicated.
CV = cardiovascular; MI = myocardial infarction.

at discharge. Baseline and echocardiographic characteristics of these groups are shown in Table 2.

Reduction of PASP was associated with significantly lower logistic EuroSCORE (22 ± 13 vs. 27 ± 17; $p < 0.01$), improved LVEF (56 ± 14 vs. 50 ± 16; $p < 0.01$), more frequently sinus rhythm (64% vs. 56%; $p = 0.04$), and lower prevalence of moderate-to-severe TR (28% vs. 39%; $p = 0.01$) compared with patients who had unchanged PASP. Reduction of PASP was more frequent among patients with higher PASP values at baseline (53% vs. 34%; $p < 0.01$). Further, patients with PASP reduction had higher maximal aortic pressure gradients before TAVR compared with patients who had constant PASP (79 ± 24 vs. 73 ± 25; $p < 0.01$).

LVEF >40%, baseline PASP ≥46 mm Hg, absence of moderate-to-severe TR, and logistic EuroSCORE <25% were independent predictors of PASP reduction at discharge (Figure 4).

OUTCOMES ACCORDING TO GROUPS OF PASP REDUCTION. The median follow-up was 370 (IQR: 84 to 500) days among all 520 patients, with no difference among PASP-reduction groups. Outcome rates and crude HRs are depicted in Online Table 6 and adjusted HRs in Table 3. Rates of all-cause mortality, CV mortality, MI, and stroke were 11% (n = 59), 5.6% (n = 29), 0.6% (n = 3), and 3.8% (n = 20) at 30 days and 32% (n = 139), 11% (n = 47), 0.3% (n = 1), and 3.7% (n = 14) at 1-year follow-up, respectively.

Kaplan-Meier estimates at 30 days, 1-year and maximal follow-up of 5.9 years showed a significantly higher incidence of all-cause and CV mortality in patients with no PASP reduction (Figure 5) compared with those who had PASP reduction. Crude HRs for all-cause and CV mortality were, respectively, 4.41 (95% CI: 2.24 to 8.71; $p < 0.001$), and 4.25 (95% CI: 1.63 to 11.1; $p = 0.003$) at 30 days, 3.69 (95% CI: 2.46 to 5.53; $p < 0.001$), and 2.84 (95% CI: 1.47 to 5.48; $p = 0.02$) at 1 year, and 2.80 (95% CI: 1.99 to 3.93; $p < 0.01$), and 2.60 (95% CI: 1.41 to 4.83; $p = 0.002$) at a maximal follow-up of 5.9 years. The survival disadvantage for both all-cause and CV mortality in patients displaying no PASP reduction after TAVR was not influenced from baseline factors known to affect mortality (Table 3). Further, the introduction in the multivariate regression models of baseline PASP as continuous covariate had no effect on outcomes (Online Table 7). No statistically significant differences in the incidence of the other outcomes (stroke and MI) were observed at all time points.

DISCUSSION

The purpose of this study was to investigate the development of baseline PH and its prognostic impact and on short, mid-, and long-term outcomes in patients undergoing TAVR for severe AS.

PH is a common finding in patients with severe AS undergoing TAVR. In our study, in an all-comers population, the prevalence of pre-procedural PH was 78% (42% with mild-to-moderate and 36% with severe PH), as previously reported (1,2,5,11,18-21). Sinning et al. (11) reported elevated PAP in >70% of patients with severe AS with approximately 45% with moderate AS and 26% with severe PAP. PH is an

established risk factor for mortality in patients undergoing SAVR and considered for baseline surgical-risk calculation (22). As observed by Zlotnick et al. (22), pre-operative PH is associated with reduced short- and long-term survival after SAVR.

However, as TAVR is performed less invasively and as "beating heart procedure," the contribution of pre-procedural PH to peri-interventional risk might be less or even negligible compared with SAVR. Several studies investigating the impact of baseline PH on outcomes post-TAVR have yielded contradictory results. This inconsistency may partially be explained by the fact that PH is frequently associated with other pathologies, such as TR and RV dysfunction, which have been shown to affect survival. In this setting, the presence of elevated PASP, RV dysfunction, and TR should be interpreted within the same disease process—each contributing to outcome—although contribution of each variable to outcome is still poorly understood (23,24).

