Clinical Relevance of Baseline TCP in Transcatheter Aortic Valve Replacement

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ABSTRACT: Aims. To investigate the influence of baseline thrombocytopenia (TCP) on short-term and long-term outcomes after transcatheter aortic valve replacement (TAVR). **Methods and Results.** A total of 732 consecutive patients with severe, symptomatic aortic stenosis undergoing TAVR from January 2012 to December 2015 were included. Primary outcomes of interest were the relationship of baseline TCP with 30-day and 1-year all-cause mortality. Secondary outcomes of interest were procedural complications and in-hospital mortality in the same subgroups. The prevalence of TCP (defined as platelet count <150 × 10^9/L) at baseline was 21.9%, of whom 4.0% had moderate/severe TCP (defined as platelet count <100 × 10^9/L). Compared to no or mild TCP, moderate/severe TCP at baseline was associated with a significantly higher 30-day mortality (23.3% vs 2.3% and 3.1%, respectively; P<.001) and 1-year mortality (40.0% vs 8.3% and 13.4%, respectively; P<.001). In Cox regression analysis, moderate/severe baseline TCP was an independent predictor of 30-day and 1-year mortality (hazard ratio [HR], 13.18; 95% confidence interval [CI], 4.49-38.64; P<.001 and HR, 5.90; 95% CI, 2.68-13.02; P<.001, respectively). **Conclusions.** In conclusion, baseline TCP is a strong predictor of mortality in TAVR patients, possibly identifying a specific subgroup of frail patients; therefore, it should be taken into account when addressing TAVR risk.

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Significant thrombocytopenia (TCP) commonly occurs in seriously ill patients and after open-heart surgery, possibly as a result of cardiopulmonary bypass, use of intraaortic balloon counterpulsation, sepsis, and post-transfusion purpura.[1] However, even severe TCP has not been clearly linked to a significant worsening in outcomes after surgical aortic valve replacement (SAVR).[2] Transcatheter aortic valve replacement (TAVR) is the standard of care in high-risk and intermediate-risk patients with symptomatic severe aortic stenosis (AS). Current evidence suggests that acquired TCP occurring after TAVR may be due to thienopyridine use and extracorporeal circulatory support,[3] and may be associated with adverse outcomes.[4,5] However, few data exist regarding clinical outcomes associated with baseline TCP in patients undergoing TAVR. In a single small study, moderate-severe TCP was not associated with mortality, although the study was underpowered.[6] Given that TAVR is most often performed in elderly subjects, many of whom are also frail and have baseline TCP, the aim of this study was to evaluate the effect of baseline TCP on clinical outcomes after TAVR.

Methods

Data were collected on consecutive patients with severe, symptomatic AS undergoing TAVR at Baylor Heart and Vascular Hospital (Dallas, Texas) and The Heart Hospital Baylor Plano (Plano, Texas) from January 2012 to December 2015. Baseline demographics, procedural data, and clinical outcomes were retrospectively collected and analyzed. For the purpose of the current analysis, data from both medical centers were pooled and a joint database was created. The study was approved by the Baylor Institutional Review Board. The following definitions were used in accordance with the Valve Academic Research Consortium (VARC)-2 standardized endpoint definitions for TAVR consensus document: vascular complication; bleeding; neurological events; and acute kidney injury.[7] Patients were stratified into two groups according to the presence/absence of TCP at baseline: group 1 = no TCP, defined as platelet counts within the "normal" reference range (150 × 10^9/L to 500 × 10^9/L); group 2 = mild baseline TCP, defined as platelet count 100 × 10^9/L to 150 × 10^9/L; and group 3 = moderate/severe baseline TCP, defined as platelet count <100 × 10^9/L.[6]

Primary outcomes of interest of this study were the incidence of all-cause 30-day and 1-year mortality; secondary outcomes of interests were procedural complications (acute kidney injury, vascular complications, minor and major bleeding, stroke/transient ischemic attack), in-hospital mortality, and cardiovascular mortality at 30-day follow-up.

