Impact of Combined Pre and Postcapillary Pulmonary Hypertension on Survival after Transcatheter Aortic Valve Implantation

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We aimed to evaluate the association between pulmonary hypertension (PH) hemodynamic classification and all-cause mortality in patients with symptomatic severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). PH is common and associated with post-TAVI outcomes in patients with severe AS. Although PH in these patients is primarily driven by elevated left-sided pressures (postcapillary PH), some patients develop increased pulmonary vascular resistance (PVR) configuring the combined pre- and postcapillary PH (CpcPH). We analyzed severe AS patients with mean pulmonary artery pressure (mPAP) measured by right heart catheterization (RHC) before TAVI between 2011 and 2017. PH hemodynamic classification was defined as: No PH (mPAP < 25 mm Hg); precapillary PH (mPAP ≥ 25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg); isolated postcapillary PH (IpcPH; mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg, PVR ≤ 3 Wood units (WU); CpcPH (mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg, PVR > 3 WU). Kaplan-Meier and Cox regression analyses were used to test the association of PH hemodynamic classification with post-TAVI all-cause mortality. We examined 561 patients (mean age 82 ± 8 years, 51% men, mean LVEF 54 ± 14%). The prevalence of no PH was 201 (36%); precapillary PH, 59 (10%); IpcPH, 189 (34%); and CpcPH, 112 (20%). During a median follow-up of 30 months, 240 all-cause deaths occurred. Patients with CpcPH had higher mortality than those with no-PH even after adjustment for baseline characteristics (Hazard ratio 1.56, 95% confidence interval 1.06 to 2.29, p = 0.025). There was no survival difference among patients with non-PH, precapillary PH and IpcPH. In conclusion, for patients with symptomatic severe AS treated with TAVI, CcpPH is independently associated with long-term all-cause mortality despite successful TAVI. **(Am J Cardiol 2020;131:60−66)**

Pulmonary hypertension (PH) is common in patients with severe aortic stenosis (AS)[1] and has shown to be an independent predictor of increased mortality in patients undergoing transcatheter aortic valve implantation (TAVI).[2−7] Integral to understanding how PH effects TAVI outcomes is recognizing the distinction between precapillary and postcapillary PH, which are defined by invasive hemodynamic parameters including mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR).[8] Precapillary PH is primarily from disease of pulmonary vasculature and postcapillary PH is primarily from left-side heart disease, although there is some pathophysiologic overlap.[9] A recent study[10] showed that markers of precapillary PH were associated with diminished survival following TAVI in patients with severe AS. Weber et al, using severe AS patients receiving either surgical aortic valve replacement or TAVI, reported that patients with combined pre- and postcapillary PH had worse survival compared with those with non-PH. However, these important findings are limited by small sample size. Therefore, this study sought to assess the effect of pre- and postcapillary PH on long-term all-cause mortality in patients with symptomatic severe AS treated with TAVI.

Methods

A retrospective analysis was performed for patients with severe AS who underwent TAVI from July 1, 2011 through January 31, 2017 at the University of Pittsburgh Medical Center, a large tertiary health care system. Patients underwent comprehensive clinical evaluation by a designated heart team and were deemed appropriate to undergo TAVI in accordance with guidelines.[11,12] We excluded patients without right heart catheterization (RHC) study prior to TAVI or with RHC study but no data of mPAP, PCWP, or

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cardiac output (CO) by Fick method. We also excluded patients who had valve in valve procedures as fundamental relationship between cardiac structure or function and clinical outcomes may be different for patients with previous aortic valve intervention. Primary outcome of this study is all-cause death after TAVI. Clinical, laboratorial and procedural data were collected from our institutional Society of Thoracic Surgeons database and augmented by chart review of electronic medical records. The study was performed according to the principles of the Declaration of Helsinki and approved by the University of Pittsburgh Institutional Review Board (IRB) with a waiver of individual consent. The IRB approved this as study # PRO16020002 on November 22, 2016 with a waiver of individual consent.