Further, the comparability of studies investigating this subject is limited because of varying PH definitions and arbitrary echocardiographic cutoff values or unavailability of long-term follow-up. In this study, baseline subgroups of PASP elevation were stratified according to guideline classification (16).

In the current study, we found that within 30 days after TAVR, moderate and severe baseline PH is significantly reversible in most patients. The mean PASP reduction is 3.0 ± 9.3 mm Hg and 12.0 ± 10.0 mm Hg in the moderate and severe PH groups, respectively. This phenomenon continues up to 1 year, and is more distinct compared with the early post-operative period (5.0 ± 9.7 mm Hg, and 18 ± 14 mm Hg for the moderate and severe PH groups, respectively).

We also found that PH reversibility post-TAVR is associated with the reduction of pre-existing moderate-to-severe TR, moderate-to-severe MR, as well as RV functional improvement at discharge and 1 year.

In patients with irreversible PH post-TAVR, the risk of all-cause mortality is significantly higher at 30 days (HR: 4.41; 95% CI: 2.24 to 8.71), at 1 year (HR: 3.69; 95% CI: 2.46 to 5.53) and long-term follow-up (HR: 2.80; 95% CI: 1.99 to 3.93) compared with patients who have reversible PH, whereas the risk of stroke and MI is comparable.

Different groups of PASP elevation at baseline had comparable mortality at 30 days, at 1 year, and at long-term follow-up. After TAVR, however, patients with irreversible PH were at higher risk of all-cause mortality and CV mortality after 1 year and at long-term follow-up. In nearly one-half of patients, pre-existing PH significantly regressed after TAVR,

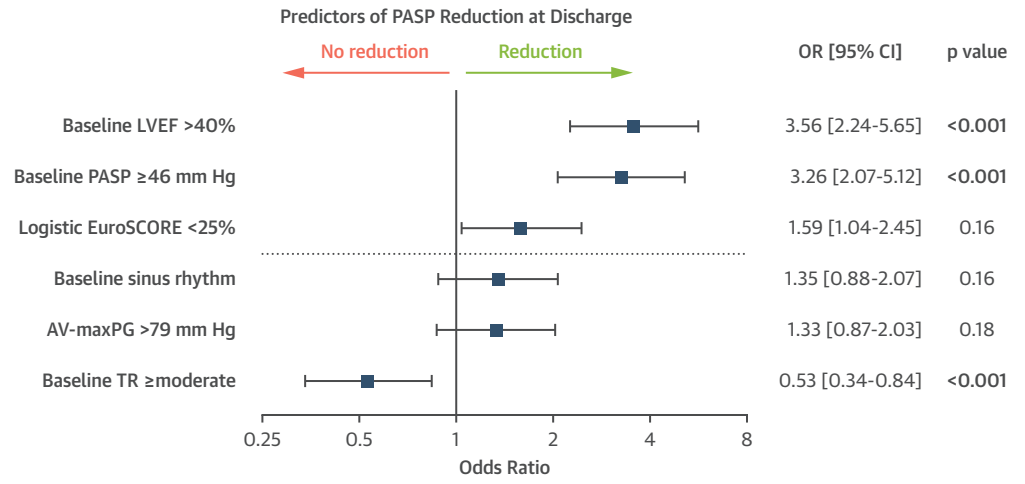
TABLE 2 Baseline Characteristics According to Groups of PASP Reduction at Discharge