Statistical analysis. Continuous variables are summarized as mean ± standard deviation or as median and interquartile range (IQR) as appropriate, and were compared using Student's t-test or Mann-Whitney rank-sum test. Categorical variables were compared using Chi-squared test or Fisher's exact test. Cox regression was used for multivariate analysis. For the prediction of 30-day and 1-year all-cause

Table 1. Characteristics of the study population.

	All Patients (n = 732)	No Thrombocytopenia (>150 x 10^9/L) (n = 571)	Baseline Thrombocytopenia		*P*-Value
			Mild (100-150 x 10^9/L) (n = 131)	Moderate-Severe (<100 x 10^9/L) (n = 30)	
Baseline characteristics					
Age (years)	81.8 ± 7.9	81.6 ± 8.1	82.7 ± 7.1	81.4 ± 7.6	.37
Male gender	395 (54.0%)	280 (49.0%)	89 (67.9%)	26 (86.7%)	<.001
Body mass index (kg/m^2)	27.5 ± 6.6	27.8 ± 6.8	26.7 ± 6.1	26.2 ± 5.3	.12
STS score	7.6 ± 3.8	7.6 ± 3.8	7.2 ± 3.7	8.4 ± 5.3	.45
Hypertension	598 (82.4%)	470 (83.2%)	103 (78.6%)	25 (83.3%)	.46
Hyperlipidemia	498 (68.9%)	389 (69.0%)	92 (70.2%)	17 (60.7%)	.61
Diabetes	269 (38.2%)	201 (36.6%)	50 (39.1%)	18 (64.3%)	.01
Chronic kidney disease	331 (45.5%)	269 (47.5%)	45 (34.4%)	17 (56.7%)	.01
End-stage renal disease	24 (3.5%)	20 (3.7%)	3 (2.4%)	1 (3.8%)	.77
Coronary artery disease	481 (66.2%)	377 (66.5%)	81 (62.3%)	23 (76.7%)	.31
Peripheral arterial disease	218 (31.1%)	176 (32.1%)	34 (26.8%)	8 (29.6%)	.50
Chronic obstructive pulmonary disease	138 (19.9%)	110 (20.3%)	23 (18.4%)	5 (18.5%)	.87
Atrial fibrillation	218 (29.8%)	166 (29.1%)	42 (32.1%)	10 (33.3%)	.58
Previous CABG/PCI	310 (43.9%)	235 (42.8%)	59 (46.1%)	16 (55.2%)	.36
Previous cerebrovascular accident	124 (18.0%)	104 (19.4%)	17 (13.6%)	3 (11.5%)	.22
Baseline platelet count (x 10^9/L)	202.6 ± 71.6	225.1 ± 63.1	129.3 ± 13.5	75.9 ± 14.7	<.001
Nadir platelet count (x 10^9/L)	128.6 ± 51.5	141.2 ± 49.9	89.3 ± 19.3	53.1 ± 18.7	<.001
Echocardiographic findings					
Left ventricular ejection fraction (%)	54.6 ± 13.4	54.5 ± 13.6	55.0 ± 13.2	56.5 ± 10.9	.67
Aortic valve mean gradient (mm Hg)	44.7 ± 14.1	44.2 ± 13.5	45.9 ± 13.6	49.7 ± 23.9	.06
Aortic valve area (mm^2)	0.68 ± 0.18	0.68 ± 0.18	0.68 ± 0.21	0.73 ± 0.21	.31
Right ventricular systolic pressure (mm Hg)	43.3 ± 14.7	43.5 ± 14.7	42.4 ± 12.1	44.1 ± 23.1	.79
Procedural characteristics					
Type of valve					.52
Balloon expandable	440 (60.1%)	349 (61.1%)	73 (55.7%)	18 (60.0%)	
Self expandable	292 (39.9%)	222 (38.9%)	58 (44.3%)	12 (40.0%)	
Approach					.70
Transfemoral	631 (86.2%)	493 (86.3%)	114 (87.0%)	24 (80.0%)	
Transapical	668 (9.2%)	50 (8.8%)	14 (10.7%)	4 (13.3%)	
Transaortic	29 (4.0%)	24 (4.2%)	3 (2.3%)	2 (6.7%)	
Subclavian	4 (0.5%)	4 (0.7%)	0 (0%)	0 (0%)	

