



Predictive value of preprocedural procalcitonin for short- and long-term mortality after transfemoral transcatheter aortic valve implantation

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Abstract

Current risk scores used for patients undergoing transcatheter aortic valve implantation (TAVI) do not reliably predict adverse events after TAVI. Procalcitonin (PCT) is associated with increased atherosclerotic burden and adverse outcomes in patients with cardiovascular disease. The aim of our study is to assess the predictive value of preprocedural serum PCT levels in comparison with established risk scores in TAVI patients. A total of 243 patients undergoing transfemoral TAVI at our institution were included prospectively in the study and 230 of these patients participated in the follow-up 1 year after TAVI. The primary endpoints were mortality at 30 days and 1 year. Multivariable analysis revealed that preprocedural PCT was the only independent predictor of 30-day mortality (HR 2.84; 95% CI 1.59–5.06; $p < 0.001$) and 1-year mortality (HR 1.90; 95% CI 1.17–3.11; $p = 0.01$), whereas high-sensitivity C-reactive protein showed no association with procedural outcomes. The results of ROC analysis showed good predictive power of PCT for both outcomes (AUC 0.75; $p = 0.0003$ for 30-day mortality and AUC 0.71; $p < 0.0001$ for 1-year mortality). An optimal cut-off value for PCT of 0.06 ng/ml for short- and long-term mortality was determined with the Youden index. A significantly higher mortality rate was observed in the high-PCT group (≥ 0.06 ng/ml) based on Kaplan–Meier analysis (log rank = 12.1; $p = 0.001$ at 30 days and log rank = 14.2; $p = 0.0002$ at 1 year). Patients in the high-PCT group also had a considerably worse clinical profile. In conclusion, preprocedural PCT is an independent predictor of 30-day and 1-year mortality after TAVI. In particular, a cut-off value of 0.06 ng/ml discriminates patients at higher risk of mortality within 30 days and 1 year of TAVI.

Keywords Procalcitonin · Biomarker · Risk factor · TAVI

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Introduction

Transcatheter aortic valve implantation (TAVI) has rapidly evolved to become the standard procedure for elderly patients with severe, degenerative, symptomatic aortic stenosis at high and intermediate surgical risk [1]. Although

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operator experience and TAVI technology have improved over the years, TAVI is still an invasive procedure associated with considerable risk of periprocedural complications, such as stroke and mortality. Moreover, it is often performed in frail and multimorbid patients [2]. Therefore, risk assessment is an essential component of patient selection for TAVI. Recent guidelines on valvular heart disease recommend the STS-PROM score as a complementary risk assessment tool for TAVI [3]. However, this score has not been validated for predicting outcomes in patients undergoing TAVI [4]. Hence, further research is necessary to identify new variables that can provide a better prediction of outcomes after TAVI.

Procalcitonin (PCT) is an inflammatory marker that is strongly upregulated in bacterial infection and is an established marker for sepsis [5]. A growing body of evidence shows that it is also associated with atherosclerotic burden and adverse events in patients with cardiovascular disease [6, 7]. Since existing evidence links atherosclerosis to an increased cardiac and all-cause mortality in patients undergoing TAVI [8], we aimed to assess the value of preprocedural PCT in predicting short- and long-term outcomes after TAVI and compare it with the performance of established risk scores.

Methods

From July 2011 to June 2013, 253 patients with severe, symptomatic aortic stenosis undergoing transfemoral TAVI were enrolled in this study. Eligibility for TAVI and choice of access route were assessed by a multidisciplinary heart team according to the patients' characteristics and the existing guideline recommendations [9]. Patients were excluded from this retrospective analysis when they met at least one of the following exclusion criteria: conversion to open-heart surgery, major complications associated with myocardial injury (ventricular perforation, annular rupture), or need for cardiopulmonary resuscitation or extracorporeal circulation during TAVI. Patients ($n = 10$) with these exclusion criteria were not further analyzed. The primary endpoints of the study were 30-day and 1-year all-cause mortality. All patients participated in the follow-up at 30 days, 13 patients were lost to follow up 1 year after TAVI.

Data on demographics, symptoms, comorbidities, and STS-PROM score were collected for all patients. Baseline characteristics were further evaluated using transthoracic and transesophageal echocardiography, coronary angiography, and multislice computed tomography of the aortic valve and aorta.

All patients enrolled in the study gave written informed consent, including consent for biomarker analyses. The

study was approved by the ethics board of the state of Hesse, Germany (FF 87/2010).

Implantations were performed according to established protocols, as previously described [10]. Either balloon-expandable (Sapien XT, Edward Lifesciences, Irvine, CA, USA) or self-expandable prostheses (Corevalve revalving system 26, 29, and 31 mm, Medtronic Inc., Minneapolis, MN, USA; Acurate neo S, M, and L, Symetis SA, Eculens, Switzerland) were used.

