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ORIGINAL ARTICLE

Quantification of perivascular adipose tissue attenuation does not add incremental prognostic value in patients undergoing transcatheter aortic valve implantation

Carolina Donà[1,†], Noemi Pavo [1,*†], Adriana Vinzens[2,3], Pimrapat Gebert[4], Dietrich Beitzke [5], Lukas Reider[5], Nidaa Mikail[2,3], Alexia Rossi [2,3], Katharina Mascherbauer[1], Susan Bengs [2,3], Achi Haider[2,3,6], Ronny R. Buechel[2], Philipp E. Bartko[1], Christian Loewe[5], Julia Mascherbauer[1,7], Christian Hengstenberg [1], Georg Goliasch [1], Max Paul Winter[1,†], and Catherine Gebhard [2,3,8,†]

[1]Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
[2]Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland
[3]Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland
[4]Institute of Biometry and Clinical Epidemiology, Charité—Universitätsmedizin Berlin, Berlin, Germany
[5]Department of Radiology and Nuclear Medicine, Medical University of Vienna, Vienna, Austria
[6]Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland
[7]Division of Cardiology, Department of Internal Medicine III, University Hospital Sankt Poelten, Sankt Poelten, Austria
[8]Department of Cardiology, Bern University Hospital Inselspital, University of Bern, Bern, Switzerland

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Abstract

Aims

Perivascular adipose tissue attenuation (PVAT) has emerged as a novel coronary computed tomography angiography (CCTA)-based biomarker predicting cardiovascular events by capturing inflammation around the coronary arteries. We assessed whether PVAT adds incremental prognostic value in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods and results

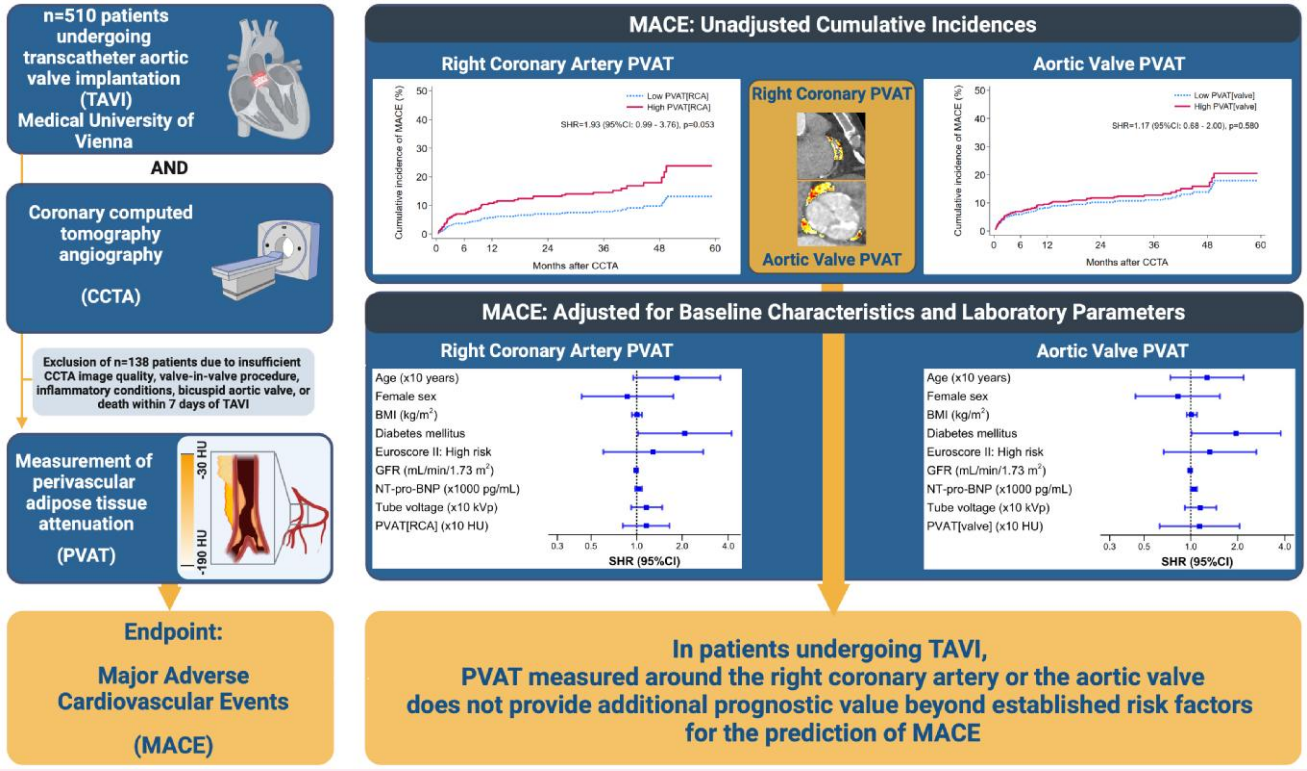
A total of 510 patients underwent CCTA imaging prior to TAVI between November 2015 and June 2020 at the Medical University of Vienna. PVAT was obtained from CCTA images and was measured around the right coronary artery [PVAT(RCA)] and the aortic valve [PVAT(valve)]. Following application of exclusion criteria, 372 patients [mean age 80.6 ± 6.8 years; 169 (45%) women] were analysed. Over a median follow-up of 3.0 (IQR 2.5–3.6) years, 52 (14%) individuals experienced a major adverse cardiovascular event (MACE, a composite of non-fatal stroke or myocardial infarction, cardiac death, or vascular intervention). Individuals exhibiting elevated PVAT[valve] displayed a heightened surgical risk according to European System for Cardiac Operative Risk Evaluation II, a lower body mass index, reduced left ventricular ejection fraction, prolonged hospitalization following TAVI, and elevated levels of circulating inflammatory markers compared

* Corresponding author. E-mail: noemi.pavo@meduniwien.ac.at
† These authors contributed equally to this work.

with those in the low PVAT[valve] group ($P < 0.05$). However, neither PVAT[valve] nor PVAT[RCA] were independently associated with the occurrence of MACE in adjusted multi-variable analyses (PVAT[valve]: sub-distribution hazard ratio [SHR] 1.14, 95% CI:0.63–2.05, $P = 0.672$); PVAT[RCA]: SHR 1.16 [95% CI: 0.81–1.66], $P = 0.417$).

Conclusion Measuring PVAT around either the right coronary artery or the aortic valve does not provide additional prognostic value beyond established risk factors for the prediction of MACE in patients undergoing TAVI.

Graphical Abstract



Keywords perivascular adipose tissue attenuation • fat attenuation index • imaging biomarker • aortic valve stenosis • coronary computed tomography angiography • transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) has become a well-established alternative treatment strategy to open heart surgery for patients with aortic valve stenosis (AVS). While post-discharge mortality rates have declined in parallel with technical refinements and the adoption of broader indications, 1-year mortality after TAVI remains substantial.[1] Despite the proven ability of risk scores such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS) to estimate procedural outcomes following TAVI, prediction of long-term mortality in an increasingly heterogeneous population of patients eligible for TAVI remains challenging. Thus, there is an emerging need for accurate risk stratification to allocate transcatheter therapy to the adequate candidates.

AVS is an inflammatory-based disease that shares a common pathophysiology with atherosclerosis.[2] Evidence suggests that inflammation is not only implicated in the pathogenetic process of AVS but might also play a role during and after valve replacement.[3] Coronary computed tomography angiography (CCTA) provides important information about the anatomy of the aortic root and ascending aorta, feasibility of vascular access as well as the extent and distribution of valve and vascular calcification. The latter is a prognostic marker for disease progression and clinical endpoints in AVS and has proven useful in determining AVS severity in patients with low aortic valve gradient.[4] Accordingly, CCTA is being recommended as a key imaging tool for pre-procedural TAVI diagnostic work-up by the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the management of valvular heart disease.[5] Perivascular adipose tissue attenuation (PVAT) has recently emerged as a reliable CCTA-based biomarker that can be used to quantify vessel inflammation and has demonstrated prognostic value in the early detection of adverse cardiovascular events.[6] Indeed, PVAT improves cardiac risk prediction over conventional CCTA, prompting significant patient reclassification for

cardiac and all-cause mortality.[7] While quantification of epicardial fat, another CCTA-based biomarker mirroring inflammation, has failed to add prognostic value in TAVI patients,[8] it is currently unknown whether aortic perivalvular and coronary PVAT adds incremental prognostic value in patients undergoing TAVI.