Data provided as mean ± standard deviation or number (percentage).
STS = Society of Thoracic Surgeons; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

mortality (dependent variables), baseline variables of clinical interest and/or satisfaction of the entry criterion of $P<.05$ in the univariable analysis were used as explanatory variables. Interaction testing was performed to determine whether the effect of TCP was consistent irrespective of Society of Thoracic Surgeon (STS) score, age, aortic mean gradient, or chronic kidney disease, on the primary endpoints of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were performed using SPSS version 19 statistical software (SPSS, Inc).[8]

Table 2. Clinical outcomes.

	All Patients (n = 732)	No Thrombocytopenia (>150 x 10^9/L) (n = 571)	Baseline Thrombocytopenia		*P*-Value
			Mild (100-150 x 10^9/L) (n = 131)	Moderate-Severe (<100 x 10^9/L) (n = 30)	
Procedural complications					
Acute kidney injury	11/732 (1.5%)	6 (1.1%)	2 (1.5%)	3 (10.0%)	<.001
Vascular complication	28/732 (3.8%)	23 (4.0%)	3 (2.3%)	2 (6.7%)	.46
Minor bleeding	47/731 (6.4%)	37 (6.5%)	6 (4.6%)	4 (13.3%)	.34
Major bleeding	12/731 (1.6%)	11 (1.9%)	1 (0.8%)	0 (0.0%)	.34
Stroke/transient ischemic attack	18/732 (2.5%)	15 (2.6%)	3 (2.3%)	0 (0.0%)	.66
In-hospital mortality	13/732 (1.7%)	8 (1.4%)	1 (0.8%)	4 (13.3%)	<.001
30-day cardiovascular mortality	19/732 (2.6%)	12 (2.3%)	1 (0.8%)	5 (16.7%)	<.001
30-day all-cause mortality	24/732 (3.3%)	13 (2.3%)	4 (3.1%)	7 (23.3%)	<.001
1-year all-cause mortality	70/672 (10.4%)	44 (8.3%)	16 (13.4%)	10 (40.0%)	<.001

Data provided as number/total patients with available data (percentage) or number (percentage).