Venous blood samples were collected in plain, gel-filled tubes for the determination of PCT and C-reactive protein (CRP) concentrations prior to TAVI. Serum was processed immediately and frozen at $-80\text{ }^{\circ}\text{C}$ until assay. CRP was measured in serum with the high-sensitivity electrochemiluminescence immunoassay (hs-CRP assay, Elecsys Analyzer 2010, Roche Diagnostics, Mannheim, Germany). The lower detection limit for the hs-CRP assay is 0.15 mg/l and the highest concentration measurable is 20.0 mg/l. The lowest concentration measurable with a coefficient of variation (CV) $< 10\%$ for this assay is 0.3 mg/l. PCT was measured in serum using a chemiluminescent immunoassay (PCT assay, Roche Elecsys Analyzer 2010, Thermo Fisher Diagnostics GmbH, Hennigsdorf, Germany). The lower detection limit of this assay is $\leq 0.002\text{ ng/ml}$, and the limit of quantitation is 0.06 ng/ml.

Continuous variables are presented as the mean \pm SD or median (25th–75th interquartile range), as appropriate. Categorical variables are expressed as numbers and percentages. Because the distribution of PCT and hs-CRP was skewed, a logarithmic transformation to the natural base was performed for these variables. Normally distributed continuous variables were compared by Welch two-sample *t*-test. The Mann–Whitney *U* test was used for non-normally distributed continuous variables. Comparisons between categorical variables were made by Chi-square or Fisher's exact test.

Receiver-operating characteristic (ROC) curves were constructed to assess the predictive value of the STS-PROM score and PCT regarding 30-day and 1-year mortality. The best PCT cut-off concentration for predicting the primary endpoints was then computed using the Youden index. The Kaplan–Meier method was used to estimate survival rate at 30 days and 1 year according to the cut-off (PCT $< 0.06\text{ ng/ml}$ or $\geq 0.06\text{ ng/ml}$). Differences in the parameters were detected by the log-rank test.

All baseline variables that yielded a *p* value < 0.1 in the univariable analysis were included in a multivariable Cox regression analysis to assess the predictive capacity of PCT in terms of 30-day and 1-year mortality.

A two-tailed *p* value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Version 19.0.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the entire patient population ($n = 243$) was 83 ± 5 years and 58% were female. The median STS-PROM score was 6% (IQR 4–8), and 54% of the patients

had an intermediate STS-PROM score of 4–8. Tables 1 and 2 show clinical and procedural characteristics of the patients stratified according to the primary endpoints.

The 30-day all-cause mortality rate was 7.4% ($n = 18$). Patients who died within 30 days after transfemoral TAVI had a higher prevalence of prior myocardial infarction, prior

Table 1 Baseline characteristics according to endpoint

Variable	30-day mortality ($n = 243$)		<i>p</i> value	1-year mortality ($n = 230$)		<i>p</i> value
	Survivors ($n = 225$)	Non-survivors ($n = 18$)		Survivors ($n = 185$)	Non-survivors ($n = 46$)	
Age, years, mean (SD)	83 (5)	82 (6)	0.63	83 (5)	83 (5)	0.97
Female sex, <i>n</i> (%)	132 (58.7%)	10 (55.6%)	0.79	102 (55.4%)	29 (63.0%)	0.29
BMI, kg/m ² , mean (SD)	28 (5)	27 (5)	0.58	28 (5)	27 (5)	0.16
STS score, median (IQR)	5 (4–8)	7 (4–10)	0.29	5.3 (4–8)	6.7 (5–10)	0.01
STS < 4, <i>n</i> (%)	49 (22.1%)	4 (22.2%)	0.99	45 (24.7%)	7 (15.2%)	0.17
STS 4–8, <i>n</i> (%)	121 (54.5%)	9 (50.0%)	0.72	100 (54.9%)	22 (47.8%)	0.38
STS ≥ 8, <i>n</i> (%)	52 (23.4%)	5 (27.8%)	0.65	37 (20.3%)	17 (37.0%)	0.02
Preprocedural PCT, ng/ml, median (IQR)	0.04 (0.04–0.05)	0.08 (0.06–0.1)	< 0.001	0.04 (0.03–0.06)	0.06 (0.05–0.09)	< 0.0001
Preprocedural hs-CRP, mg/l, median (IQR)	3 (2.4–3.7)	4.7 (1.4–6.3)	0.77	3.17 (1.43–7.17)	3.91 (1.53–7.70)	0.4
Cardiovascular risk factors, <i>n</i> (%)						
Hypertension	211 (93.8%)	18 (100%)	0.29	173 (94.0%)	44 (95.7%)	0.67
Diabetes	70 (31.1%)	8 (44.4%)	0.23	55 (29.9%)	18 (39.1%)	0.23
Insulin	24 (10.8%)	3 (16.7%)	0.43	19 (10.4%)	7 (15.2%)	0.36
Hypercholesterolemia	88 (39.1%)	8 (44.4%)	0.64	75 (40.8%)	18 (39.1%)	0.84
Clinical history, <i>n</i> (%)						
COPD	45 (20%)	4 (22.2%)	0.84	33 (17.9%)	12 (26.1%)	0.21
CAD	125 (55.6%)	12 (66.7%)	0.38	101 (54.9%)	29 (63.0%)	0.32
Prior MI	30 (13.3%)	6 (33.3%)	0.02	26 (14.1%)	8 (17.4%)	0.58
Prior PCI	75 (33.3%)	7 (38.9%)	0.64	61 (33.2%)	15 (32.6%)	0.94
Prior CABG	33 (14.7%)	4 (22.2%)	0.37	26 (14.1%)	9 (19.6%)	0.36
ACI stenosis	22 (9.8%)	1 (5.6%)	0.58	19 (10.3%)	4 (8.7%)	0.74
Atrial fibrillation	91 (40.4%)	9 (50.0%)	0.44	70 (38.0%)	24 (52.2%)	0.08
Prior stroke	39 (17.3%)	2 (11.1%)	0.51	31 (16.8%)	9 (19.6%)	0.67
Peripheral artery disease	28 (12.4%)	4 (22.2%)	0.28	21 (11.4%)	10 (21.7%)	0.07
Symptoms, <i>n</i> (%)						
Dyspnea NYHA ≥ III	207 (92.0%)	18 (100.0%)	0.22	168 (91.3%)	45 (97.8%)	0.13
Syncope	30 (13.3%)	1 (5.6%)	0.35	23 (12.5%)	6 (13.0%)	0.92
Prior cardiac decompensation	76 (33.8%)	10 (55.6%)	0.06	55 (29.9%)	23 (50.0%)	0.01
Echocardiographic findings						
LVEF, %, mean (SD)	54 (14)	49 (14)	0.15	54 (14)	52 (14)	0.47
LVEF < 35%, <i>n</i> (%)	36 (16%)	6 (33.3%)	0.05	31 (16.8%)	10 (21.7%)	0.44
PG mean, mmHg, median (IQR)	42 (32–52)	35 (24–47)	0.23	42 (32–52)	38 (24–47)	0.17
PG max, mmHg, median (IQR)	68 (50–81)	58 (41–87)	0.44	68 (51–81)	61 (41–80)	0.29
Renal function						
eGFR, ml/min/1.73 m ² , median (IQR)	63 (45–82)	63 (45–75)	0.70	63.01 (50–84)	60 (40–76)	0.02