Given (i) the need to improve current risk prediction models for patients undergoing TAVI, (ii) the known involvement of inflammatory phenotypes in AVS progression and post-procedural outcomes, and (iii) the established role of CCTA in pre-TAVI diagnostic work-up, we sought to investigate whether coronary and aortic PVAT offers additive prognostic value in patients with severe AVS undergoing TAVI.

Methods

Study population

We enrolled retrospectively 510 consecutive patients with severe symptomatic AVS (= non-indexed aortic valve area ≤1.0 cm^2 or aortic valve mean pressure gradient >40 mmHg) and intermediate or high operative risk (EuroSCORE II of 5.26 ± 4.29% and STS score of 3.71 ± 1.37%) who had undergone TAVI and pre-TAVI CCTA between November 2015 and June 2020 at the Department of Cardiology, Medical University of Vienna, Austria. The inclusion criteria encompassed ≥18 years of age and the existence of a CCTA exam conducted within 14 days prior to TAVI. Patients with acute or chronic infection, systemic inflammatory or autoimmune disease, bicuspid aortic valve, patients undergoing a valve-in-valve procedure were excluded. In addition, 81 patients were excluded due to insufficient CCTA image quality or technical issues comprising breathing artefacts ($n = 15$), excessive slice thickness ($n = 23$), missing anatomical information of the entire aortic root or distal RCA ($n = 16$), motion artefacts ($n = 15$), and small, non-dominant RCA, too small to be traced ($n = 10$). A flow chart depicting selection and exclusion criteria is shown in *Figure 1*. The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments were approved by the institutional ethics committee of the Medical University of Vienna (EK 1471/2021). The need for informed written consent was waived due to the retrospective nature of the study. Details regarding data acquisition and definitions are provided in Supplementary Material.

TAVI procedure

All TAVI procedures were performed under local anaesthesia with transfemoral [$n = 349$ (94.3%) patients], transapical [$n = 15$ (4.1%)], sub-clavian [$n = 5$ (1.4%)], or transaortal [$n = 1$ (0.3%)] access using new generation prostheses including Portico valve [Abbott, $n = 51$ (13.8%)], Sapien 3 and Sapien XT valve [Edwards Lifesciences, $n = 153$ (41.5%)], Evolut R valve [Medtronic, $n = 44$ (11.9%)], and AcurateNeo Symetis valve [Boston Scientific, $n = 118$ (32%)]. Periprocedural data of the study population are presented in Supplementary data online, *Table S1*.

Cardiac computed tomography image acquisition and reconstruction

All patients underwent CCTA on either the dual-source CT scanner SOMATOM Force or the SOMATOM Definition Edge scanner (both Siemens Healthineers) using a contrast-enhanced method with helical scanning. CCTA acquisition and analysis were performed following the guidelines provided by the Society of Cardiovascular Computed Tomography.[9,10] The scanning parameters included a tube voltage of 70–140 kilovoltage peak (kVp) and a tube current of 120–240 mAs (mean 187.7 ± 7 mAs). The majority of images were acquired at 80 kVp (58.6%) followed by 90 kVp (21.0%), 100 kV (7.0%), 120 kVp (6.7%), 140 kVp (4.3%), and 110 kVp (1.6%). Only three scans (0.8%) were performed at 70 kVp. For PVAT quantification, the PVAT value was adjusted using a scaling parameter accounting for differences in tube voltage, derived from our previous investigation and consistent with existing literature.[7,11] The reconstruction was performed in axial and multi-planar reformatted images. Starting in January 2018, all patients scheduled for TAVI underwent a non-contrast CT scan for coronary and aortic valve calcium scoring. Prior to this date, calcium scoring of the aortic valve was primarily performed on patients with suspected low-flow low-gradient AVS or unclear AVS gradient findings (between severe and moderate) to assist in treatment decision-making. For calcium scoring, the above scanners (Siemens SOMATOM) were used with the following scanning parameters: 64 × 2.5 mm collimation, rotation time of 0.35 s, tube voltage of 120 kVp and tube current of 200 mAs. Segments with prior bypass-vessels or coronary artery stent implantation were excluded from CACS quantification, which was performed manually using semi-automatic post-processing software on a dedicated workstation (CaScoring, Syngo. Via VB30A, Siemens Healthineers).

Measurement of PVAT

PVAT, a novel method for assessing coronary inflammation by analysing routine CCTA, captures changes in perivascular adipose tissue composition driven by inflammatory signals from the inflamed vessel wall. Briefly, the presence of vascular inflammation leads to the release of inflammatory mediators into the local perivascular adipose tissue, inducing regional lipolysis and inhibiting adipogenesis.[12] The latter is associated with an increased water content of perivascular adipose tissue which can be detected by CCTA as an increased attenuation (Hounsfield Unit, HU) surrounding the affected vessel.[12] PVAT was measured around the right coronary artery [PVAT(RCA)] as well as around the aortic root between the aortic annulus and the sinotubular junction PVAT[valve] using PMOD 4.003 software (PMOD Technologies, Zurich, Switzerland) as previously described.[13] A detailed description of PVAT quantification is provided in Supplementary Material. Representative images demonstrating quantification of PVAT are shown in *Figure 2*.

Follow-up and study outcome

Follow-up was performed by telephone calls (patient, relatives, referring cardiologist, or general practitioner) or a follow-up appointment in our cardiology outpatient clinic. In addition, the electronic database of the hospital and the state-wide Austrian death registry database were used to evaluate and confirm deaths. Study endpoints were defined according to VARC-2 criteria.[14] Adjudication of events was independently performed by two cardiologists (C.D. and N.P.) who were blinded to imaging data. The primary endpoint of the study was the occurrence of major adverse cardiovascular event (MACE), which was defined as non-fatal stroke, non-fatal myocardial infarction, peripheral vascular intervention, or cardiac death. Cardiac death comprised sudden cardiac death, deaths resulting from myocardial infarction, heart failure, stroke, cardiovascular haemorrhage, as well as death due to cardiovascular procedures.[15] Peripheral vascular intervention included all patients who underwent a peripheral vascular intervention during follow-up comprising patients with progression of peripheral vascular disease, aneurysms/pseudoaneurysm, dissections, or embolic events. Patients who experienced major vascular complications during TAVI, and subsequently underwent vascular intervention during hospitalization, were excluded from this endpoint.

Statistical analysis

Descriptive statistics were presented as appropriate. Statistical testing was done within an exploratory framework at a two-sided significance level of $\alpha = 0.05$ without adjustment for multiple testing. For bivariate and multivariable analyses, we performed Fine and Gray's proportional subdistribution hazards model for MACE, considering non-cardiac death as a competing risk. In the multi-variable analysis, we included all independent factors that achieved $P < 0.05$ in the bivariate analysis. Given the significant association between kVp levels on PVAT observed in our analysis and previous studies, tube voltage was included in our model.[16] Similarly, female sex, BMI, tube current (mAs), pre-existing CAD disease, arterial hypertension, and platelet-to-lymphocyte ratio (PLR) were included in the model, based on our and previous data showing an association between these variables and PVAT.[17] The latter three variables were added one by one to the existing model to ensure robustness of the model and avoid overfitting. To prevent multi-collinearity between PVAT[RCA] and PVAT[valve] parameters (correlation between PVAT parameters between $r = 0.62$, $P < 0.001$), two separate models were created using the same confounding factors. Time-to-event for MACE was defined as the time lag between the date of the TAVI procedure and the date of events, depending on which one came first. Patients who remained event-free were censored as the last