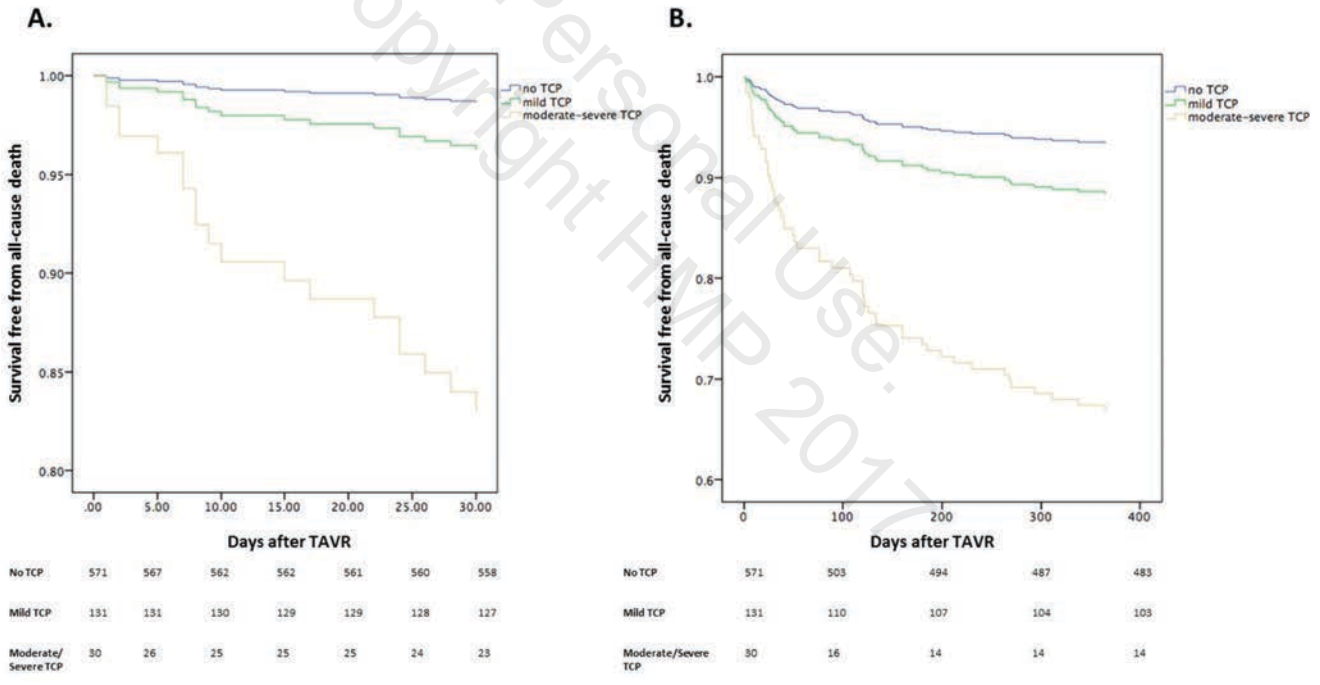

FIGURE 1. Cox proportional model plot for the primary endpoints of all-cause mortality. (A) 30-day survival according to the severity of thrombocytopenia (TCP) at baseline. (B) 1-year survival according to the severity of TCP at baseline.

Results

The study population consisted of 732 patients. Baseline patient characteristics are summarized in Table 1. The prevalence of TCP at baseline was 21.9%, of which 17.9% had mild TCP and 4.0% had moderate/severe TCP. At admission, mean platelet count was 202.6 ± 71.6 x 10^9/L. Mean nadir platelet count after TAVR was 128.6 ± 51.5 x 10^9/L. There were no differences in age or procedural characteristics. However, patients with moderate/severe TCP at baseline were more frequently male, and more commonly had diabetes and chronic kidney disease. Moreover, in this same patient group, the prevalence of liver cirrhosis was 16.7% (5/30), whereas in the rest of the population only 4 patients had liver disease (4/702; 0.6%). Of the remaining 22 patients with moderate/severe TCP, 20 were reported to suffer from pancytopenia. However, a complete hematological work-up was not available for every patient. Study subjects were followed for 1 year after the procedure, with clinical and echocardiographic

Table 3. Predictors of 30-day all-cause mortality.

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.07 (1.00-1.14)	.04	1.06 (0.99-1.15)	.11
Male sex	1.01 (0.45-2.28)	.99	–	–
Chronic kidney disease	3.53 (1.38-9.05)	<.01	3.06 (0.97-9.60)	.06
Baseline TCP				
Mild	1.35 (0.43-4.13)	.60	–	–
Moderate/severe	13.06 (4.46-35.83)	<.001	13.18 (4.49-38.64)	<.001
Non-transfemoral access	3.06 (1.08-8.62)	.04	5.15 (1.27-20.97)	.02
RVSP	1.03 (1.01-1.06)	.02	1.01 (0.99-1.04)	.23
STS score >8	1.12 (0.39-3.19)	.83	–	–

HR = hazard ratio; CI = confidence interval; RVSP = right ventricular systolic pressure; STS = Society of Thoracic Surgeons.