Values are given as number (%), median (IQR), or mean (SD)

BMI body mass index, *STS* society of thoracic surgeons (low = STS < 4, intermediate = STS 4–8, high STS ≥ 8), *hsCRP* high-sensitivity C-reactive protein, *CAD* coronary artery disease, *ACI* Arteria carotis interna, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *NYHA* New York Heart Association, *LVEF* left-ventricular ejection fraction, *PG* pressure gradient, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction

Table 2 Procedural characteristics according to endpoint

Variable	30-day mortality (n = 243)		p value	1-year mortality (n = 230)		p value
	Survivors (n = 225)	Non-survivors (n = 18)		Survivors (n = 185)	Non-survivors (n = 46)	
Procedural variables, median (IQR)						
Time of procedure, min	46 (37–60)	48 (36–83)	0.31	46 (37–60)	47 (37–70)	0.4
Contrast amount, ml	100 (75–120)	120 (80–140)	0.09	100 (80–130)	100 (70–120)	0.4
Postprocedural findings						
Pacemaker implantation, n (%)	42 (18.7%)	1 (5.6%)	0.16	29 (15.8%)	9 (19.6%)	0.53
Any vascular complication, n (%)	41 (18.2%)	2 (11.1%)	0.45	37 (20.1%)	5 (10.9%)	0.15
Any bleeding, n (%)	36 (16.1%)	2 (11.8%)	0.63	26 (14.2%)	10 (22.7%)	0.16
Stroke (major + minor), n (%)	7 (3.1%)	4 (22.2%)	0.005	6 (3.3%)	5 (10.9%)	0.03
Echocardiography						
LVEF, %, mean (SD)	57 (12)	50 (15)	0.07	57 (12)	53 (13)	0.03
PG mean, mmHg, median (IQR)	10 (7–12)	10 (7–11)	0.95	10 (7–12)	8 (7–11)	0.18
Aortic regurgitation \geq II, n (%)	16 (7.5%)	2 (16.7%)	0.26	14 (8.0%)	4 (10.5%)	0.61

Values are given as number (%), median (IQR), or mean (SD)

ICU intensive-care unit, LVEF left-ventricular ejection fraction, PG pressure gradient

cardiac decompensation, and left-ventricular ejection fraction $< 30\%$ (Table 1). The 30-day all-stroke rate after TAVI was 4.5% ($n = 11$) (Table 2). There were 7 major strokes (modified Rankin scale 4–5) and 4 minor strokes (modified Rankin scale 0–3). Thirty-day mortality in patients with postprocedural stroke was higher (36% vs. 6%; $p < 0.001$).