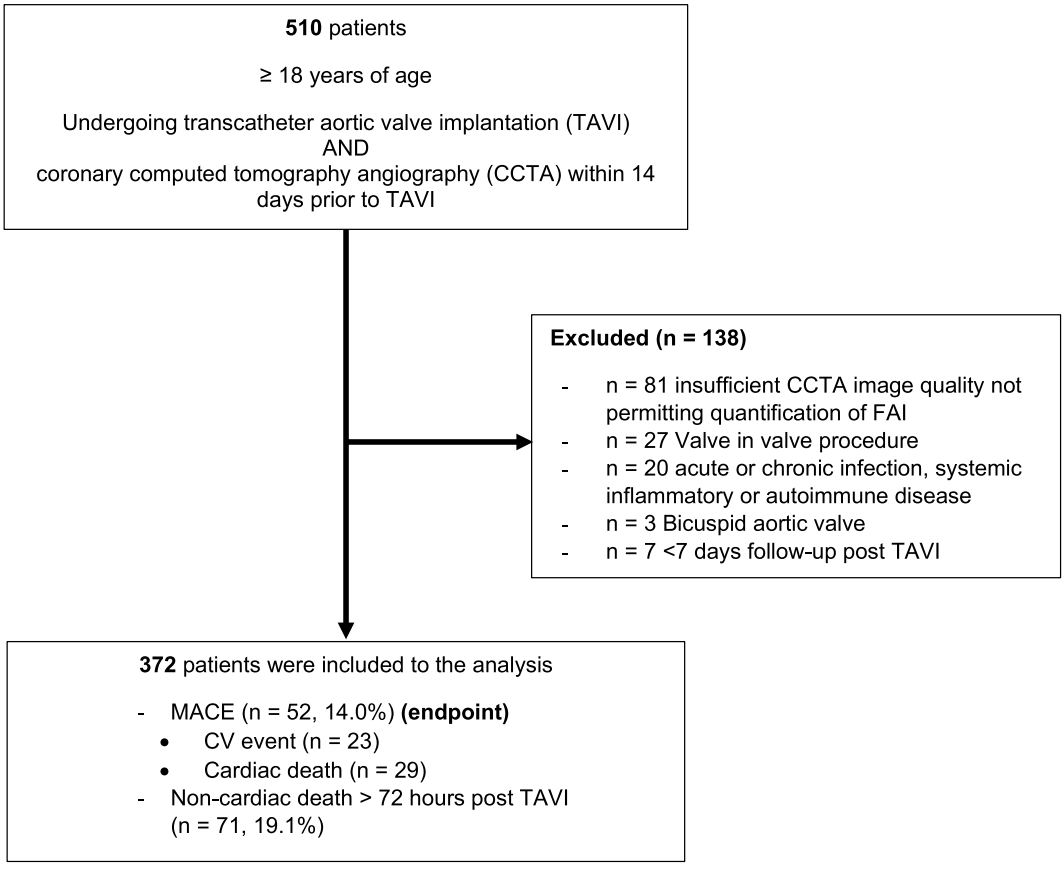


Figure 1 Flow chart depicting patient recruitment. MACE, major adverse cardiovascular event.

follow-up date. The relationship between PVAT parameters and the study endpoint was examined using both continuous and dichotomized variables. To further explore the association between PVAT and MACE outcomes, PVAT[RCA] and PVAT[valve] were also categorized into tertiles and modelled as a restricted cubic spline. The selection of high vs. low PVAT[RCA] thresholds was determined according to the established cut-off point of −70.1, as validated by Oikonomou *et al.*[7] As validated cut-off values are unavailable for other regions including the aortic valve, the median (≥−61.5) was employed to establish binary cut-off values for PVAT[valve].

We performed multiple linear regression to explore the correlation between patient-related and technical variables and PVAT. Both standardized and unstandardized coefficients, along with 95% CI, were presented.

All statistical tests were performed using Stata MP/18 (StataCorp, 2023, College Station, TX, USA).

Results

Patient baseline and procedural characteristics stratified by high vs. low PVAT

Relevant procedural, baseline clinical, laboratory, and imaging parameters of the study participants stratified by PVAT[valve] are listed in *Tables 1* and *2*; Supplementary data online, *Table S1*. In total, 372 patients [mean age 80.6 ± 6.8 years; 169 (45%) women] were included in this study (*Table 1*). The overall patient population was at intermediate to high risk (mean EuroSCORE II 5.2 ± 4.0% and mean STS score of 3.7 ± 1.4%, *Table 2*). The mean EuroSCORE was higher in the high PVAT[valve] group than in the low PVAT[valve] group (5.6 ± 4.8 vs. 4.7 ± 2.9, $P = 0.040$). Patients in the high PVAT[valve] group had a longer median hospital stay [6 (inter-quartile range, IQR 4–9) days] than individuals in the low PVAT[valve] group [5 (IQR 4–8) days, $P = 0.047$, *Table 2*]. Post-TAVI LVEF and post-TAVI mean aortic valve pressure gradient (APG) were lower in individuals with high PVAT[valve] than in individuals with low PVAT[valve] (57.66 ± 14.63 vs. 63.96 ± 11.18%, $P = 0.016$ and 10.09 ± 4.53 vs. 11.16 ± 5.09 mmHg, $P = 0.038$, respectively). There was no significant difference between the groups for procedural complications, except for the occurrence of acute renal failure, which was slightly higher in the low PVAT[valve] group (6.90% vs. 2.01%, $P = 0.042$, *Table 2*).

PVAT measurement with high accuracy was feasible in 84.1% of patients (*Figure 1*). In $n = 81/510$ patients insufficient CCTA image quality did not permit quantification of PVAT. Individuals with high PVAT[valve] had a lower body mass index (BMI, 25.84 ± 4.83 vs. 28.75 ± 4.86 kg/m^2, $P < 0.001$), higher inflammatory markers (PLR: 201.8 ± 102.44 vs. 164.4 ± 78.5, $P < 0.001$), higher B-type natriuretic peptide (NT-pro-BNP, 2150 [IQR 807–6791] vs. 1225 [IQR 541–2472] pg/mL, $P < 0.001$, *Table 1*), and more often abnormal LVEF ($P = 0.022$) as compared with individuals who categorized in the low PVAT[valve] group (see Supplementary data online, *Table S1*). On the contrary, individuals who categorized in the low PVAT[valve] group exhibited a higher prevalence of cardiovascular risk factors, such as arterial hypertension (93.0% vs. 85.5%, $P = 0.019$), and dyslipidaemia (78.9% vs. 62.9%, $P < 0.001$), compared with those with high PVAT[valve] (*Table 1*). A sub-group of 156 patients underwent pre-procedural aortic valve and coronary calcium