Table 4. Predictors of 1-year all-cause mortality.

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.00 (0.97-1.03)	.99	–	–
Male sex	2.32 (1.35-3.99)	<.01	2.01 (1.06-3.79)	.03
Chronic kidney disease	2.04 (1.22-3.39)	<.01	1.88 (1.04-3.39)	.04
Baseline TCP				
Mild	1.71 (0.93-3.15)	.08	–	–
Moderate/severe	7.33 (3.11-17.29)	<.001	5.90 (2.68-13.02)	<.001
Non-transfemoral access	3.83 (1.56-9.68)	<.01	7.58 (3.12-18.38)	<.001
RVSP	1.02 (1.00-1.04)	.02	1.01 (0.99-1.03)	.11
STS score >8	1.00 (0.56-1.79)	.10	–	–

HR = hazard ratio; CI = confidence interval; RVSP = right ventricular systolic pressure; STS = Society of Thoracic Surgeons.

evaluation at 30 days, 6 months, and 12 months; 92.2% of the initial population completed 1-year follow-up. Clinical outcomes are described in Table 2. Patients with moderate/severe baseline TCP showed the worst outcomes; indeed, moderate/severe TCP at baseline was associated with significantly higher 30-day and 1-year all-cause mortality when compared to patients with no or mild TCP (23.3% vs 2.3% and 3.1% [*P*<.001] and 40.0% vs 8.3% and 13.4% [*P*<.001], respectively) (Table 2, Figure 1A). Moreover, when compared to patients without TCP, patients with baseline moderate/severe TCP showed an increased rate of in-hospital and 30-day cardiovascular mortality (13.3% vs 1.4% [*P*<.001] and 16.7% vs 2.3% [*P*<.001], respectively) (Table 2, Figure 1B). Procedural complications (vascular complications, minor and major bleedings, stroke/transient ischemic attack) were not different among groups apart from a higher incidence of acute kidney injury in patients with baseline moderate/severe TCP (10.0% vs 1.1%; *P*<.001) (Table 2). Cox regression analysis results for 30-day and 1-year mortality are reported in Table 3 and Table 4. Baseline moderate/severe TCP and non-transfemoral access were independent predictors of 30-day all-cause mortality (hazard ratio [HR], 13.18; 95% confidence interval [CI], 4.49-38.64 [*P*<.001] and HR, 5.15; 95% CI, 1.27-20.97 [*P*=.02], respectively) (Table 3). Baseline moderate/severe TCP, non-transfemoral access, male gender, and chronic kidney disease were independent predictors of 1-year all-cause mortality (HR, 5.90; 95% CI, 2.68-13 [*P*<.001]; HR, 7.58; 95% CI, 3.12-18.38 [*P*<.001]; HR, 2.01; 95% CI, 1.06-3.79 [*P*=.03]; HR, 1.88; 95% CI, 1.04-3.39 [*P*=.04], respectively) (Table 4).

In a subgroup sensitivity analysis in which patients were stratified according to presence/absence of risk factors (age, STS score, aortic mean gradient, chronic kidney disease), 30-day and 1-year all-cause mortality were not affected by the tested potential confounders (all interaction *P*-values >.05) (Figures 2A and 2B).

Discussion

This is the largest study of the impact of baseline TCP on the early and long-term outcomes after TAVR with both self-expandable and balloon-expandable valves. The main findings of this study are the following: (1) baseline TCP is common (21.9%) in elderly patients undergoing TAVR; (2) moderate/severe TCP at baseline, identified by a platelet count <100 × 10^9/L, increases the risk of mortality at 30 days and 1 year after TAVR by 13.2-fold and 5.9-fold, respectively; and (3) the impaired survival of patients with significant TCP is independent from any other risk factor.