	PASP reduction		
	Yes (n = 237, 46%)	No (n = 283, 54%)	p Value
Age	80 ± 8	81 ± 7	0.38
Age >85 yrs	57 (24)	81 (29)	0.27
Male	121 (51)	132 (47)	0.33
BMI, kg/m^2	27 ± 4	27 ± 5	0.46
Hypertension	220 (93)	255 (90)	0.35
NIDDM	112 (47)	135 (48)	0.93
CAD	165 (70)	199 (70)	0.92
MI	51 (22)	70 (25)	0.41
PCI	45 (19)	56 (20)	0.83
CABG	38 (16)	44 (16)	0.90
Stroke/TIA	40 (17)	41 (14)	0.47
PAD	55 (23)	87 (31)	0.06
CVA	15 (6)	20 (7)	0.86
COPD stage ≥II	10 (4)	13 (5)	1.00
NYHA functional class >II	200 (84)	243 (86)	0.71
Logistic EuroSCORE, %	22 ± 13	27 ± 17	<0.01
Creatinine	1.3 ± 0.8	1.7 ± 1.7	0.07
Baseline rhythm			0.04
Sinus rhythm	152 (64)	157 (56)	
Atrial fibrillation	44 (19)	66 (23)	
Previous pacemaker	41 (17)	60 (21)	
Valve type			0.62
CV	70 (30)	79 (28)	
ES	143 (60)	165 (58)	
Lotus	2 (0.9)	4 (1.4)	
Jena	15 (6.3)	28 (9.9)	
Portico	7 (3.0)	7 (2.5)	
Access site			0.90
Transfemoral	194 (82)	228 (81)	
Transapical	43 (18)	54 (19)	
Trans-subclavian	0 (0)	1 (0)	
Echocardiographic characteristics			
LVEF, %	56 ± 14	50 ± 16	<0.01
LVEDD, mm	49 ± 7	50 ± 8	0.50
AVA, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.59
Mean PG, mm Hg	46 ± 15	44 ± 16	0.16
Max PG, mm Hg	79 ± 24	73 ± 25	<0.01
LA volume	84 ± 27	83 ± 31	0.82
AR ≥ moderate	37 (17)	34 (13)	0.37
MR ≥ moderate	64 (28)	93 (34)	0.21
TR ≥ moderate	60 (28)	103 (39)	0.01
PASP, mm Hg	46 ± 10	45 ± 14	0.29
PASP ≥46 mm Hg	125 (53)	96 (34)	<0.01
TAPSE, mm	21 ± 6	20 ± 5	0.44
TAPSE <17 mm	55 (76)	57 (71)	0.58
e/E′	17 ± 6	16 ± 5	0.18

Values are mean ± SD with p values from Student's *t*-test or n (%) with p values from Fisher exact test.

BMI = body mass index; AR = aortic regurgitation; AVA = aortic valve area; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular arteriopathy; e/E′ = end-diastolic filling index; LA = left atrial; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; Max PG = maximal pressure gradient; Mean PG = mean pressure gradient; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; NIDDM = non-insulin-dependent diabetes; PAD = peripheral artery disease; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

FIGURE 4 Independent Predictors of PASP-Reduction Post-TAVR



The **symbols** indicate the point estimate (odds ratios [OR]) and the **lines** the [95% confidence intervals] from multivariate logistic regression. LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; AV-maxPG = aortic valve maximal pressure gradient; TR = tricuspid regurgitation.

which continued up to 1-year of follow-up. This regression was significantly more accentuated and affected a larger proportion of patients in the severe versus mild-to-moderate PH group.

The mechanisms underlying the development of PH following TAVR are complex and related to the rigidity of the hypertrophied LV, which require increased filling pressures that are transmitted to the left atrium and the pulmonary circulation. LV remodeling after valve replacement takes a long time and is only incompletely reversible (25,26). Therefore, short-term effects as observed in this study are likely not related to LV remodeling but can be attributed to the acute reduction of LV afterload and filling pressure in the setting of TAVR. This is observed in the current study in only approximately one-half of patients. In the other half, remodeling processes in the pulmonary vasculature can be hypothesized from longstanding PH, which may require longer periods of time to reverse. We therefore hypothesize that the failure of PH-regression after TAVR may be associated with longstanding PH or progressive vascular remodeling and therefore translate to an unfavorable prognosis.