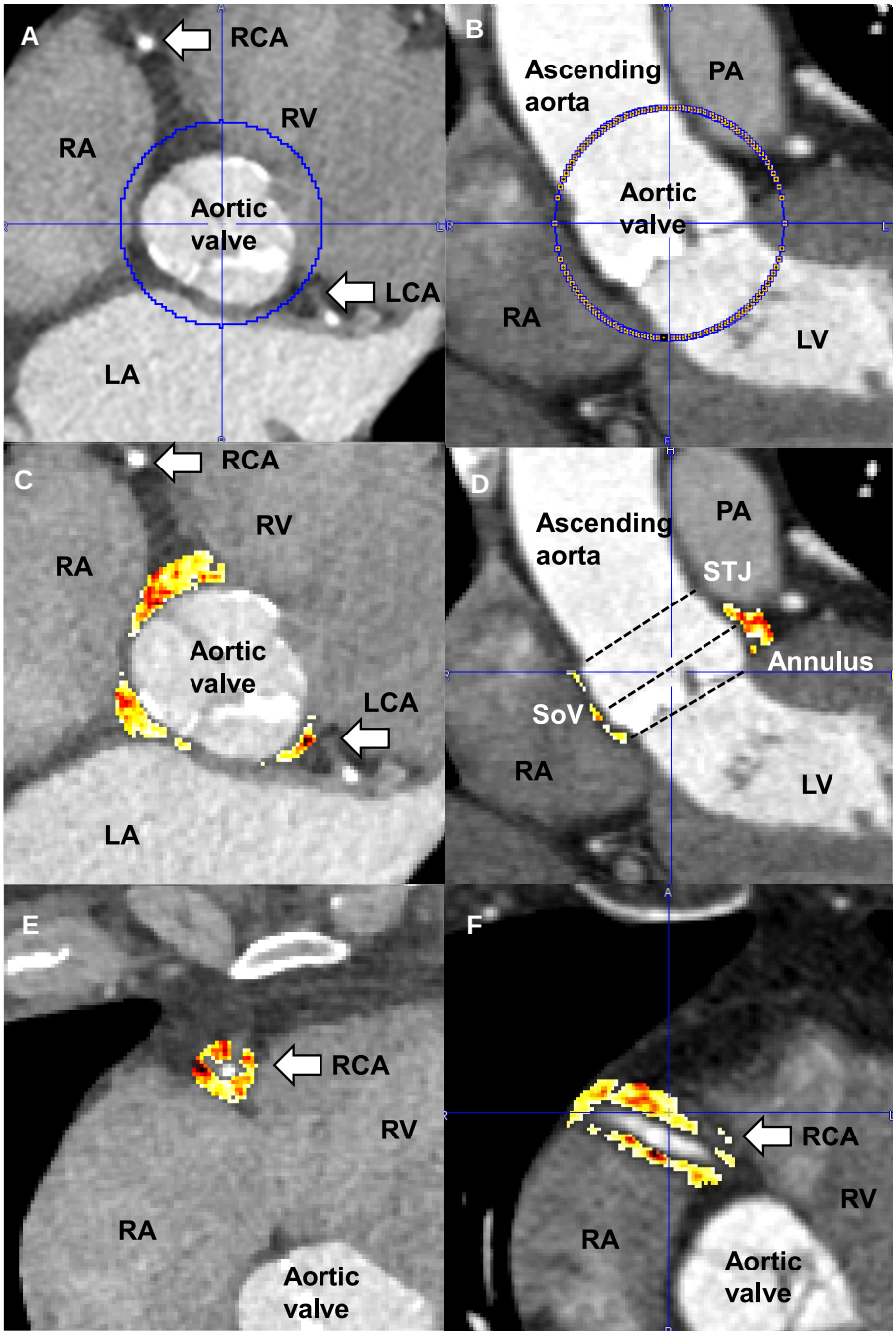


Figure 2 PVAT phenotyping of the aortic valve and the right coronary artery (RCA) from CCTA. Volumes of interest (VOI) in the transaxial (*A*), and oblique-sagittal (*B*) views of the aortic valve. Attenuation index phenotyping of the aortic valve in transaxial (*C*), and oblique-sagittal views (*D*). Attenuation index phenotyping of the RCA in transaxial views (*E* and *F*). RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PA, pulmonary artery, LCA, left coronary artery; STJ, sinotubular junction; SoV, Sinus of Valsalva.

scoring (CACS) by non-contrast CT. In these patients, the average calcium score was high for both the aortic valve (2418 [1613–3554] as well as for all coronaries. No group differences were observed for valvular calcium scoring and CACS (see Supplementary data online, *Table S1*). There was no difference in PVAT[valve] or PVAT[RCA] mean values between women and men (PVAT[valve]: -61.52 ± 6.56 HU vs. -61.99 ± 6.5 HU in men, $P = 0.49$; PVAT[RCA]: -68.29 ± 9.51 HU vs. -68.27 ± 9.56 HU in men, $P = 0.99$).

Study endpoint

During a median follow-up of 3.0 (range IQR 2.5–3.6) years, 52 patients (14%) experienced a MACE (combined primary endpoint) amongst

Table 1 Patient's baseline characteristics, laboratory parameter, and echocardiography findings stratified by high vs. low perivascular adipose tissue attenuation around the aortic valve [PVAT (valve)]

Variable	Total ($n = 372$)	Low PVAT [valve] ($n = 186$)	High PVAT [valve] ($n = 186$)	*P*-value
Demographic variables				
Age (year)—Mean (SD)	80.63 (6.83)	80.04 (6.44)	81.22 (7.17)	0.098
Female sex—*n* (%)	169 (45.43%)	83 (44.62%)	86 (46.24%)	0.75
BMI—Mean (SD)	27.30 (5.05)	28.75 (4.86)	25.84 (4.83)	<0.001
Heart rate, bpm—Mean (SD)	72.19 (14.12)	70.96 (12.18)	73.29 (15.65)	0.29
Comorbidities				
Pre-existing CAD—*n* (%)	225 (60.48%)	113 (60.75%)	112 (60.22%)	0.92
Previous myocardial infarction—*n* (%)	53 (14.25%)	33 (17.74%)	20 (10.75%)	0.054
Previous PCI/CABG—*n* (%)	155 (41.67%)	80 (43.01%)	75 (40.32%)	0.60
Previous cardiac (non-coronary) surgery—*n* (%)	34 (9.97%)	18 (10.47%)	16 (9.47%)	0.76
Atrial fibrillation—*n* (%)	128 (34.41%)	68 (36.56%)	60 (32.26%)	0.38
Cerebrovascular disease—*n* (%)	31 (8.36%)	15 (8.06%)	16 (8.65%)	0.84
Chronic obstructive lung disease—*n* (%)	42 (11.32%)	25 (13.51%)	17 (9.14%)	0.18
Liver disease—*n* (%)	14 (3.77%)	9 (4.84%)	5 (2.70%)	0.28
Terminal renal failure—*n* (%)	5 (1.34%)	2 (1.08%)	3 (1.61%)	0.65
Peripheral/carotid vascular disease—*n* (%)	77 (20.70%)	36 (19.35%)	41 (22.04%)	0.52
Implanted pacemaker—*n* (%)	45 (12.10%)	27 (14.52%)	18 (9.68%)	0.15
Cardiovascular risk factors				
Arterial hypertension—*n* (%)	332 (89.25%)	173 (93.01%)	159 (85.48%)	0.019
Diabetes mellitus—*n* (%)	111 (29.84%)	64 (34.41%)	47 (25.27%)	0.054
Dyslipidaemia—*n* (%)	263 (70.89%)	146 (78.92%)	117 (62.90%)	<0.001
Smoking—*n* (%)	24 (6.45%)	11 (5.91%)	13 (6.99%)	0.67
Medical treatment				
Diuretics—*n* (%)	209 (56.18%)	106 (56.99%)	103 (55.38%)	0.75
Mineralocorticoid-receptor antagonists—*n* (%)	109 (29.62%)	56 (30.27%)	53 (28.96%)	0.78
ACE inhibitors—*n* (%)	129 (35.05%)	61 (32.97%)	68 (37.16%)	0.40
Ca2 + antagonists—*n* (%)	95 (25.82%)	54 (29.19%)	41 (22.40%)	0.14
Beta-blockers—*n* (%)	223 (60.60%)	120 (64.86%)	103 (56.28%)	0.092
Platelet inhibitors—*n* (%)	224 (60.22%)	115 (61.83%)	109 (58.60%)	0.53
Oral anti-coagulation—*n* (%)	127 (34.14%)	71 (38.17%)	56 (30.11%)	0.10
Lipid-lowering drugs—*n* (%)	250 (67.20%)	139 (74.73%)	111 (59.68%)	0.002
Laboratory parameters pre-TAVI				
Creatinine, mg/dL—Mean (SD)	1.25 (0.68)	1.21 (0.59)	1.28 (0.76)	0.38
GFR, mL/min/1.73 m^2 –Mean (SD)	55.60 (25.10)	57.60 (23.19)	53.53 (26.84)	0.13
NT-pro-BNP, pg/mL—median (IQR)	1448 (612–3667)	1225 (541–2472)	2150 (807–6791)	<0.001
Troponin T ($n = 107$), ng/L—median (IQR) (Missing = 265)	26 (16–46)	24 (13–47)	30 (22–46)	0.088
Inflammatory parameters pre-TAVI				
Neutrophils, 1000/μL—Mean (SD) (Missing = 92)	5.20 (3.49)	5.38 (4.62)	5.03 (1.80)	0.40
Lymphocytes, 1000/μL—Mean (SD) (Missing = 92)	1.53 (1.90)	1.52 (0.60)	1.55 (2.61)	0.88
NLR—Mean (SD) (Missing = 92)	4.41 (3.53)	4.18 (3.98)	4.64 (3.02)	0.28
Ferritin, ng/mL—median (IQR) (Missing = 178)	127.8 (64.4–218.3)	118.6 (61.2–202.9)	133.0 (65.3–219.1)	0.48
CRP, mg/dL—median (IQR) (Missing = 78)	0.31 (0.12–0.89)	0.29 (0.11–0.90)	0.34 (0.12–0.89)	0.55
PLR—median (IQR) (Missing = 95)	183.41 (93.20)	164.38 (78.48)	201.76 (102.44)	<0.001
CRP-to-albumin ratio—Mean (SD) (Missing = 100)	0.03(0.07)	0.03 (0.09)	0.03 (0.06)	0.40

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACE, angiotensin converting enzyme; TAVI, transcatheter aortic valve implantation; GFR, glomerular filtration rate; IQR, inter-quartile range; NT-pro-BNP, B-type natriuretic peptide; NLR, neutrophil-to-lymphocyte-ratio, CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio.