Patients underwent RHC using standard Swan-Ganz catheters by ultrasound-guided femoral or internal jugular vein access. Systolic, diastolic, and mean pulmonary artery pressure and mean PCWP (mPCWP) were measured. Measurements were obtained at end-expiration, mPCWP was calculated over the entire cardiac cycle, and V waves were included to determine mPCWP. In patients with atrial fibrillation at least 5 cardiac cycles were used to assess mPAP and mPCWP. CO was assessed by the indirect Fick method. PVR calculations were performed based on the standard formula: [(mPAP − mPCWP)/CO (by Fick method)]. Transpulmonary gradient (TPG) was calculated as mPAP − mPCWP. Diastolic pulmonary gradient (DPG) was calculated as diastolic PAP − mPCWP.

PH was defined as mPAP ≥ 25 mm Hg and was classified as pre-capillary PH (mPCWP ≤ 15 mm Hg), isolated postcapillary PH (IpcPH; mPCWP > 15 mm Hg, PVR ≤ 3 Wood units [WU]), or combined pre- and postcapillary PH (CpcPH; mPCWP > 15 mm Hg, PVR > 3 WU).[13] Given the recent controversy about using the DPG for the definition of CpcPH,[14] we decided to use only the PVR criterion.

Categorical variables are presented as frequency (percentage); groups are compared using the Chi-squared test. Continuous variables are presented as mean ± standard deviation and compared using Analysis of Variance (ANOVA). Survival after TAVI within each group is displayed using Kaplan-Meier curves. Univariable and Multivariable Cox regression analyses were performed to identify predictors of all-cause mortality. A 2-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM, Armonk, New York).

Results

A total of 730 patients received TAVI at our institution during the study period. Two patients were excluded as they received 2nd TAVI bioprosthesis implant for early valve failure. In addition, we excluded 82 patients who had RHC not performed prior TAVI, 21 patients who underwent valve-in-valve procedures for bioprosthesis failure and 11 patients who had available RHC but no mPAP data (Figure 1). Of 614 patients with mPAP measured by RHC prior to TAVI, 201 patients had normal mPAP value (< 25 mm Hg): non PH group, and 413 patients (67.3%) had baseline PH. After we excluded 53 patients without mPCWP or PVR data from 413 patients with baseline PH, precapillary PH (PCWP ≤ 15 mm Hg) was found in 59 patients. Patients with PH and PCWP > 15 mm Hg: postcapillary PH were further divided into two groups based on PVR. Thus, 4 groups of TAVI patients were identified: (1) non PH, n = 201; (2) precapillary PH, n = 59; (3) IpcPH, n = 189; and (4) CpcPH, n = 112. Therefore, the final study cohort included 561 patients (mean age 82.4 ± 7.8 years, 49% female, mean STS-PROM score 8.17 ± 4.58%).

The prevalence of atrial fibrillation and STS-PROM score gradually increased across the 4 groups (Table 1).