There was no association between 30-day mortality and STS-PROM score ($p = 0.29$), hs-CRP ($p = 0.77$) (Table 1). However, the preprocedural PCT levels were strongly associated with 30-day mortality ($p < 0.001$). In a multivariable Cox analysis adjusted for the baseline variables associated with the primary endpoint, preprocedural PCT was the only independent predictor of 30-day mortality (HR 2.84; 95% CI 1.59–5.06; $p < 0.001$; Suppl. Table 1). ROC curve analysis confirmed that the STS-PROM score had low predictive value for 30-day mortality (AUC 0.57, $p = 0.29$) (Fig. 1). In contrast, the preprocedural serum PCT concentration showed good predictive power for 30-day mortality in ROC curve analysis (AUC 0.75; $p = 0.0003$) (Fig. 1). A direct comparison between the AUC for 30-day mortality of the STS-PROM score and the PCT concentration demonstrated the superiority of baseline PCT ($p = 0.05$).

The 1-year all-cause mortality rate was 20% ($n = 46$). Patients who died within 1 year after transfemoral TAVI had a higher prevalence of atrial fibrillation, peripheral arterial disease and prior cardiac decompensation. They also showed lower postprocedural ejection fraction and eGFR. Higher preprocedural PCT and STS-PROM score were strongly associated with 1-year all-cause mortality ($p < 0.0001$ for preprocedural PCT and $p = 0.01$ for STS-PROM score). However, in a multivariable Cox analysis adjusted for the

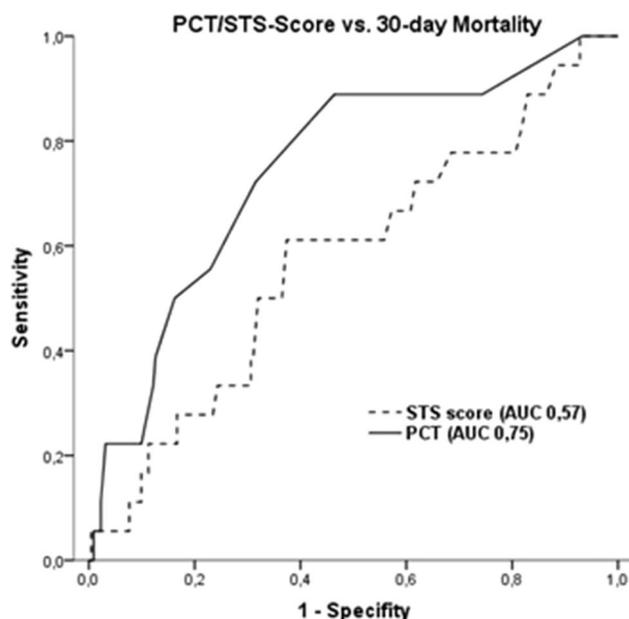


Fig. 1 Prediction of 30-day mortality. Receiver-operating characteristics curve showing the predictive power of preprocedural PCT and STS-PROM score for 30-day mortality after TAVI

baseline variables associated with the primary endpoint, preprocedural PCT was the only independent predictor of 1-year mortality (HR 1.90; 95% CI 1.17–3.11; $p = 0.01$; Suppl. Table 2).

ROC curve analysis revealed a good predictive power of preprocedural PCT for 1-year mortality (AUC 0.71, $p < 0.0001$, Fig. 2). Predictive power of STS-PROM score

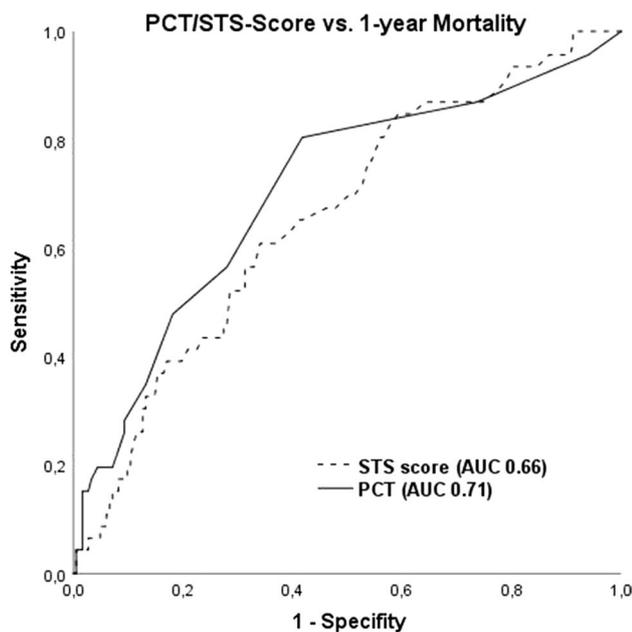


Fig. 2 Prediction of 1-year mortality. Receiver-operating characteristics curve showing the predictive power of preprocedural PCT and STS-PROM score for 1-year mortality after TAVI

for 1-year mortality was lower (AUC 0.66, $p=0.001$), but was no significant difference between the AUCs of STS-PROM score and preprocedural PCT in terms of 1-year mortality ($p=0.4$).

