International Journal of Cardiology 286 (2019) 29–35

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Epicardial adipose tissue volume is associated with adverse outcomes after transcatheter aortic valve replacement

Matthias Eberhard [a,1], Daniel Stocker [a,1], Martin Meyer [b,1], Julia Kebernik [b,1], Barbara E. Stähli [b,1], Thomas Frauenfelder [a,1], Francesco Maisano [b,1], Frank Ruschitzka [b,1], Fabian Nietlispach [b,1], Thi D.L. Nguyen-Kim [a,1,2], Felix C. Tanner [b,*,1,2]

[a] Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, University of Zürich, Switzerland
[b] University Heart Center Zurich, University of Zürich, Switzerland

ARTICLE INFO

Article history:
Received 2 November 2018
Received in revised form 17 January 2019
Accepted 21 January 2019
Available online 25 January 2019

Keywords:
Aortic stenosis
Computed tomography
Epicardial adipose tissue
Transcatheter aortic valve replacement

ABSTRACT

Background: Epicardial adipose tissue (EAT) is involved in inflammation and associated with cardiovascular risk factors. It is not known whether EAT affects outcome of patients undergoing transcatheter aortic valve replacement (TAVR).
Methods: 503 consecutive patients undergoing TAVR at our institution between May 2008 and November 2015 were enrolled in a prospective registry. Multi-detector computed tomography (CT) was used for EAT quantification. Outcome was assessed by 1-, 2-, and 3-year mortality and the early safety endpoint at 30 days according to the VARC-2 criteria.
Results: EAT volume was larger in males than females ($p = 0.003$), while EAT volume indexed to BSA was similar in both genders ($p = 0.348$). There was a weak correlation of EAT volume with body mass index (BMI; $r = 0.24$; $p < 0.001$) and body surface area (BSA; $r = 0.26$; $p < 0.001$). Patients with larger EAT volume had an increased all-cause 1-, 2-, and 3-year mortality after TAVR in Kaplan-Meier analyses using different binary cut-off values of 100 mm^3 (log-rank $p = 0.002$; HR: 1.94, 95%CI: 1.15–3.26), 125 mm^3 (log-rank $p = 0.001$; HR: 1.70, 95%CI: 1.06–2.68), and 130 mm^3 (log-rank $p = 0.001$; HR: 1.69, 95%CI: 1.10–2.60). Similarly, a larger EAT volume indicated an increased risk to reach the early safety endpoint for cut-off values of 125 mm^3 (OR: 1.82; 95%CI: 1.06–3.11; $p = 0.029$), and 130 mm^3 (OR: 1.91; 95%CI: 1.13–3.23; $p = 0.016$). Indexing EAT volume did not strengthen correlation of EAT with outcome.
Conclusion: EAT volume is independently associated with all-cause 1-, 2-, and 3-year mortality as well as the early safety endpoint in patients with severe aortic stenosis undergoing TAVR.

1. Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established alternative to surgical aortic valve replacement in patients with severe symptomatic aortic valve stenosis and high to intermediate surgical risk [1,2]. Several risk factors predicting adverse outcome after TAVR such as female gender, renal failure, atrial fibrillation, low gradient aortic stenosis, age and diabetes have been identified, whereas overweight and obesity were associated with better short- and long-term survival [3,4].

Epicardial adipose tissue (EAT) is visceral fat located between the myocardium and the visceral pericardium [5]. EAT is biochemically different from visceral fat of other origin and correlates with cardiac risk factors [6,7]. It is metabolically active and can function as a source of pro- and anti-inflammatory mediators as well as cytokines such as adiponectin, interleukin 6 and tumor necrosis factor α [8,9]. In patients with calcific aortic stenosis, EAT has an increased thickness and is a source of inflammatory mediators [10].