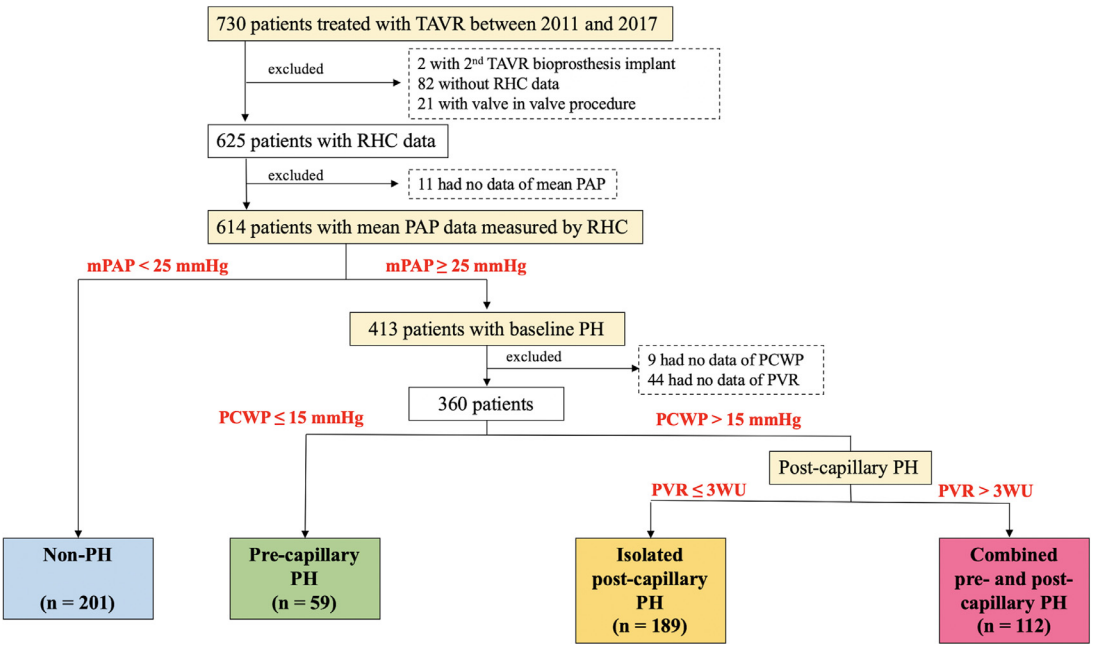

Figure 1. Data flow chart. A total of 730 severe aortic stenosis patients underwent transcatheter aortic valve implantation (TAVI) at our institution during the study period. A total of 169 patients were excluded, leaving 561 patients included in the final analysis.

Table 1
Baseline clinical characteristics

Variable	non-PH	Pulmonary Hypertension			p value
	(n = 201)	pre-capillary (n = 59)	Isolated post-capillary (n = 189)	Combined capillary (n = 112)	
Age (years)	82.9 ± 7.2	81.8 ± 5.9	82.1 ± 8.5	82.5 ± 8.3	0.71
Women	104 (52%)	28 (48%)	85 (45%)	58 (52%)	0.53
Body mass index (kg/m^2)	26.1 ± 5.5	26.5 ± 5.7	28.8 ± 6.5	28.6 ± 6.8	< 0.001
Diabetes mellitus	73 (36%)	27 (46%)	84 (44%)	50 (45%)	0.29
Dyslipidemia[†]	153 (76%)	49 (83%)	137 (73%)	95 (85%)	0.06
Hypertension	176 (88%)	54 (92%)	168 (89%)	104 (93%)	0.48
Previous CABG	52 (26%)	10 (17%)	63 (33%)	35 (31%)	0.07
Previous MI	58 (29%)	25 (42%)	75 (40%)	46 (41%)	0.05
Atrial fibrillation	53 (26%)	16 (27%)	80 (42%)	50 (45%)	0.001
Chronic lung disease	68 (34%)	30 (51%)	69 (37%)	43 (38%)	0.12
STS-PROM score (%)	7.16 ± 3.60	7.29 ± 3.31	8.87 ± 5.49	9.26 ± 4.63*	< 0.001
NYHA class III/IV	148 (74%)	39 (66%)	161 (85%)	88 (79%)	0.31

Values are shown as number (percentage), mean ± standard deviation.

CABG = coronary artery bypass graft; Chronic Lung Disease included patients with chronic obstructive pulmonary disease, chronic bronchitis or emphysema; MI = myocardial infarction; NYHA = New York Heart Association functional class; STS-PROM = The Society of Thoracic Surgeons Predicted Risk of Mortality.

* $p < 0.05$ vs Pre-capillary PH.

[†] Dyslipidemia is defined as total cholesterol >200 mg/dL, or LDL ≥ 130 mg/dL, or HDL <40 mg/dL in men and <50 mg/dL in women, or current usage of antilipidemic treatment.

Left ventricular ejection fraction (LVEF), right ventricular (RV) function, and tricuspid regurgitation (TR) gradually worsened across the groups (Table 2). Similarly, given the PH hemodynamic classification criteria used, there were significant differences across groups in virtually hemodynamic variables assessed. There is no significant difference in the severity of AS (either by aortic valve area index and/or aortic valve mean gradient) across the groups (Table 2).

All patients received successful TAVI. There were no significant differences among the groups regarding procedural characteristics including valve type, access site, or the degree of paravalvular leak at discharge (supplemental Table 1). Baseline clinical and echocardiographic characteristics to the excluded due to RHC not performed prior TAVI (n = 82) is available on supplemental Table 2.

During a median follow-up of 30 months after TAVI (interquartile range: 19 to 42 months), 240 all-cause deaths occurred (cumulative event rate 42.8%), 68 of those with non PH (33.8%), 23 (39.0%) in those with precapillary PH, 83 (43.9%) of those with IpcPH, and 66 (58.9%) of those with CpcPH (Figure 2, Panel A, Chi-square 13.7, $p = 0.003$). Patients with CpcPH had significantly higher all-cause mortality compared with patients with non-PH (hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.32 to 2.69, $p < 0.001$; Table 3); on the other hand, patients with precapillary PH or IpcPH did not have statistically significantly greater risk compared with patients with non-PH.