An optimal PCT cut-off value of 0.06 ng/ml for both endpoints was determined. The baseline and procedural characteristics of patients with low PCT (<0.06 ng/ml; $n=158$) and high PCT (≥ 0.06 ng/ml; $n=85$) are shown in Table 3. Patients in the high-PCT group had a considerably worse clinical profile with a higher prevalence of diabetes, coronary artery disease, prior myocardial infarction, peripheral artery disease, prior cardiac decompensation, lower glomerular filtration rate, lower left-ventricular ejection fraction, and a higher STS-PROM score. Accordingly, Kaplan–Meier analysis showed a markedly higher incidence of 30-day mortality (log rank = 12.1; $p=0.001$; Fig. 3) and 1-year mortality (log rank = 14.2; $p=0.0002$ Fig. 3) for patients with PCT ≥ 0.06 ng/ml (Table 4).

Three patients had a preprocedural PCT >0.5 ng/ml, which is a commonly accepted cut-off for sepsis [7]. One of these patients died at day 12 after TAVI. None of them suffered a stroke in this period. Sepsis is associated with a strong increase in short- and long-term mortality [5]. To ensure that a preprocedural PCT >0.5 ng/ml had no impact on outcomes, we excluded these three patients and performed a second analysis. The results were comparable to those of the first analysis. Preprocedural PCT remained an independent predictor of 30-day and 1-year mortality (Suppl. Tables 3 and 4).

Discussion

Serum PCT is known to correlate with adverse cardiovascular events. The present study examined the predictive value of preprocedural PCT in patients with severe aortic stenosis undergoing TAVI. The main findings are: (1) PCT is an independent predictor of 30-day and 1-year mortality after transfemoral TAVI; (2) PCT is superior to the STS score in predicting 30-day mortality; (3) a PCT cut-off value of 0.06 ng/ml can reliably differentiate between patients with high and low mortality risk.

The established scores for risk assessment in patients undergoing TAVI, such as the STS-PROM score, were originally developed to predict operative mortality of cardiac surgery in adults and are based on a patient population that differs from the typical cohort of elderly TAVI patients with comorbidities. A number of studies that analyzed STS-PROM scores in the setting of TAVI yielded conflicting results regarding its predictive value in TAVI patients [11–14]. Our data showed that the STS-PROM score was not reliable in predicting 30-day mortality. Although it showed an association with 1-year mortality, it did not have high predictive power for this endpoint in the ROC analysis.

PCT is an important marker that is commonly used to indicate bacterial sepsis. It is produced in monocytes and parenchymal cells, and the expression of PCT-mRNA is strongly induced by circulating bacterial endotoxins [15–18]. Importantly, other inflammatory mediators such as interleukin-1 β , interleukin-2, and tumor necrosis factor- α were also shown to stimulate the production of PCT [7, 15, 19, 20]. These inflammatory cytokines play a major role in the formation of atherosclerotic plaques. The recent CANTOS trial showed a significantly lower rate of cardiovascular events during anti-inflammatory therapy with canakinumab, a monoclonal antibody targeting interleukin-1 β , in patients with prior myocardial infarction and hs-CRP >2 mg/l [21].

There is growing evidence linking PCT to an increased atherosclerotic burden and higher risk for adverse events in patients with cardiovascular disease. Erren et al. demonstrated that elevated PCT concentrations correlated with the extent of atherosclerosis in patients with CAD and peripheral artery disease [7]. Furthermore, PCT was associated with higher mortality in patients with CAD, and PCT levels were higher in patients with ACS, 3-vessel CAD, and diabetes than patients with stable CAD, 1-vessel CAD, and without diabetes [15].

In the present study, preprocedural PCT was an independent predictor of 30-day and 1-year mortality after TAVI. Patients with preprocedural PCT ≥ 0.06 ng/ml had a markedly higher prevalence of cardiovascular

Table 3 Baseline characteristics according to serum PCT level

Variable	PCT < 0.06 ng/ml (n = 158)	PCT ≥ 0.06 ng/ml (n = 85)	p value
Age, years, mean (SD)	83 (5)	82 (6)	0.55
Female sex, n (%)	91 (57.6%)	51 (60.0%)	0.72
BMI, kg/m ² , mean (SD)	27 (5)	28 (6)	0.34
STS score, median (IQR)	5.0 (3–6)	6.3 (4–8)	0.03
STS < 4, n (%)	40 (25.5%)	13 (15.7%)	0.08
STS 4–8, n (%)	85 (54.1%)	45 (54.2%)	0.99
STS ≥ 8, n (%)	32 (20.4%)	25 (30.1%)	0.09
Cardiovascular risk factors, n (%)			
Hypertension	150 (94.9%)	79 (92.9%)	0.57
Diabetes	42 (26.6%)	36 (42.4%)	0.01
Insulin	12 (7.6%)	15 (18.1%)	0.02
Hypercholesterolemia	61 (38.6%)	35 (41.2%)	0.7
Clinical history, n (%)			
COPD	38 (24.1%)	11 (12.9%)	0.04
CAD	78 (49.4%)	59 (69.4%)	0.003
Prior MI	17 (10.8%)	19 (22.4%)	0.02
Prior PCI	50 (31.6%)	32 (37.6%)	0.4
Prior CABG	22 (13.9%)	15 (17.6%)	0.44
ACI stenosis	17 (10.8%)	6 (7.1%)	0.9
Atrial fibrillation	61 (38.6%)	39 (45.9%)	0.27
Prior stroke	28 (17.7%)	13 (15.3%)	0.63
Peripheral artery disease	14 (8.9%)	18 (21.2%)	0.007
Symptoms, n (%)			
Dyspnea NYHA ≥ III	144 (91.1%)	81 (95.3%)	0.24
Syncope	23 (14.6%)	8 (9.4%)	0.25
Prior cardiac decompensation	45 (28.5%)	41 (48.2%)	0.002
Echocardiographic findings			
LVEF, %, mean (SD)	60 (50–65)	55 (45–60)	0.08
LVEF < 30%, n (%)	25 (15.8%)	17 (20.0%)	0.44
PG mean, mmHg, median (IQR)	43 (33–52)	40 (29–49)	0.1
PG max, mmHg, median (IQR)	68 (53–82)	64 (44–80)	0.2
Renal function			
eGFR, ml/min/1.73 m ² , median (IQR)	67.20 (54–89)	50.99 (37–68)	< 0.001