While different imaging modalities have been used to quantify EAT, computed tomography (CT) seems to be the most accurate method, given its high spatial resolution and volume coverage of the entire heart [5]. Significant associations of EAT volume with coronary artery disease as well as with atrial fibrillation have been described [11–16].

Abbreviations list: AVC, aortic valve calcification; BMI, body mass index; BSA, body surface area; CAC, coronary artery calcification; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EAT, epicardial adipose tissue; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; TAVR, transcatheter aortic valve replacement; VAT, visceral adipose tissue.

* Corresponding author at: University Heart Center Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.
E-mail address: felix.tanner@usz.ch (F.C. Tanner).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Contributed equally.

https://doi.org/10.1016/j.ijcard.2019.01.068
0167-5273/

Furthermore, EAT volume was recognized as a predictor of adverse cardiac events including myocardial infarction and all-cause mortality [6,7,17–20]. In this context, most of the studies revealed that EAT volume provides incremental prognostic value over coronary artery calcification [6,7,19,21].

The prognostic value of image-derived signs and measurements are of special interest in TAVR patients as virtually every patient is undergoing extensive pre-interventional imaging for aortic stenosis quantification, prosthesis sizing, and access route evaluation [22]. In such patients, no correlation was observed between body fat mass derived from baseline CT and outcome after TAVR [23]. The purpose of this study was to evaluate the association of EAT volume measured in baseline CT with outcome of patients undergoing TAVR for symptomatic severe aortic valve stenosis.

2. Methods

2.1. Study design

Baseline and outcome data were collected in the context of a nationwide prospective registry (SWISS TAVI registry). A total of 503 consecutive patients undergoing TAVR between May 2008 and November 2015 at the University Hospital Zurich were included in this analysis. All the patients exhibited a severe aortic valve stenosis as determined by echocardiographic quantification according to current guidelines. The study complied with the Declaration of Helsinki. The study was approved by the local ethics committee. All patients provided written informed consent.

2.2. CT protocol

Patients underwent contrast-enhanced CT for pre-interventional assessment of aortic root and evaluation of access pathways using two different scanners.

448 patients (89%) underwent prospectively ECG-gated high-pitch CT angiography on a multidetector 128-slice dual source CT scanner (CT1, Somatom Definition Flash; Siemens Healthineers, Forchheim, Germany) with the following scan parameters: tube voltage, 100kVp; tube current time product, automated attenuation-based tube current modulation applied with a reference tube current-time product of 320mAs/rotation; pitch, 3.2; gantry rotation time, 0.25s. 54 patients (11%) underwent prospectively ECG-gated high-pitch CT angiography on a multidetector 192-slice dual source CT scanner (CT2, Somatom Force; Siemens Healthineers, Forchheim, Germany) with the following scan parameters: tube voltage, automated attenuation-based tube voltage selection algorithm applied with a reference tube voltage of 100kVp; tube current time product, automated attenuation-based tube current modulation applied with a reference tube current-time product of 130mAs/rotation; pitch, 3.2; gantry rotation time 0.25s.

Contrast media injection protocol for CT1 was: 45 mL iopromide (Ultravist 370; Bayer Vital, Leverkusen, Germany) at a flow rate of 5 mL/s was intravenously injected, followed by 35 mL of a second bolus of iopromide and a 60-mL bolus of saline chaser (both at a flow rate of 2.5 mL/s). For CT2 volume and flow rate of contrast media (iopromide, Ultravist, 370 mg/mL; Bayer Vital, Leverkusen, Germany) were chosen according to the automatically selected tube voltages, as previously described [24]. For both contrast media injection protocols, bolus tracking was performed in the ascending aorta with a signal attenuation threshold of 100 Hounsfield units at a tube voltage of 120 kV.