TABLE 3 Clinical Outcomes at 30-Day, 1-Year, and Long-Term Follow-Up According to Groups of PASP Reduction at Discharge

	PASP Reduction				
	Total (N = 520, 100%)	Yes (n = 237, 46%)	No (n = 283, 54%)	Hazard Ratio (95% CI)	p Value
30 days					
All-cause mortality	59 (11)	10 (4.2)	49 (17)	3.49 (1.74–6.99)	0.001
CV mortality	29 (5.6)	5 (2.1)	24 (8.5)	3.35 (1.26–8.94)	0.02
1 year					
All-cause mortality	139 (32)	30 (15)	109 (45)	3.12 (2.06–4.72)	<0.001
CV mortality	47 (11)	12 (6.2)	35 (15)	2.27 (1.16–4.45)	0.017
Long term (5.9 yrs)					
All-cause mortality	172 (34)	46 (20)	126 (45)	2.47 (1.74–3.49)	<0.001
CV mortality	51 (9.9)	14 (6.0)	37 (13)	2.14 (1.14–4.04)	0.018

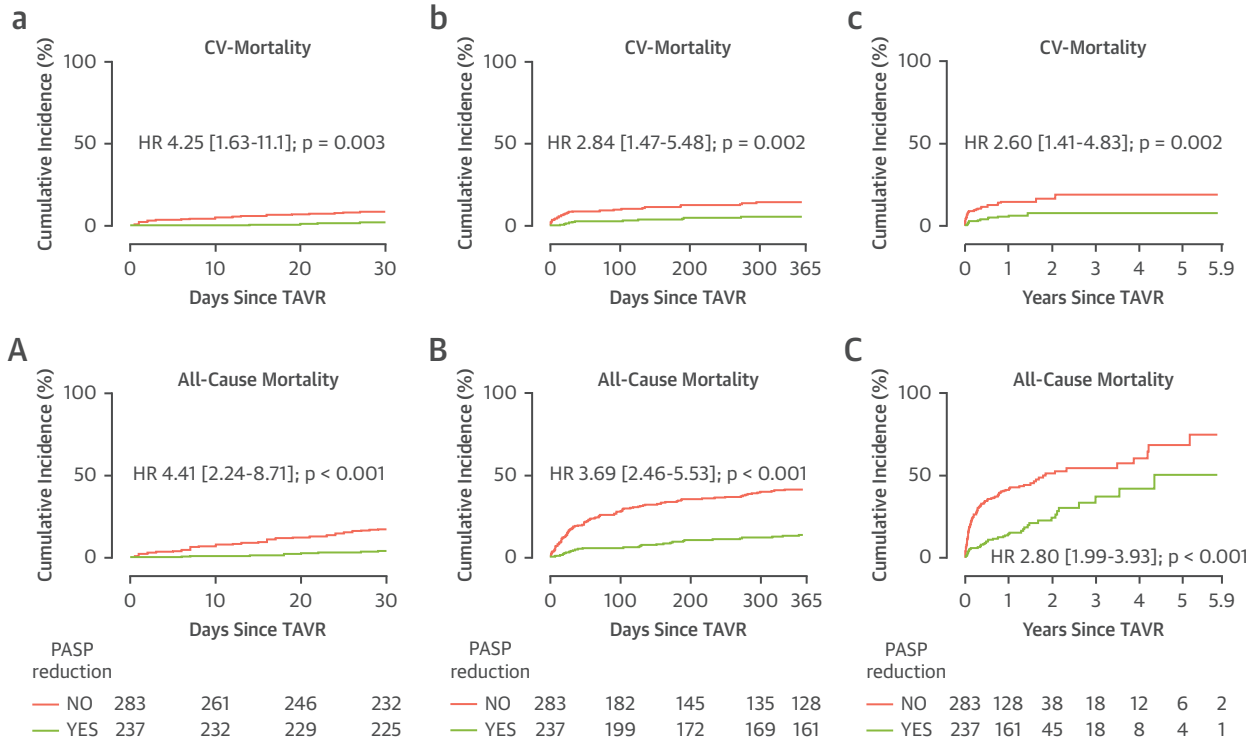
Values are n (%) unless otherwise indicated. Adjustment covariates were age >85 years, sex, body mass index, diabetes mellitus, coronary artery disease, previous MI or coronary artery bypass, peripheral artery disease, COPD stage >II, logistic EuroSCORE, atrial fibrillation, LVEF <35%, NYHA functional class >II at discharge.