Values are given as number (%), median (IQR), or mean (SD)

BMI body mass index, *STS* society of thoracic surgeons (low = STS < 4, intermediate = STS 4–8, high STS ≥ 8), *hsCRP* high-sensitivity C-reactive protein, *CAD* coronary artery disease, *ACI* Arteria carotis interna, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *NYHA* New York Heart Association, *LVEF* left-ventricular ejection fraction, *PG* pressure gradient, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction

comorbidities such as diabetes, CAD, peripheral artery disease, prior myocardial infarction, prior cardiac decompensation, lower glomerular filtration rate, and lower left-ventricular ejection fraction.

In addition, PCT was associated with a higher 30-day stroke rate after TAVI. Interestingly, most of the strokes in patients with PCT ≥ 0.06 ng/ml were periprocedural strokes that occurred within 48 h after TAVI, whereas there were no periprocedural strokes in the PCT < 0.06 ng/ml

group. Periprocedural strokes are usually of embolic origin, as reported by several diffusion-weighted MRI studies [22–24] and are caused by atheromatous or calcified debris dislocated during aortic passage, retrograde passage of the aortic valve, balloon valvuloplasty, or deployment of the prosthesis [24–26]. The higher stroke rate is indicative of advanced atherosclerotic disease, which is a possible explanation for the increased PCT concentration.

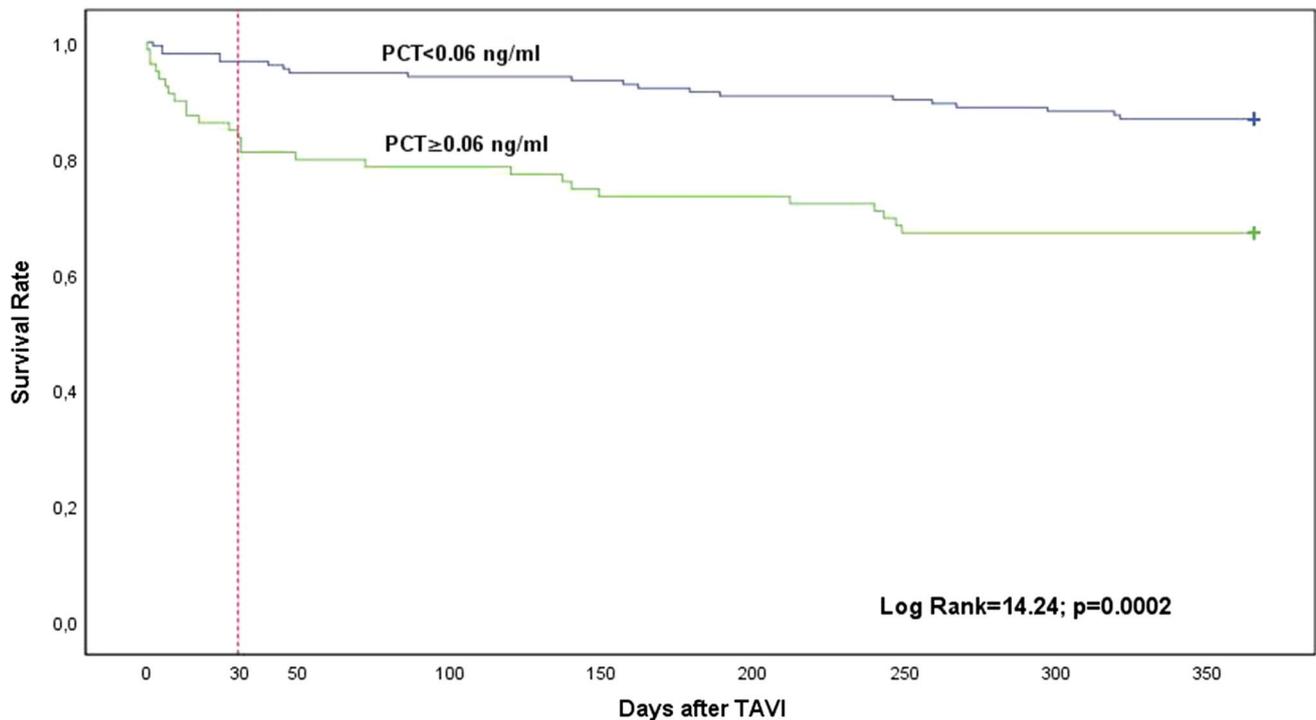


Fig. 3 Survival rate according to PCT level. Kaplan–Meier curves showing survival rate in patients with $PCT \geq 0.06$ ng/ml and $PCT < 0.06$ ng/ml. Dotted red line indicates day 30-day survival rate