In the univariable Cox regression analysis, atrial fibrillation, STS-PROM score, LVEF, left atrial volume index, TAPSE, greater than moderate RV dysfunction and tricuspid regurgitation (TR), low flow low gradient AS and PH hemodynamic classification were independently associated with all-cause mortality (Table 4). On the multivariable Cox regression analysis, PH hemodynamic classification, atrial fibrillation and STS-PROM score remained independently associated with all-cause mortality. Figure 2. Panel B demonstrates the adjusted survival curves, after accounting for the variables that used in the multivariable Cox regression model. Worse mortality in those with CpcPH remained unchanged (Chi-square 49.6, $p < 0.001$). After adjustment for these baseline characteristics, only patients with CpcPH had significantly higher post-TAVI all-cause mortality than those with non-PH (HR 1.56, 95% CI 1.06 to 2.29, $p = 0.025$; Table 3).

Discussion

In this study, we evaluated the association of baseline PH hemodynamic classification with post-TAVI all-cause mortality using a large, single center, well phenotyped, cohort of symptomatic severe AS patients treated with TAVI. Our study has 2 key findings. First, combined pre- and postcapillary PH defined by mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg and PVR > 3 WU is common (20% of our study cohort), which is 31% of patients with baseline PH. Second, even after comprehensive adjustment for baseline characteristics including not only LV but also RV function and TR, patients with CpcPH had significantly higher all-cause mortality than those with non-PH. On the other hand, there was no significant difference in post-TAVI mortality among patients with non-PH, precapillary PH, and IpcPH.

PH frequently coexists with severe AS. Although previous studies have reported a strong associated between baseline PH and worse post-TAVI outcomes,[2–7] the majority of these studies is limited to echocardiographic measurements with little detail regarding pre- and postcapillary PH markers. The challenge remains to identify the etiology of the PH as there are numerous causes with combined cardiac and pulmonary components. Although detailed RHC measurements provide further insight into the interplay between pre- and postcapillary PH,[15–17] there is some controversy

Table 2
Baseline echocardiographic and hemodynamic characteristics

Variable	non-PH (n = 201)	PH			p value
		pre-capillary (n = 59)	Isolated post-capillary (n = 189)	Combined capillary (n = 112)	
		Echocardiographic variables			
LV ejection fraction (%)	57.3 ± 11.2	56.2 ± 12.7	52.3 ± 14.4	50.2 ± 15.2*	< 0.001
LV mass index (g/m^2)	123.1 ± 38.3	118.9 ± 28.9	135.8 ± 37.1	128.0 ± 37.0	0.002
Stroke volume index (ml/m^2)	39.1 ± 9.9	37.5 ± 11.3	36.1 ± 13.2	30.7 ± 9.1*,†	< 0.001
Left atrium volume index (ml/m^2)	46.2 ± 17.2	45.4 ± 20.1	49.3 ± 17.5	50.1 ± 15.5	0.13
TAPSE (cm)	1.99 ± 0.50	1.82 ± 0.42	1.82 ± 0.54	1.62 ± 0.44*,†	< 0.001
RV dysfunction ≥ moderate	2 (1%)	2 (3%)	10 (6%)	8 (8%)	0.032
PASP (mmHg)	36.4 ± 11.4	44.5 ± 21.1	44.2 ± 13.5	53.0 ± 18.6	< 0.001
Mod-severe tricuspid regurgitation	20 (10%)	10 (17%)	31 (16%)	26 (23%)*	0.02
Mod-severe mitral regurgitation	16 (8%)	3 (5%)	28 (15%)	21 (19%)	0.009
Mod-severe aortic regurgitation	10 (5%)	4 (7%)	12 (6%)	6 (5%)	0.92
Low flow low gradient aortic stenosis	21 (11%)	4 (7%)	39 (22%)	32 (30%)	< 0.001
		Hemodynamic variables			
Aortic SBP (mmHg)	135 ± 30	136 ± 23	139 ± 28	147 ± 27	0.019
Cardiac index by Fick method	2.8 ± 0.7	2.7 ± 0.5	2.8 ± 1.0	2.3 ± 0.5*,†	< 0.001
Right arterial pressure (mmHg)	5 ± 3	7 ± 3	11 ± 5	12 ± 5*,†	< 0.001
Systolic PAP (mmHg)	33 ± 7	49 ± 13	53 ± 12	70 ± 14*,†	< 0.001
Mean PAP (mmHg)	19 ± 4	30 ± 6	34 ± 7	44 ± 9*,†	< 0.001
PCWP (mmHg)	12 ± 6	13 ± 3	24 ± 6	25 ± 6*	< 0.001
LVEDP (mmHg)	6.0 ± 10.0	6.3 ± 7.9	12.3 ± 13.9	14.4 ± 15.8*	< 0.001
TPG (mmHg)	7.7 ± 6.5	17.7 ± 6.9	10.1 ± 3.5	19.0 ± 6.5†	< 0.001
DPG (mmHg)	-0.27 ± 6.65	5.12 ± 5.16	-3.09 ± 5.57	1.23 ± 5.84*,†	< 0.001
AV area index (cm^2/m^2)	0.41 ± 0.13	0.40 ± 0.13	0.41 ± 0.13	0.37 ± 0.12	0.21
AV mean gradient (mmHg)	43 ± 15	48 ± 13	45 ± 17	45 ± 15	0.45