Table 2 Patient's procedural data during TAVI

TAVI procedural data	Total ($n = 372$)	Low PVAT [valve] ($n = 186$)	High PVAT [valve] ($n = 186$)	*P*-value
Overall surgical risk				
EuroSCORE II—Mean (SD) (Missing = 73)	5.17 (4.00)	4.68 (2.94)	5.63 (4.75)	0.040
STS score—Mean (SD) (Missing = 205)	3.70 (1.38)	3.55 (1.25)	3.83 (1.48)	0.19
Post-procedural parameters				
Change in creatinine pre-/post-TAVI, mg/dL—Mean (SD)	0.07 (0.49)	0.11 (0.58)	0.03 (0.40)	0.17
ICU admission, *n* (%)	117 (31.45)	54 (29.03)	63 (33.87)	0.31
Length of ICU stay (days)—Median (IQR)	2 (2–3)	2 (2–3)	2 (2–4)	0.31
Hospital length of stay (days)—Median (IQR)	5 (4–9)	5 (4–8)	6 (4–9)	0.047
Mean APG post-TAVI, mmHg—Mean (SD)	10.63 (4.84)	11.16 (5.09)	10.09 (4.53)	0.038
Max APG post-TAVI, mmHg—Mean (SD)	19.62 (8.80)	20.30 (9.13)	18.92 (8.42)	0.14
Aortic regurgitation post-TAVI, *n* (%)	31 (9.14)	13 (7.60)	18 (10.71)	0.32
LVEF post-TAVI, %—Mean (SD)	60.45 (13.52)	63.96 (11.18)	57.66 (14.63)	0.016
LVMI, g/m^2—Mean (SD)	139.82 (39.29)	132.20 (34.69)	145.72 (41.87)	0.083
Procedural complications	147 (39.52%)	77 (41.40%)	70 (37.63%)	0.46
Valve thrombosis/embolization, *n* (%)	5 (1.37%)	3 (1.64%)	2 (1.09%)	0.65
Cardiac arrest during procedure, *n* (%)	13 (3.67%)	4 (2.20%)	9 (5.23%)	0.13
Vascular complications, *n* (%)	69 (19.49%)	39 (21.43%)	30 (17.44%)	0.34
Periprocedural stroke, *n* (%)	15 (4.03%)	7 (3.76%)	8 (4.30%)	0.79
Pacemaker implantation, *n* (%)	42 (11.29%)	23 (12.37%)	19 (10.22%)	0.51
Coronary obstruction by implanted valve, *n* (%)	2 (0.56%)	0 (0.00%)	2 (1.16%)	0.14
Requirement of blood transfusion, *n* (%)	43 (11.56%)	24 (12.90%)	19 (10.22%)	0.42
Acute renal failure, *n* (%)	13 (4.42%)	10 (6.90%)	3 (2.01%)	0.042
Pleural effusion/cardiac decompensation, *n* (%)	5 (1.34%)	3 (1.61%)	2 (1.08%)	0.65

SD, standard deviation; STS score, Society of Thoracic Surgery (STS) score; ICU, intensive care unit; APG, aortic valve pressure gradient; LVEF; left ventricular ejection fraction; LVMI, left ventricular mass index. Data are presented as number and percentage, median and inter-quartile range, or mean and standard deviation as appropriate.

whom 10 (2.7%) experienced a non-fatal myocardial infarction, 11 (3.0%) a stroke, and 29 patients (7.8%) died from cardiac causes (*Table 3*). There was no difference in the occurrence of MACE when the study population was stratified by high vs. low PVAT[valve] or PVAT[RCA] (*Figure 3*).

Association between patient-related and technical variables and PVAT

Prior to assessing the independent association between PVAT and MACE, we performed a multi-variable linear regression analysis to evaluate the influence of demographic, clinical, laboratory, and technical parameters on PVAT[valve] and PVAT[RCA]. Consistent with previous reports,[7,12,17] BMI, known coronary artery disease, CVRFs, markers of cardiac dysfunction, inflammatory markers, and tube voltage were all associated with PVAT (see Supplementary data online, *Table S2*). These variables accounted for 40% of PVAT[valve] variation, and for 24% of PVAT[RCA] variation, respectively.

Prognostic value of PVAT for TAVI outcomes

The unadjusted associations between all demographic, clinical, laboratory, and imaging parameters and MACE are displayed in *Table 4*.

In bivariate analyses, there was no association between PVAT, as a continuous variable, and MACE for both PVAT[valve] [SHR 1.21 (95% CI: 0.77–1.91), $P = 0.409$] and PVAT[RCA] [SHR 1.15 (95% CI: 0.84–1.57), $P = 0.389$], while there was a weak association between dichotomized PVAT[RCA] and MACE [SHR 1.93 (95% CI: 0.99–3.76), $P = 0.053$]. Conversely, increasing age by 10 years [SHR 1.05 (95% CI: 1.01–1.10), $P = 0.027$], diabetes mellitus [SHR 1.88 (95% CI: 1.09–3.25), $P = 0.024$], higher surgical risk as indicated by STS score [SHR 1.27 (95% CI: 1.02–1.58), $P = 0.031$], a lower GFR [SHR 0.981 (95% CI: 0.968–0.994), $P = 0.005$], elevated troponin [SHR 1.003 (95% CI: 1.002–1.003), $P < 0.001$], or elevated NT-pro-BNP by 1000 pg/mL [SHR 1.052 (95% CI: 1.020–1.085), $P = 0.001$] were all associated with the occurrence of MACE. Notably, routine inflammatory parameters did not show associations with the study endpoint in the univariate analysis, except for a weak association between (CRP)-to-albumin ratio [SHR 1.028 (95% CI: 0.998–1.058), $P = 0.069$] or neutrophil-to-lymphocyte-ratio [NLR, SHR 1.047 (95% CI: 0.998–1.098), $P = 0.058$] and MACE. *Figure 4* presents unadjusted Kaplan–Meier curves for the cumulative incidence of MACE in individuals with high vs. low PVAT[valve] (*Figure 4A*) and high vs. low PVAT[RCA] (*Figure 4B*).

In a multi-variable model, where the covariates were defined based on their significant association with study outcomes in the bivariate analysis (shown in *Table 4*) as well as known associations with PVAT observed in our cohort and by others,[16,17] neither PVAT[valve] [adjusted SHR 1.14 (95% CI: 0.63–2.05), $P = 0.672$, *Figure 5A*] nor PVAT[RCA] [adjusted SHR 1.16 (95% CI: 0.81–1.66), $P = 0.417$] were independently associated with the study outcome of MACE, *Figure 5B*). Similarly, when PVAT[valve] and PVAT[RCA] were categorized into tertiles or modelled as a restricted cubic spline with three knots no associations with MACE were observed (data not shown).

Table 3 Outcomes following TAVI stratified by high vs. low perivascular adipose tissue attenuation around the aortic valve [PVAT (valve)]

Outcomes	PVAT [valve]			
	Total ($n = 372$)	Low PVAT [valve] ($n = 186$)	High PVAT [valve] ($n = 186$)	*P*-value
MACE, *n* (%)	52 (13.98%)	24 (12.90%)	28 (15.05%)	0.55
Non-fatal MI, *n* (%)	10 (2.69%)	8 (4.30%)	2 (1.08%)	0.054
Stroke, *n* (%)	11 (2.96%)	2 (1.08%)	9 (4.84%)	0.032
Cardiac death, *n* (%)	29 (7.80%)	12 (6.45%)	17 (9.14%)	0.33
Peripheral vascular intervention, *n* (%)	6 (1.61%)	3 (1.61%)	3 (1.61%)	1.00
All-cause mortality, *n* (%)	110 (29.57%)	47 (25.27%)	63 (33.87%)	0.069
30-day mortality, *n* (%)	9 (2.42%)	1 (0.54%)	8 (4.30%)	0.018
6-months mortality, *n* (%)	29 (7.80%)	9 (4.84%)	20 (10.75%)	0.033
12-months mortality, *n* (%)	44 (11.83%)	20 (10.75%)	24 (12.90%)	0.52

MACE, major adverse cardiovascular events; MI, myocardial infarction. Data are presented as absolute number and percentage.