Table 4 Procedural characteristics according to serum PCT level

Variable	PCT < 0.06 ng/ml (n = 158)	PCT \geq 0.06 ng/ml (n = 85)	p value
Procedural variables, median (IQR)			
Procedure duration, min	46 (36–62)	46 (39–58)	0.96
Contrast medium, ml	100 (77–130)	90 (70–120)	0.19
Post-procedural findings			
ICU length of stay, days, median (IQR)	2 (2–3)	3 (2–5)	0.04
Pacemaker implantation, n (%)	27 (17.1%)	16 (18.8%)	0.34
Acute kidney injury, n (%)	14 (8.9%)	11 (12.9%)	0.32
Any vascular complication, n (%)	30 (19.0%)	13 (15.3%)	0.47
Any bleeding, n (%)	20 (12.7%)	18 (21.7%)	0.07
Echocardiography			
LVEF, %, mean (SD)	58 (11)	54 (13)	0.006
PG mean, mmHg, median (IQR)	10 (7–12)	8 (6–12)	0.15
Aortic regurgitation \geq II, n (%)	13 (8.7%)	5 (6.7%)	0.6
Endpoints, n (%)			
30-day stroke (minor + major)	4 (2.5%)	7 (8.2%)	0.04
30-day all-cause mortality	5 (3.2%)	13 (15.3%)	0.001

Values are given as number (%), median (IQR), or mean (SD)

ICU intensive-care unit, LVEF left-ventricular ejection fraction, PG pressure gradient

Our data did not show any correlation between outcomes and preprocedural hs-CRP levels, which is an established inflammatory marker of atherosclerosis. A number of studies associate hs-CRP with an increased risk of cardiovascular

events [21, 27, 28]. These studies, however, were performed in younger populations with more favorable risk profiles. The results of a recent study by Ruparelia and colleagues, performed in a cohort similar to ours in terms of mean

age and risk profile, are consistent with our findings that preprocedural CRP does not predict outcomes after TAVI [29]. Therefore, PCT could be a more specific marker of advanced atherosclerosis than hs-CRP in elderly, high-risk populations.

The existing evidence shows that atherosclerotic burden has a prognostic impact on mortality and stroke rate in patients with CAD undergoing percutaneous coronary intervention [30]. In patients undergoing TAVI, total aortic calcification burden is an independent predictor of cardiac and all-cause mortality [8]. Therefore, the ability of PCT to predict advanced atherosclerotic disease might explain its better predictive value for 30-day and 1-year mortality compared with the STS-PROM score. The combination of preprocedural PCT level and STS-PROM score could, thus, be used in clinical practice for a better risk assessment of patients considered for TAVI.

The study has several limitations. This is a single-center study of observational nature; thus, the observed association may not be causal. Although the data were collected prospectively, this is a retrospective analysis. Investigation of the predictive value of preprocedural PCT for 30-day mortality is limited by the small event count, thus, limiting the sample size. Our analysis, however, reflects a “real-world” patient collective rather than a highly selected trial population, which strengthens the validity of our findings.

In summary, preprocedural PCT is an independent predictor of 30-day and 1-year mortality after transfemoral TAVI. Patients with serum PCT > 0.06 ng/ml have a markedly worse cardiovascular profile. Further research is necessary to validate these findings and elucidate a possible association of PCT with atherosclerotic burden and periprocedural stroke in TAVI patients.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