Values are shown as number (percentage), mean ± standard deviation.

AV = aortic valve; DPG = diastolic pulmonary gradient; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PAP = pulmonary artery pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion; TPG = transpulmonary gradient.

Low flow low gradient aortic stenosis as defined stroke volume index <35ml/m$_2$ and aortic valve mean gradient < 40 mg.

* $p < 0.05$ vs precapillary PH.

† $p < 0.05$ vs. Isolated postcapillary PH.

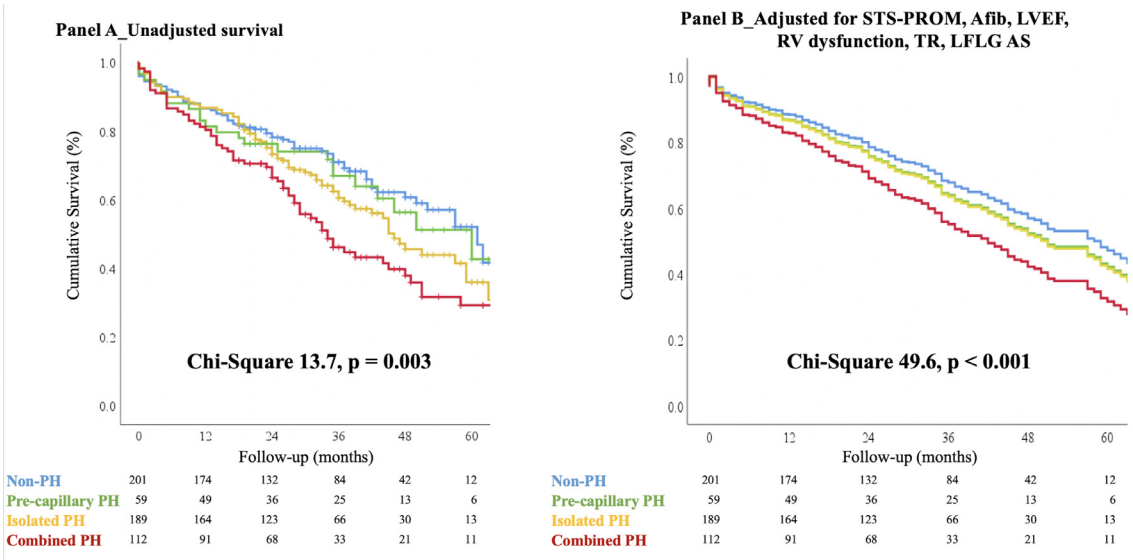

Figure 2. All-cause mortality after TAVI according to baseline PH classification

Panel A - Unadjusted Kaplan-Meier survival curves. Patients with combined pre- and postcapillary PH had higher mortality than those with non-PH ($p < 0.001$) and those with pre-capillary PH ($p = 0.036$). There was no survival difference among patients with non-PH, precapillary PH and isolated postcapillary PH.