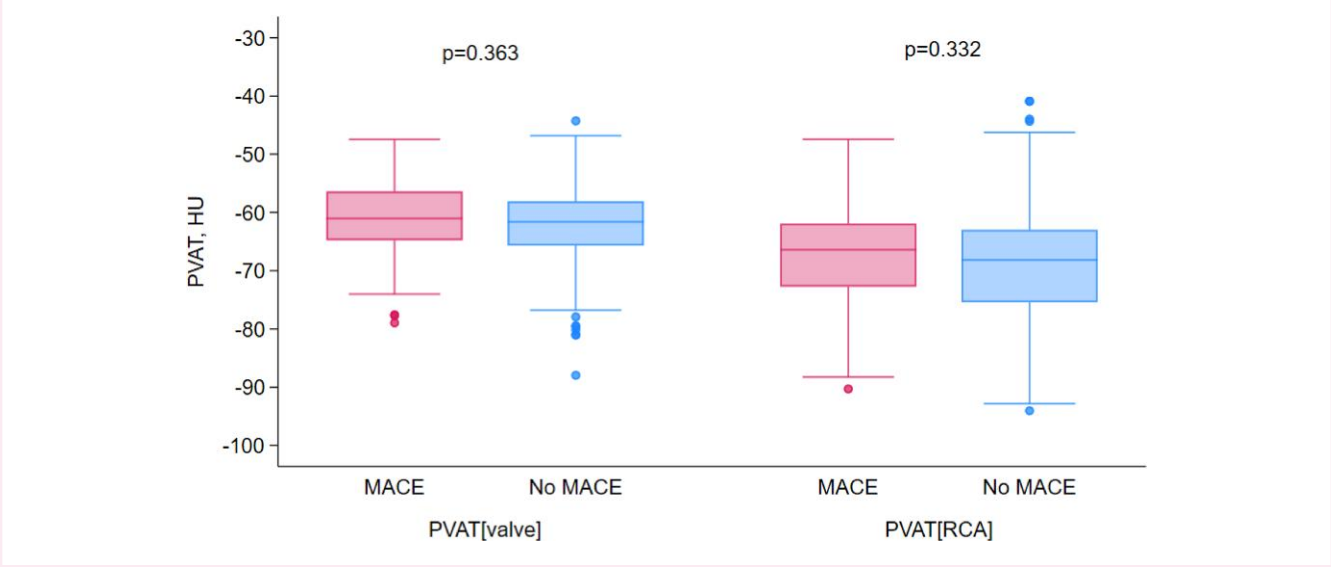


Figure 3 Box plots depicting PVAT for MACE. HU, Hounsfield units. RCA, right coronary artery. *P*-values for endpoint occurrence vs. non-occurrence are indicated.

Only dichotomized PVAT[RCA], based on the previously established cut-off point of −70.1,[7] showed a significant association with MACE [adjusted SHR 2.25 (95% CI: 1.08–4.69), $P = 0.030$, Supplementary data online, *Table S3*]. Based on previous data[16,17] and the results of our own multi-variable linear regression analysis, we also tested the inclusion of tube current (mAs), pre-existing CAD, arterial hypertension, and PLR in the models by adding these variables one by one to the existing model. None of these variables altered the association between PVAT[valve] or PVAT[RCA] and MACE in the multi-variable models (data not shown). Further, a sub-group analysis in patients with diabetes revealed no significant association between PVAT[valve] or PVAT[RCA] and MACE (data not shown). Finally, no significant association was found between a four-level variable categorizing high and low PVAT[valve] and PVAT[RCA] and MACE (data not shown). When an inter-action term consisting of female sex*PVAT[valve] or female sex*PVAT[RCA] was included in the multi-variable model, this term was not significant (PVAT[valve]: SHR 3.07[95% CI: 0.87–10.85], $P = 0.081$; PVAT[RCA]: SHR 1.37[95% CI: 0.28–6.63], $P = 0.696$).

Discussion

Traditional risk scores for TAVI (e.g. STS score or EuroSCORE II) do not include important parameters such as nutritional status, frailty, or inflammation, all considered important risk factors for increased mortality in AVS patients undergoing TAVI. Hence, it is clear that additional parameters are needed in the prognostic evaluation of such patients. PVAT can serve as a sensitive and specific metric of the vascular inflammatory burden around epicardial coronary arteries, however, its prognostic value for predicting MACE when measured in the perivascular tissue surrounding the aortic valve has not previously been described. In addition to investigating PVAT[RCA], previously scrutinized and

Table 4 Results of the univariate analysis for MACE

Factors	Crude SHR (95% CI)	*P*-value
Demographic variables		
Age (×10 years)	1.67 (1.06, 2.65)	0.027
Female sex	0.91 (0.53, 1.56)	0.732
BMI (kg/m^2)	0.97 (0.91, 1.03)	0.333
Comorbidities		
Pre-existing CAD	1.29 (0.73, 2.28)	0.376
Previous myocardial infarction	1.11 (0.52, 2.34)	0.792
Previous PCI/CABG	1.06 (0.61, 1.83)	0.843
Atrial fibrillation	0.86 (0.48, 1.55)	0.616
Previous stroke	0.41 (0.10, 1.63)	0.205
Chronic obstructive pulmonary disease	1.44 (0.68, 3.07)	0.345
Liver disease	0.50 (0.07, 3.45)	0.486
Peripheral/carotid vascular disease	0.85 (0.42, 1.69)	0.634
Cardiovascular risk factors		
Arterial hypertension	1.13 (0.45, 2.84)	0.802
Diabetes mellitus	1.88 (1.09, 3.25)	0.024
Dyslipidaemia	0.71 (0.40, 1.23)	0.220
Smoking	1.24 (0.44, 3.52)	0.683
Symptoms		
NYHA class		
I		
II	0.72 (0.24, 2.18)	0.555
III	0.90 (0.32, 2.53)	0.842
IV	2.31 (0.64, 8.30)	0.199
Surgical risk		
Euroscore II score	1.03 (0.98, 1.07)	0.281
STS score	1.27 (1.02, 1.58)	0.031
Medical treatment		
Diuretics	1.09 (0.63, 1.88)	0.763
MRA	0.89 (0.48, 1.64)	0.706
ACE inhibitor	0.97 (0.55, 1.71)	0.913
Ca2 + antagonists	0.78 (0.40, 1.52)	0.464
Beta-blockers	1.19 (0.67, 2.11)	0.544
Platelet inhibitors	1.17 (0.66, 2.08)	0.584
Oral anti-coagulation	1.03 (0.58, 1.83)	0.913
Lipid-lowering drugs	0.65 (0.38, 1.12)	0.124
Laboratory parameters pre-TAVI		
GFR (mL/min/1.73 m^2)	0.981 (0.968, 0.994)	0.005
NT-pro-BNP (×1000 pg/mL)	1.052 (1.020, 1.085)	0.001
TroponinT (ng/L)	1.003 (1.002, 1.003)	<0.001
Hemoglobin	0.962 (0.845, 1.096)	0.561
Platelet count	0.999 (0.995, 1.002)	0.446
Inflammatory parameters pre-TAVI		
CRP to albumin ratio (%)	1.028 (0.998, 1.058)	0.069
Neutrophils (1000/μL)	1.031 (0.992, 1.073)	0.122
Lymphocytes (1000/μL)	0.743 (0.436, 1.266)	0.274
NLR	1.047 (0.998, 1.098)	0.058
Ferritin (ng/mL)	1.000 (0.998, 1.002)	0.773
CRP (ng/mL)	1.000 (0.984, 1.015)	0.981
PLR	1.000 (0.997, 1.003)	0.915
Prosthesis and procedural characteristics		
Use of cerebral protection system	0.83 (0.50, 1.36)	0.462
Ballon expandable valve	0.93 (0.61, 1.41)	0.719
Prosthesis size	0.97 (0.90, 1.04)	0.388
Left ventricular function		
Normal	1	
Mildly reduced	1.10 (0.48, 2.52)	0.816
Moderately reduced	1.00 (0.37, 2.71)	0.997
Severly reduced	2.26 (0.84, 6.04)	0.106
Imaging parameters		
PVAT as continuous variable		
PVAT [valve](×10 HU)	1.21 (0.77, 1.91)	0.409
PVAT [RCA](×10 HU)	1.15 (0.84, 1.57)	0.389
Dichotomized PVAT		
PVAT [valve] ≥ −61.5	1.17 (0.68, 2.00)	0.580
PVAT [RCA] ≥ −70.1	1.93 (0.99, 3.76)	0.053
Calcium score (×10 000)	0.60 (0.04, 8.59)	0.706
Tube voltage (×10 kVp)	1.01 (0.85, 1.21)	0.882
Tube current (×10 mAs)	1.00 (0.97, 1.03)	0.918

BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; STS score, Society of Thoracic Surgery (STS) score; MRA, mineralocorticoid-receptor antagonists; ACE, angiotensin converting enzyme; GFR, glomerular filtration rate; NT-pro-BNP, B-type natriuretic peptide; NLR, Neutrophil-to-lymphocyte-ratio, CRP, C-reactive protein; PLR, Platelet-to-lymphocyte ratio; PVAT, perivascular adipose tissue attenuation; RCA, right coronary artery; HU, Hounsfield unit.

validated for predicting MACE in patients with coronary artery disease, we quantified and analysed PVAT surrounding the aortic valve.[7]

We found that neither PVAT[RCA] nor PVAT[valve] provides additional prognostic value beyond established risk factors for the prediction of MACE in patients undergoing TAVI. This lack of association between PVAT and MACE aligns with prior studies demonstrating that circulating inflammatory markers do not correlate with an elevated risk of MACE in TAVI patients.[18,19] Moreover, while some studies have linked systemic inflammatory markers to early all-cause mortality post-TAVI,[20–24] only one study, involving 120 patients with severe AVS undergoing TAVI, reported an association between an inflammatory index comprising neutrophil, platelet, and lymphocyte counts, and 30-day MACE.[19] Consistent with these previous findings, significantly more patients with high PVAT[valve] as compared with those with low PVAT[valve] died from any cause 30 days and 6 months after TAVI, while such difference was not observed for MACE in our study. However, our findings differ from a recent single-centre study involving 62 patients, which reported a significant association between PVAT[RCA] and MACE in patients undergoing TAVI.[25] In our study, this association was observed only when PVAT[RCA] was dichotomized according to the previously established cut-off value of −70.1 HU,[7] but not for the continuous variable. The discrepancies between their study and ours can be attributed to differences in study

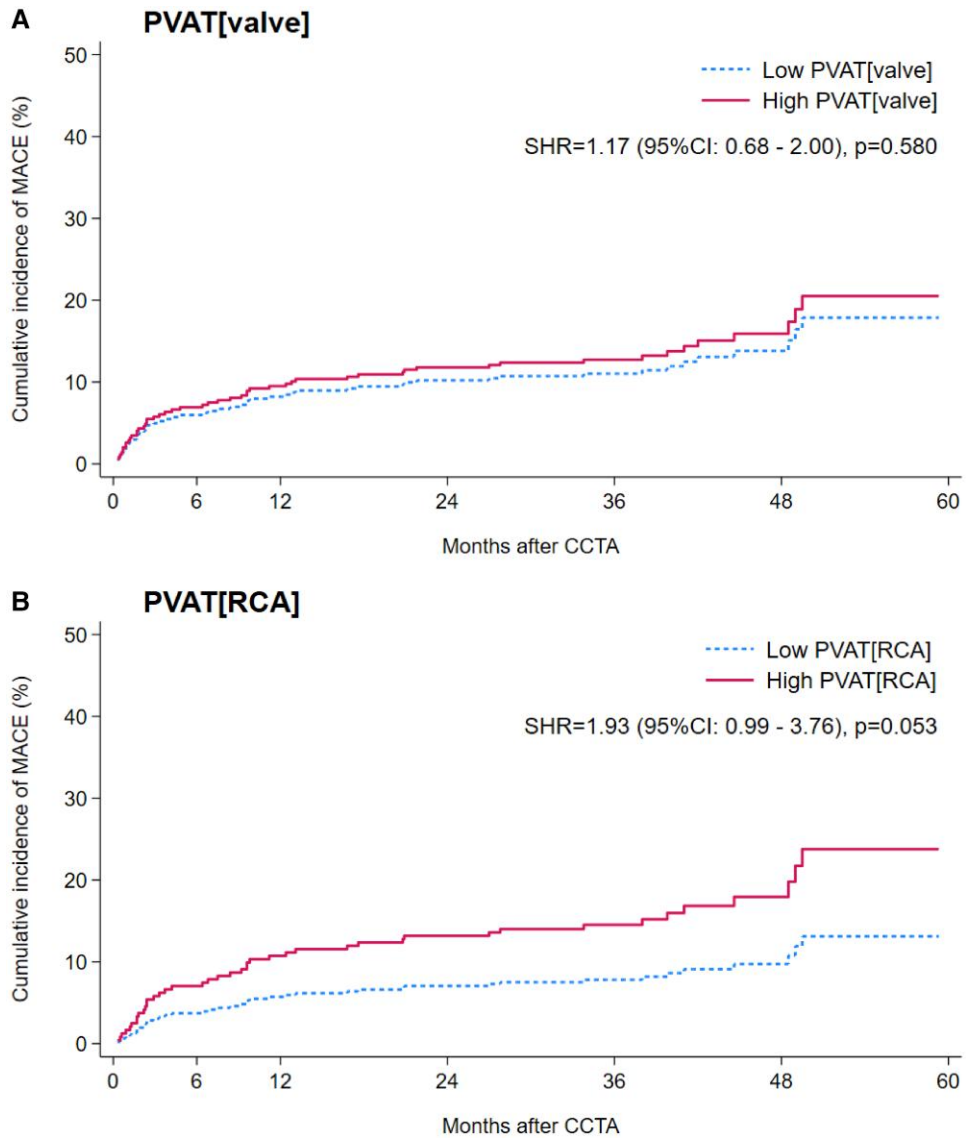


Figure 4 Kaplan–Meier curves depicting unadjusted cumulative incidences of MACE for PVAT measured around the aortic valve [PVAT (valve)] (*A*) and the right coronary artery [PVAT (RCA)] (*B*). CCTA, coronary computed tomography angiography; HU, Hounsfield units.

design and population, including a larger sample size and longer follow-up time as well as a substantially higher proportion of patients with pre-existing CAD and female patients in our study. Additionally, it is noteworthy that only one myocardial infarction occurred during the 2-year follow-up in the study by Steyer *et al.*, with the majority of the 15 events being related to cardiac death (unspecified and due to heart failure).

Individuals with high PVAT[valve] exhibited a heightened surgical risk based on EuroSCORE II, a lower BMI, and reduced left ventricular ejection fraction compared with those with lower PVAT[valve]. This observation suggests that systemic or vascular inflammation may reflect an individual's overall health status rather than specific cardiovascular risk. However, the clinical significance of a correlation between PVAT and pre-mature death may be limited, particularly in a frail patient population with high overall mortality rates. Moreover, the high prevalence of comorbidities in our cohort, leading to early non-cardiac deaths (75% of all-cause deaths in our study had a non-cardiovascular cause), or the potential modifying effects of medical therapies, such as statins or platelet inhibitors, might explain the lack of association between PVAT and MACE in our study. Indeed, in patients with coronary artery disease, PVAT lost its prognostic value for MACE in a previous study when treatment with aspirin and/or statins was initiated following a CCTA-based diagnosis.[7] Similarly, initiation of statin treatment or anti-inflammatory therapy after baseline CCTA was associated with a decrease in mean PVAT in follow-up CCTAs in three previous studies.[26–28] Aligned with these previous reports, individuals in the low PVAT[valve] group had a higher BMI and a greater prevalence of dyslipidaemia and arterial hypertension compared with those with high PVAT[valve]. Similarly, an inverse association between previous PCI/CABG and PVAT was seen in our multi-variable linear regression analysis. These unexpected findings might reflect the anti-inflammatory effect of cardiovascular drugs, rather than indicating the presence of CVRFs and CV disease state.