References

- Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, Investigators PT (2011) Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 364:2187–2198
- Walther T, Hamm CW, Schuler G, Berkowitsch A, Kottling J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Mollmann H, Board GE (2015) Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY registry. *J Am Coll Cardiol* 65:2173–2180
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Group ESCSD (2017) 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 38:2739–2791
- O’Sullivan CJ, Stortecky S, Heg D, Juni P, Windecker S, Wenaweser P (2015) Impact of B-type natriuretic peptide on short-term clinical outcomes following transcatheter aortic valve implantation. *EuroIntervention* 10:e1–8
- Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K (2007) Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med* 33:606–618
- Schiopu A, Hedblad B, Engstrom G, Struck J, Morgenthaler NG, Melander O (2012) Plasma procalcitonin and the risk of cardiovascular events and death: a prospective population-based study. *J Intern Med* 272:484–491
- Erren M, Reinecke H, Junker R, Fobker M, Schulte H, Schurek JO, Kropf J, Kerber S, Breithardt G, Assmann G, Cullen P (1999) Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries. *Arterioscler Thromb Vasc Biol* 19:2355–2363
- Harbaoui B, Montoy M, Charles P, Boussel L, Liebgott H, Girerd N, Courand PY, Lantelme P (2016) Aorta calcification burden: towards an integrative predictor of cardiac outcome after transcatheter aortic valve implantation. *Atherosclerosis* 246:161–168
- Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S (2012) Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 33:2451–2496
- Mollmann H, Kim WK, Kempfert J, Blumenstein J, Liebetrau C, Nef H, Van Linden A, Walther T, Hamm C (2014) Transfemoral aortic valve implantation of Edwards SAPIEN XT without predilatation is feasible. *Clin Cardiol* 37:667–671
- Barbash IM, Finkelstein A, Barsheshet A, Segev A, Steinvil A, Assali A, Ben Gal Y, Vaknin Assa H, Fefer P, Sagie A, Guetta V, Kornowski R (2015) Outcomes of patients at estimated low, intermediate, and high risk undergoing transcatheter aortic valve implantation for aortic stenosis. *Am J Cardiol* 116:1916–1922
- D’Ascenzo F, Capodanno D, Tarantini G, Nijhoff F, Ciuca C, Rossi ML, Brambilla N, Barbanti M, Napodano M, Stella P, Saia F, Ferrante G, Tamburino C, Gasparetto V, Agostoni P, Marzocchi A, Presbitero P, Bedogni F, Cerrato E, Omede P, Conrotto F, Salizzoni S, Biondi Zoccai G, Marra S, Rinaldi M, Gaita F, D’Amico M, Moretti C (2014) Usefulness and validation of the survival post TAVI score for survival after transcatheter aortic valve implantation for aortic stenosis. *Am J Cardiol* 114:1867–1874
- Silaschi M, Conradi L, Seiffert M, Schnabel R, Schon G, Blankenberg S, Reichenspurner H, Diemert P, Treede H (2015) Predicting risk in transcatheter aortic valve implantation: comparative analysis of EuroSCORE II and established risk stratification tools. *Thorac Cardiovasc Surg* 63:472–478
- Arsalan M, Maren W, Hecker F, Filardo G, Kim WK, Pollock BD, Van Linden A, Arsalan-Werner A, Renker M, Doss M, Kalbas S, Hamm CW, Liebetrau C, Mack MJ, Walther T (2018) TAVI risk scoring using established versus new scoring systems: role of the new STS/ACC model. *EuroIntervention* 13:1520–1526

15. Sinning CR, Sinning JM, Schulz A, Schnabel RB, Lubos E, Wild PS, Papassotiropoulos J, Bergmann A, Blankenberg S, Munzel T, Bickel C (2011) Association of serum procalcitonin with cardiovascular prognosis in coronary artery disease. *Circ J* 75:1184–1191
16. Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Muller B (2004) Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med* 32:1715–1721
17. Meisner M (2005) Biomarkers of sepsis: clinically useful? *Curr Opin Crit Care* 11:473–480
18. Wiedermann FJ, Kaneider N, Egger P, Tiefenthaler W, Wiedermann CJ, Lindner KH, Schobersberger W (2002) Migration of human monocytes in response to procalcitonin. *Crit Care Med* 30:1112–1117
19. Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, Jager L, Reinhart K (1999) Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. *J Lab Clin Med* 134:49–55
20. Reilly MP, Rohatgi A, McMahon K, Wolfe ML, Pinto SC, Rhodes T, Girman C, Rader DJ (2007) Plasma cytokines, metabolic syndrome, and atherosclerosis in humans. *J Investig Med* 55:26–35
21. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 377:1119–1131
22. Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D (2010) Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol* 55:1427–1432
23. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H (2010) Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 121:870–878
24. Werner N, Zeymer U, Schneider S, Bauer T, Gerckens U, Linke A, Hamm C, Sievert H, Eggebrecht H, Zahn R (2016) Incidence and clinical impact of stroke complicating transcatheter aortic valve implantation: results from the German TAVI registry. *Catheter Cardiovasc Interv* 88:644–653
25. Stortecky S, Wenaweser P, Windecker S (2012) Transcatheter aortic valve implantation and cerebrovascular accidents. *EuroIntervention* 8(Suppl Q):Q60–Q69
26. Tay EL, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Cheung A, Ye J, Lichtenstein SV, Carere R, Thompson C, Webb JG (2011) A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 4:1290–1297
27. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979
28. Ridker PM, Hennekens CH, Buring JE, Rifai N (2000) C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342:836–843
29. Ruparel N, Panoulas VF, Frame A, Ariff B, Sutaria N, Fertleman M, Cousins J, Anderson J, Bicknell C, Chukwuemeka A, Sen S, Malik IS, Colombo A, Mikhail GW (2016) Impact of clinical and procedural factors upon C reactive protein dynamics following transcatheter aortic valve implantation. *World J Cardiol* 8:425–431
30. Korn-Lubetzki I, Farkash R, Pachino RM, Almagor Y, Tzivoni D, Meerkin D (2013) Incidence and risk factors of cerebrovascular events following cardiac catheterization. *J Am Heart Assoc* 2:e000413

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