Abbreviations as in Table 1.

It is known that the degree of MR influences PH (27,28). The overall presence of ≥ moderate MR and TR was low in our cohort (28% each), with a higher prevalence of MR in the severe PASP group. Severity of MR and TR improved significantly after TAVR in all PASP groups, likely associated with the reduction of LV pressure overload after TAVR (Online Table 2, Figure 3).

In patients with PH, clinical outcomes are also related to RV function. Recently, Schwarz et al. (29) observed that RV dysfunction, rather than TR, might be the main driver of adverse outcomes in the presence of multifactorial PH. The mechanisms responsible for RV dysfunction in patients undergoing TAVR are multifactorial, related to increased LV-filling pressures, PH with resultant pressure overload, compounded by TR and annulus dilatation (30).

FIGURE 5 Kaplan-Meier Estimates of Early, Mid-, and Long-Term All-Cause and CV Mortality According to the Presence or Absence of PASP-Reduction Post-TAVR



(A) All-cause and **(a)** CV-mortality at 30 days; **(B)** all-cause and **(b)** CV mortality at 1 year; **(C)** all-cause and **(c)** CV-mortality at 5.9 years of follow-up. Cumulative incidence (%) of events is from Kaplan-Meier, crude hazard ratios (HRs) and 95% confidence intervals (CIs) are from Cox regressions. CV = cardiovascular; TAVR = transcatheter aortic valve replacement; PASP = pulmonary artery systolic pressure.

Improvement of RV function is likely secondary to a decrease in RV afterload following TAVR as well as the reduction of MR (31-33). In our study, patients with reduced RV function were equally distributed among all PASP groups. But after TAVR, those with higher baseline PASP showed significant improvement of their RV function, which was not observed in patients with normal baseline PASP. Furthermore, in the subgroup of patients with reduced RV function, only those with pre-procedural PH showed significant improvement post-TAVR. The concomitant reduction of PASP, MR, TR, and improvement of RV dysfunction over time underlines the fact that severe pre-procedural PH should not be a contraindication to TAVR.

POST-TAVR REDUCTION OF PASP IS AN INDEPENDENT PREDICTOR OF CLINICAL OUTCOMES. Several studies have shown a prognostic role of PH on mid- and long-term mortality in patients undergoing SAVR (3,4). Only recently, few authors investigated the role of PH in the setting of TAVR (11,12,14,34). The results of these studies show some inconsistency regarding a weak association of PH with short- and mid-term mortality. Luçon et al. (14) and Tamburino et al. (15) could not show a significant role of PH in 30-day mortality, whereas several other authors in studies using different noninvasive cutoffs (>49 mm Hg, >60 mm Hg) for the severity of PASP have reported PASP as a predictor of mid-term mortality (11,34,35). However, only a few of these studies, yielding controversial results, focused on the predictive value of PASP after TAVR and the impact of TAVR-induced changes of PASP on clinical outcomes (11,12,14,34). Sinning et al. (11) and Medvedofsky et al. (34) reported better prognoses for patients showing reduction of their pre-procedural PASP values and persistent elevated PASP associated with higher mid-term mortality. Testa et al. (12) reported a reduction of PASP in patients previously in the mild-to-moderate and severe PASP groups but failed to show a benefit of PASP reduction in terms of survival, whereas Luçon et al. (14) reported a 20-mm Hg change in baseline PASP to be associated with better

overall survival. In our study, patients with reduced PASP had lower risk of all-cause and CV mortality at 30-day, 1-year, and long-term follow-up.