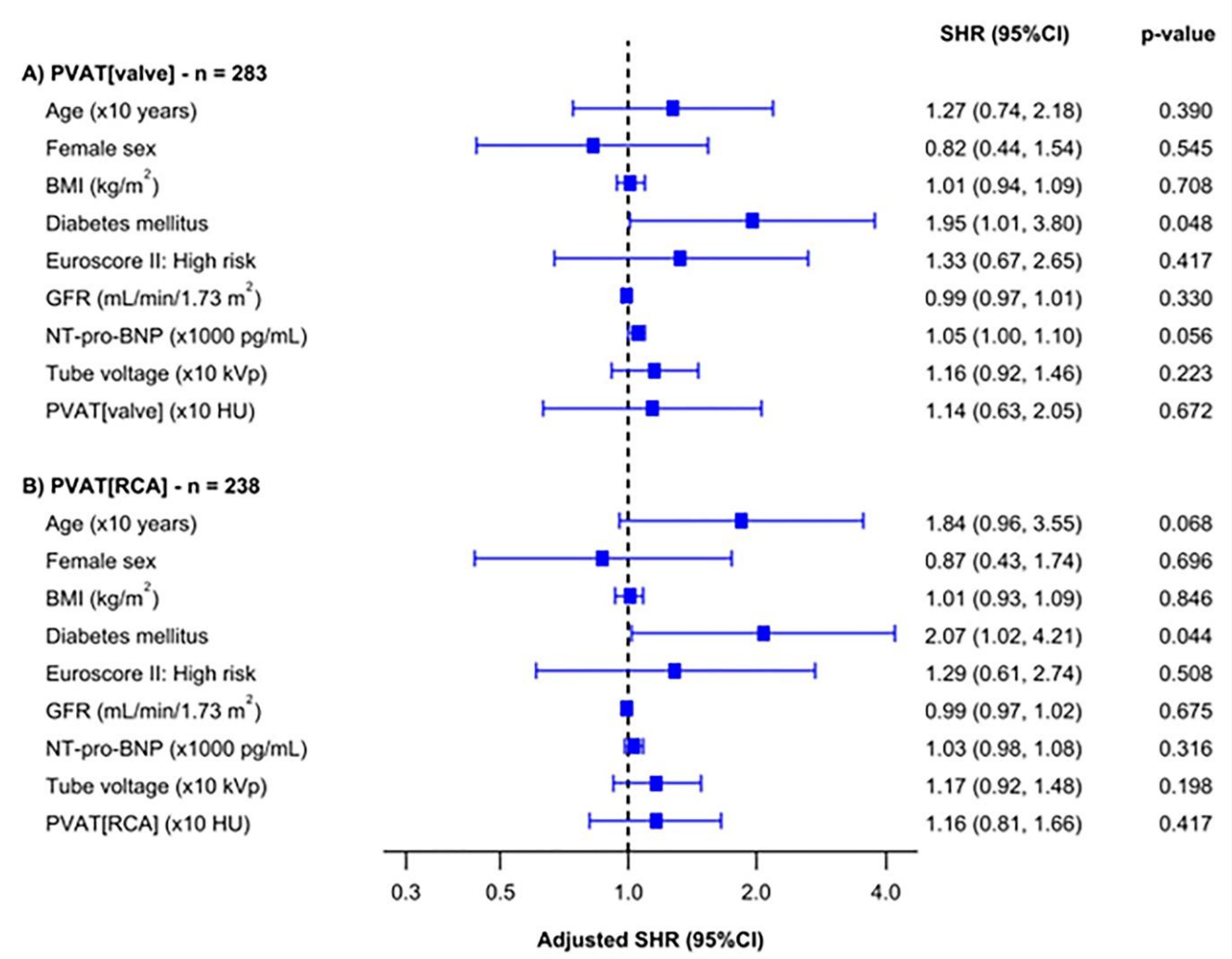


Figure 5 Adjusted models for MACE. BMI, body mass index; GFR, glomerular filtration rate; NT-pro-BNP, B-type natriuretic peptide; kVp, kilovoltage peak; PVAT, perivascular adipose tissue attenuation; RCA, right coronary artery; SHR, sub-distribution hazard ratio PVAT is presented as continuous variable.

An alternative explanation for the lack of association between PVAT[valve] and MACE might be a limited ability of PVAT to accurately assess inflammation of the aortic valve. This notion is supported by findings from Botezatu *et al*., who recently demonstrated that there were no discernible differences in PVAT[valve] between patients with AVS and a matched cohort without AVS.[29] Additionally, in their study, PVAT[valve] exhibited no correlation with the presence or progression of AVS, nor with other imaging markers of inflammation, such as 18F-NaF-PET.[29] Furthermore, the considerable inter-individual variability in aortic valve area and morphology, along with the inherent distribution pattern of PVAT amongst different individuals, might contribute to the limited prognostic value of PVAT[valve]. Given its larger volume, PVAT surrounding the aortic valve [PVAT(valve)] may be more susceptible to systemic influences and potential confounders such as BMI, other fat depots, alterations in blood pressure, and medication, compared with PVAT around the coronary arteries.[30] Consistent with this assumption baseline demographic, laboratory, and technical parameters accounted for 40% of PVAT[valve] variation, but only 24% of PVAT[RCA] variation. Additionally, our study population exhibited a high degree of aortic valvular calcification as indicated by the aortic valve calcium score. Hence, it is conceivable that inflammation becomes less pronounced during the final stages of macroscopic calcification, as previously documented, and may therefore no longer provide prognostic information once this stage is reached.[31]

There are limitations to this study that should be pointed out. First, this study is a single-centre analysis conducted in individuals of advanced age with a high prevalence of comorbidities, which limits its generalizability. Second, our findings reflect associations, not causality, and do, therefore not provide information on the underlying mechanisms. Third, although a comprehensive group of adjustment variables was employed, unmeasured factors may have affected our endpoints. Fourth, the lack of standardized approaches to quantify PVAT makes it difficult to compare different studies. Similarly, there are no established quantitative categories for PVAT. The previously suggested PVAT cut-off point of −70.1 has only been validated for PVAT around the RCA by Oikonomou *et al*., but not for other coronary arteries or the aortic valve.[7] Although our results remained consistent across different categorization approaches, the determination of an optimal

PVAT cut-off point requires further studies. It should also be noted that our software, including the HU attenuation assessment, was originally optimized for coronary rather than aortic valve PVAT analysis. This could affect the validity of the results due to anatomical differences between the coronary artery and the aortic valve. Fifth, inter-individual differences in CCTA scan parameters might have influenced our results. However, to minimize the impact of varying scan acquisition parameters, we adjusted for differences in tube voltage using a scaling parameter that we previously validated.[11] Additionally, tube voltage (kVp) was included in our multi-variable models. Finally, our study is not comparative, and we did not measure PVAT against any other imaging/histological exams. Additionally, given the focus on the aortic valve, we did not measure total plaque burden or specific plaque characteristics, which prevents further analysis of the association between PVAT and coronary plaque features. These limitations are substantially counterbalanced by several important strengths and innovations, including the extended follow-up time, and the unique data obtained from a real-world setting where CCTA is used in daily clinical routine for TAVI procedural planning, as recommended by recent guidelines.

In summary, our study suggests that measuring PVAT around the RCA or the aortic valve does not provide additional prognostic value beyond established risk scores for cardiovascular outcomes following TAVI. While PVAT may reflect the overall health status in typical aged and frail cardiovascular patients and might contribute to general risk assessment, it does not seem to be informative for cardiovascular endpoints in TAVI. Our findings support previous research indicating that systemic inflammatory markers do not enhance risk stratification for cardiovascular endpoints in TAVI patients. Hence, there remains a need for alternative risk markers to improve risk stratification in TAVI and to appropriately select candidates for transcatheter therapy.

Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Consent for publication

Not applicable

Ethics approval and consent to participate

The study complies with the Declaration of Helsinki and its later amendments, and the research protocol was approved by the responsible ethics committee of the Medical University of Vienna (EK Nr: 1471/2021). The need to obtain informed consent was waived by the ethics committee due to the retrospective nature of the study.

Conflict of interest statement: C.G. has received research grants and speakers fees from the Novartis Foundation Switzerland, Roche Switzerland, Sanofi Genzyme, Bayer Pharmaceuticals, Gerresheimer AG, Olten Switzerland, AMGEN, Switzerland, and Advisis AG, Switzerland, outside of the submitted work. The University Hospital Zurich holds a research contract with GE Healthcare outside of the submitted work. C.G. and C.H. have received travel fees from Siemens Healthineers outside of the submitted work. All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Authors contributions

N.P. and C.G. conceptualized and designed the study. S.B., M.P.W., and G.G. co-ordinated the study. C.D., N.P., P.E.B., M.P.W., and K.M. collected the clinical data. D.B., L.R., A.V., N.M., and A.R. performed the image analysis. C.G., C.D., and P.G. have verified the underlying data. P.G., A.V., and C.G. performed the statistical analysis and prepared tables and figures. C.D. and C.G. wrote the first manuscript draft. A.H., R.R.B., C.L., J.L., and C.H. critically revised the manuscript. All authors approved the final manuscript. C.G. is the guarantor for the study. The corresponding author (N.P.) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability

Based on the ethics committee of the Medical University of Vienna ethics approval, the non-anonymized raw data cannot be shared publicly. However, anonymised data that underlie the results reported in this article will become available to interested parties for non-commercial reasons after the publication upon reasonable requests made to the corresponding author. Data requestors will need to sign a data access agreement.

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