Panel B - Adjusted survival curves. Worse mortality in patients with combined pre- and postcapillary PH remained unchanged even after adjustment for STS-PROM score, atrial fibrillation, left ventricular ejection fraction, more than moderate right ventricular dysfunction and tricuspid regurgitation, and low flow low gradient aortic stenosis. PH = pulmonary hypertension; STS-PROM = the Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 3
Association between pulmonary hypertension hemodynamic classification and outcomes

	Unadjusted			Adjusted for STS-PROM, Afib, LVEF, RV dysfunction, ≥ moderate TR, LFLG AS		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p value
Non-PH	1.0 (reference)			1.0 (reference)		
Pre-capillary PH	1.12	0.70-1.80	0.64	1.18	0.72-1.92	0.51
Isolated post-capillary PH	1.35	0.98-1.87	0.06	1.18	0.83-1.66	0.36
Combined pre- and post- capillary	1.85	1.32-2.69	< 0.001	1.59	1.09-2.32	0.015

Afib = atrial fibrillation; LFLG AS = low flow low gradient aortic stenosis as defined stroke volume index < 35 ml/m_2 and aortic valve mean gradient < 40mg; LVEF = left ventricular ejection fraction; PH = pulmonary hypertension; RV = right ventricular; STS-PROM = The Society of Thoracic Surgeons Predicted Risk of Mortality; TR = tricuspid regurgitation.

Table 4
Univariable and multivariable Cox regression analysis of all-cause death

	Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	0.99	0.97-1.00	0.15			
Women	0.81	0.63-1.05	0.11			
Body mass index (kg/m^2)	1.00	0.98-1.02	0.97			
Diabetes mellitus	1.07	0.82-1.38	0.63			
Hypertension	1.26	0.80-1.99	0.33			
Atrial fibrillation	1.55	1.20-2.00	0.001	1.37	1.04-1.81	0.024
Chronic Lung Disease	1.13	0.87-1.46	0.36			
STS-PROM score	1.06	1.04-1.09	< 0.001	1.05	1.02-1.07	< 0.001
Echocardiographic variables						
LV ejection fraction (%)	0.98	0.98-0.99	< 0.001	0.99	0.98-1.00	0.17
LV mass index (g/m^2)	1.00	1.00-1.01	0.20			
Left atrium volume index (ml/m^2)	1.01	1.00-1.02	0.013			
TAPSE (cm)	0.75	0.57-0.98	0.034			
RV dysfunction ≥ moderate	2.27	1.36-3.77	0.002	1.37	0.75-2.49	0.31
Tricuspid regurgitation ≥ moderate	1.67	1.22-2.29	0.001	1.06	0.75-1.52	0.74
Low flow low gradient aortic stenosis	1.56	1.15-2.12	0.005	1.07	0.75-1.54	0.70
Hemodynamic variables						
Aortic valve area index (cm^2/m^2)	1.67	0.44-6.4	0.45			
Aortic valve mean gradient (mmHg)	0.99	0.98-1.00	0.09			
Combined pre- and post-capillary PH	1.59	1.20-2.11	0.001	1.43	1.05-1.95	0.022

Chronic Lung Disease included patients with chronic obstructive pulmonary disease, chronic bronchitis or emphysema; CI = confidence interval; HR = hazard ratio; LV = left ventricular; PH = pulmonary hypertension; RV = right ventricular; STS-PROM = The Society of Thoracic Surgeons Predicted Risk of Mortality; TAPSE, tricuspid annular plane systolic excursion.

Low flow low gradient aortic stenosis as defined stroke volume index < 35ml/m_2 and aortic valve mean gradient <40 mg.

as to what RHC parameters are the most relevant for defining precapillary PH due to pulmonary vascular remodeling in patients with left heart disease.[18] TPG has been used to describe precapillary PH, although it has been considered unreliable due to being flow dependent and influenced by left atrial pressure.[18–20] DPG has also been described as a reliable precapillary PH marker,[21] although multiple studies have since discredited DPG as a dependable prognostic indicator in patients with left heart disease and PH.[18,22] Albeit with some limitations, elevated PVR has been considered a reliable measurement to predict outcomes in patients with a precapillary component to PH.[18,23,24] Although guidelines suggest using the criterion of PVR > 3 WU and/or DPG ≥ 7 mm Hg for the definition of CpcPH,[13] given these previous results, we decided to use only the PVR as an indicator of CpcPH in this study.