PREDICTORS OF PASP REDUCTION. Emerging evidence indicates that, when it comes to clinical outcomes, PH reversibility after TAVR is more important than baseline PH (11,12,34). To date, a limited number of small studies identified independent predictors of PASP reduction post-TAVR. Testa et al. (12) found that the absence of atrial fibrillation, functional causes of MR, and absence of severely depressed LVEF are independent predictors of PASP reduction of at least 15 mm Hg. Medvedofsky et al. (34) demonstrated the presence of COPD to be the only predictor of persistently elevated PASP post-TAVR. Ben-Dor et al. (13) identified LV dysfunction, AVA, and pulmonary artery wedge pressure to be independent predictors of PH regression.

In line with these results, we found that the absence of moderate-to-severe TR, LVEF >40%, logistic EuroSCORE <25%, and the presence of severe baseline PASP are independent predictors of reversible PH. Persistence of elevated PASP, secondary to left-heart disease, leads to an increase in RV size, worsening of RV function, and severity of TR. Despite severe, long-standing PH, the absence of significant TR observed in our study is probably associated with reversible RV modifications, leading to a regression of PH after the causal treatment of the high LV filling pressure. Indeed, our observation of a concomitant improvement of TR and TAPSE accompanying the PH reversibility post-TAVR may support this assumption. Also, the identification of logistic EuroSCORE <25% and severely elevated baseline PASP as predictors of PASP reduction indicates that multimorbid patients with severe baseline PH are more likely to profit from the beneficial effects of TAVR on PH.

STUDY LIMITATIONS. RHC is considered the gold standard for the measurement of PAP. However, the wide availability, inexpensiveness, and non-invasiveness make echocardiography a widely accepted and established method for the evaluation of PASP. In our study, RHC measurements of PASP demonstrated a good correlation with baseline PASP values measured with echocardiography with good agreement among the methods ($r = 0.60$; $p < 0.001$) (Online Figure 1). Interestingly, a systematic review of 29 studies demonstrated a good correlation ($r = 0.70$) with a sensitivity and specificity of 83% and 72%, respectively, of echo-measured PASP compared with RHC-PASP (36). Second, no data on interobserver variability of echocardiographic measurements was available. Third, clinical and echocardiographic data at 1-year follow-up were incomplete in part of the patients, as depicted in Online Table 8; nonetheless, our study is one of the largest on the topic with the longest echocardiographic and clinical follow-ups. Last, only limited data on loading conditions and different diuretic regimes, which can affect PASP measurements, were available; therefore, the results should be interpreted accordingly.

CONCLUSIONS

PH is a frequent finding among patients with severe AS undergoing TAVR. In this study, TAVR is associated with a regression of PH in most patients and a significant reduction of concomitant MR, TR, and improvement of RV dysfunction. However, patients with residual PH are at higher risk for all-cause and CV mortality at early, mid-, and late term. The severity of PH at baseline does not predict post-procedural early or late mortality and therefore should not be considered a contraindication for TAVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PH is a frequent comorbidity among patients with severe AS undergoing TAVR; however, PH severity at baseline is not a predictor of early and late mortality. After TAVR, most patients present a significant regression of PH. In contrast, patients with residual PH are at higher risk for all-cause and CV mortality at early, mid-, and long-term follow-up. Lower logistic EuroSCORE, preserved LVEF, and absence of moderate-to-severe TR, despite severe baseline PH, are independent predictors of reversible PH after TAVR. Therefore, the presence of PH should not preclude treatment with TAVR.

TRANSLATIONAL OUTLOOK: Early characterization of reversible or residual PH may help to link TAVR outcomes with appropriate follow-up care. Further studies are needed to assess whether persistent PH can be improved by therapeutic strategies beyond TAVR.

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KEY WORDS aortic stenosis, aortic valve, dysfunction, pulmonary hypertension, right ventricular, TAVR, tricuspid regurgitation

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