TCP has been widely studied in cardiovascular patients. Cardiopulmonary bypass commonly results in a 30%-60% fall in platelet count, mainly secondary to hemodilution, platelet consumption, and blood loss.[1] The rate of TCP after percutaneous coronary intervention (PCI) reported in large clinical studies is lower (0.7%-13.0%).[9] After percutaneous closure of congenital heart defects, moderate/severe TCP occurred in 11.7%.[10] In the setting of SAVR, platelet activation may be involved in the mechanism of platelet count decrease.[11-13] Indeed, except for extracorporeal circulation, several steps of SAVR that promote platelet activation are present in the TAVR procedure, ie, endothelial damage caused by prosthesis implantation, fibrinogen binding on metallic armatures,

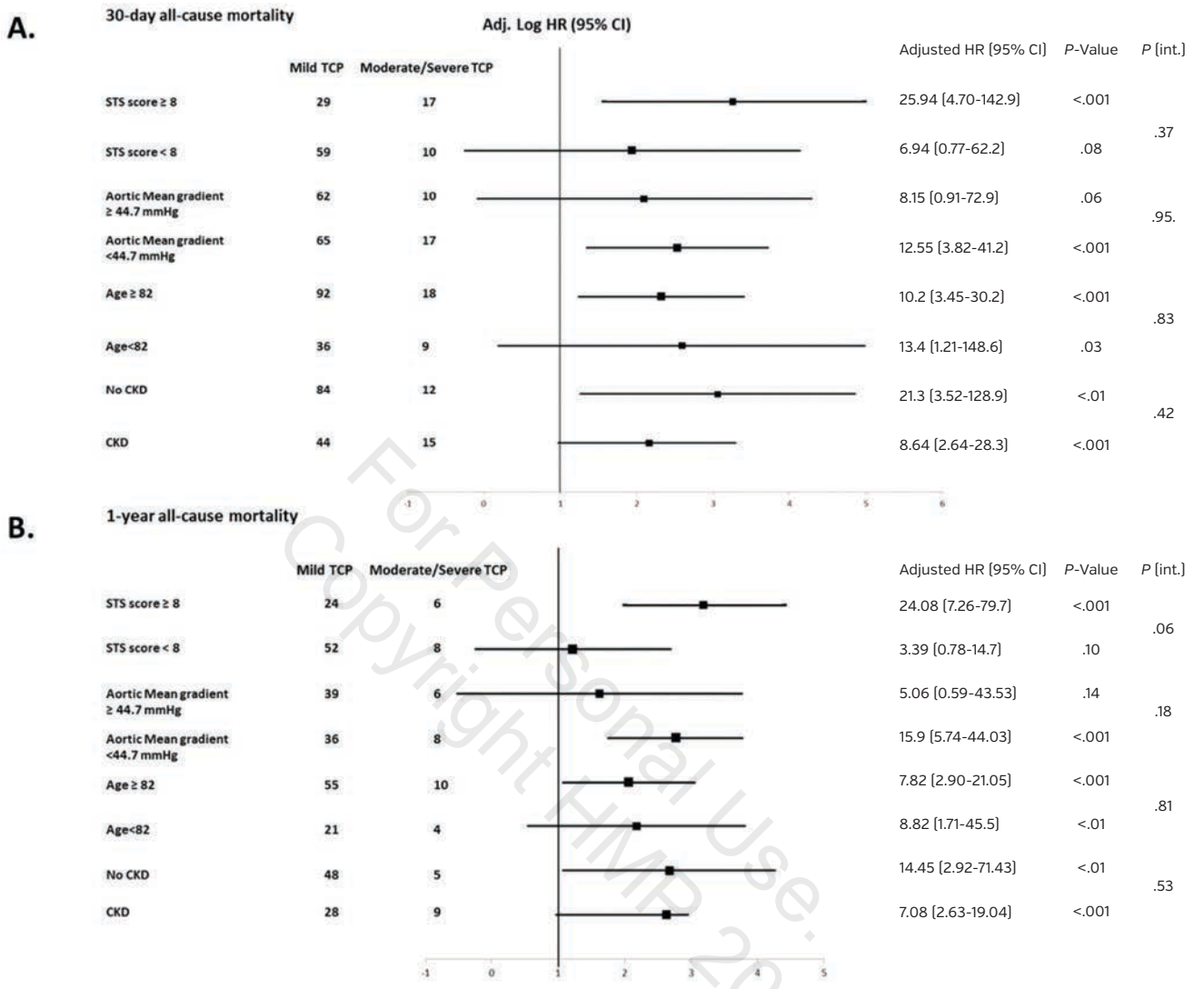

FIGURE 2. Interaction between baseline thrombocytopenia (TCP) and Society of Thoracic Surgeons (STS) score, aortic mean gradient, age, and chronic kidney disease on primary outcomes. (A) Thirty-day all-cause mortality subgroup analysis. (B) One-year all-cause mortality subgroup analysis.

and shear stress modifications due to prosthesis implantation.[14] In the setting of TAVR, TCP has been frequently reported as a common event after the procedure; however, few data exist regarding the impact of baseline TCP on outcomes. Indeed, the majority of the data reported in literature refer to: (1) small populations;[4-6,15] (2) patients treated mainly with balloon-expandable valves;[4-6,16] (3) post-TAVR TCP;[5,16] and (4) inconsistent effects on in-hospital or 30-day outcomes. Flaherty et al[6] found no effect of baseline TCP on in-hospital mortality in a small study of 90 patients undergoing TAVR. Our study is the first large evaluation of baseline TCP in patients treated with both self-expandable and balloon-expandable valves, showing a clear and strong impact of baseline TCP on both early and long-term survival. TCP occurring early after TAVR (<4 days) is likely related to procedural/early postprocedural adverse events, such as vascular complications, bleeding, and multiple blood transfusions, and results in a physiological reaction that increases bone marrow production of platelets.