In a study which used invasive hemodynamic metrics to stratify 433 TAVI patients based on preoperative PH, O'Sullivan et al[25] using left ventricular end-diastolic pressure for dividing pre or postcapillary and DPG for dividing IpcPH or CpcPH, showed that baseline CpcPH was independently associated with post- TAVI 1-year mortality. A recent study by Weber et al, using 503 severe AS patients receiving either surgical aortic valve replacement (n = 361) or TAVI (n = 142), reported that patients with CpcPH defined by PCWP and PVR had worse survival compared with those with non-PH.

We build on their findings by showing that, in a homogeneous large cohort of symptomatic severe AS patients, all receiving contemporary TAVI devices, that baseline CpcPH defined by mPAP, PCWP, and PVR is independently associated with post-TAVI all-cause mortality in these patients, despite adjustment for multiple confounders. Furthermore, the association with all-cause mortality persists with up to 5-years of follow-up.

The ability to identify subgroups of patients with PH undergoing TAVI that could respond poorly has far

reaching implications. In patients with severe AS and pre-existing PH, TAVI has a strong associated with both early and late reduction in pulmonary artery systolic pressure.[26] However, patients with residual PH following TAVI have a higher risk of both short and long-term mortality.[26,27] Of special note, atrial fibrillation was associated with baseline IpcPH and CpcPH. Atrial fibrillation may be a marker of left ventricular dysfunction, but may also further aggravate left-sided dysfunction. Indeed, on multivariable analysis, atrial fibrillation remained significantly associated with worse survival after TAVI, suggesting an additive independent effect on survival along with CpcPH. Thus, patients with comorbid atrial fibrillation and CpcPH may represent a high-risk subgroup.

Based on these previous results and on our current findings, patients with baseline CpcPH and/or persistent PH derive benefit from TAVI, however they will need a closer follow-up and potential additional therapies beyond TAVI. The use of targeted pulmonary vasodilator therapy (e.g., PDE-5 inhibitors) postsurgical valvular correction (mostly mitral valve either isolated or combined with valvular disease), has recently shown to not have significant benefits when compared with placebo, and was potentially associated with increased risk for heart failure readmissions. This trial however included only 3 patients who received TAVI, and more than one-third of patients who received Sildenafil had already undergone prior valve surgery, and were enrolled after redo valvular intervention.[28] Given the continued worldwide growth of TAVI, elucidating tailored treatment regimens will continue to be important, as well as earlier AV intervention in the presence of PH, but absence of symptoms.[29]

There are limitations in our study. First, this was a single-center, retrospective study. However, the number of events and patients treated with TAVI was relatively large allowing for comprehensive multivariable analysis and adjustments. Second, cause of death was not available for all patients, limiting the causal relationship analysis. Finally, invasive PAPs were only measure prior TAVI but not afterward routinely in these patients and therefore this data is not available.

In conclusion, for patients with severe AS treated with TAVI, baseline combined pre- and post- PH defined by elevated mPAP, PCWP, and PVR is common and independently associated with long-term all-cause mortality, despite successful TAVI. The hemodynamic assessment of PH using RHC, as a routine part of patient assessment prior to TAVI, may therefore provide useful information to identify patients at higher all-cause mortality and potentially inform additional therapies beyond TAVI.

Author Contributions

Concept – JLC, IS, GH, DEK. Methodology – JLC, MF. Software – FWT, DEK, JSL, JTS. Validation – IS, MF, VB, JAB, AK. Analysis – MF, JLC, IS, VB, AK, FWT. Resources – JAB, TGG, JSL, JTS, IS, GH, AK, TGG. Data curation – FWT, GH, DEK, JAB, VB, JTS. Writing original draft – VB, IS, MF. Writing review and edits – JLC, IS, MF, VB, JAB. Supervision – JLC, JSL, TGG. Final approval – All authors.

Disclosures

Dr. Schindler has served on the advisory board of Boston Scientific; and on the speakers' bureau for Edwards Lifesciences; Dr. Gleason has received research funding from Medtronic and Boston Scientific; and has been a consultant for Abbott; Dr. Cavalcante has received research funding and consultant fees from Medtronic Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.06.037.

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