[13] Although postoperative TCP has been reported to identify adverse outcomes after TAVR, this only happens after the procedure has been performed,[5,15] therefore limiting its value as a predictor of risk. In our study, pre-TAVR moderate/severe TCP was associated with a 17.1-fold increased risk of death at 30 days and 5.3-fold increased risk of death at 1 year. Our data suggest that baseline TCP should be considered in determining risk of TAVR, and perhaps used in risk calculators. The typical TAVR patient is elderly, and low platelet counts may be due to multiple causes (myelodysplasia, thrombocytopenic purpura, malignancy, drugs, etc), which may explain the worse clinical outcomes of these

patients. It is possible that baseline TCP represents an objective marker of frailty – a possibility that merits further study. In our patient cohort, a subgroup sensitivity analysis showed that patients with higher mortality (both at 30 days and at 1 year) were those with moderate/severe TCP at baseline, higher STS score, older age, and lower aortic mean gradient.

This study adds to the current knowledge that in patients being evaluated for TAVR, a low platelet count ($<100 \times 10^9$/L) before the procedure needs to be recognized, since it helps identify a subgroup of higher-risk patients. The role of baseline TCP needs to be tested in a larger-scale population in order to specifically identify the additive value it might bring if included in a specific TAVR risk score.

Study limitations. The study design (retrospective and observational) carries all the limitations inherent to retrospective analyses, especially the inability to determine the mechanism of TCP at baseline. There is a fairly high loss to follow-up rate; however, 92.2% of the initial patient population completed the 1-year follow-up. Additionally, this study leaves open questions of how to improve the prognosis of patients who have pre-TAVR TCP.

Conclusion

The impact on daily practice is the following: (1) baseline TCP represents a strong predictor of mortality in TAVR patients, both at short-term and long-term follow-up; (2) in patients being evaluated for TAVR, a low platelet count before the procedure needs to be recognized, since it helps identify a subgroup of higher-risk patients; and (3) baseline TCP, which is easy to detect, should be included in *ad hoc* TAVR risk scores.

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