2.3. Measurement of EAT and aortic valve calcification

Measurements were performed on axial image reconstructions: slice thickness, 2.0 mm; increment 1.5 mm; kernel, soft tissue convolution kernel. For quantification of EAT volume, CT scans were exported to a stand-alone workstation with dedicated software (Myrian; Intrasense, Montpellier, France). The pericardium was traced semi-automatically from the level of the bifurcation of the pulmonary trunk to that of the diaphragm. Thresholds (−195 HU to −15 HU) were used to define fat voxels within the epicardium as previously suggested for EAT volume measurements on CT angiography scans (see Fig. 1A–F) [25]. Manual adjustments were performed when necessary. Segmentation was carried out by a board-certified radiologist with 8 years' experience (observer 1) blinded to clinical data. To assess intra- and inter-observer reproducibility, EAT volume segmentation of a subset of 25 randomly selected patients was performed twice by observer 1 and by a second observer (board-certified radiologist with 6 years' experience). Aortic valve calcification (AVC) was quantified on CT angiography scans using a previously published formula [26].

2.4. Data collection

Patient demographics and echocardiography measurements were recorded pre-interventionally. Clinical follow-up data was obtained after 30 days, at 12 months and yearly thereafter checking the medical records. Events after TAVR were defined according to the updated Valve Academic Research Consortium-2 (VARC-2) consensus document [27].

2.5. Statistical analysis

Data are presented as median and interquartile range (IQR) for non-normally distributed continuous variables and mean and standard deviation for normally distributed continuous variables. Counts and percentages are shown for categorical variables. Continuous variables with a non-parametric distribution were compared using Mann-Whitney-*U* test.

EAT volume was evaluated with absolute values and indexed to BSA. We performed Kaplan-Meier analysis of survival applying a previously suggested binary cut-off of 125 mm^3 [20,21,28]. Furthermore, Kaplan-Meier analysis was performed according to median value and tertiles as previously described [18,19]. Log rank p-value was applied to assess differences between groups.

Logistic regression analyses were performed with four different cut-off values: 100 mm^3 (cut-off between first and second EAT volume tertile), 125 mm^3 (previously published), 130 mm^3 (median EAT volume) and 71 mm^3/m^2 (median indexed EAT volume). A univariate logistic regression analysis was performed to obtain odds ratios (OR) with 95% confidence interval (95%CI) for procedural outcomes. The multivariable model was built by selecting baseline characteristics with significant differences in EAT volume or indexed EAT volume and those characteristics that satisfied the entry criterion of $p < 0.1$ in a univariate analysis of reaching the early safety endpoint: Gender, diabetes mellitus, peripheral vascular disease, previous cardiovascular intervention and previous kidney transplantation [29]. Furthermore, we included the logistic EuroSCORE II in the final model.

A univariate Cox regression analysis was performed to obtain hazard ratios (HR) with 95% CI for cumulative mortality rates at 3 years after TAVR. The multivariable model was built by selecting baseline characteristics with significant differences in EAT volume or indexed EAT volume and those characteristics that satisfied the entry criterion of $p < 0.1$ in a univariate analysis of 3-year mortality: Gender, diabetes mellitus, peripheral vascular disease, previous cardiovascular intervention, body surface area, previous kidney transplantation and COPD [29]. Furthermore, we included the logistic EuroSCORE II in the final model.

A p value < 0.05 was considered significant. All analyses were performed using SPSS 25.

3. Results

3.1. Baseline characteristics

503 patients were included in the analysis (250 females; 50%). 8 patients (1.6%) had a bicuspid aortic valve. 1 patient had rheumatic aortic valve disease (0.2%). Median age was 83 years with an IQR of 79–87 years. BMI was in the overweight range for both men (26 kg/m^2; IQR: 23–30 kg/m^2) and women (26 kg/m^2; IQR: 23–29 kg/m^2) with no significant difference between gender ($p = 0.883$). Men exhibited a significantly larger BSA than women with a median of 1.90 m^2 (IQR: 1.79–2.01 m^2) versus 1.73 m^2 (IQR: 1.61–1.86 m^2; $p < 0.001$). 287 patients (58%) were taking statins before TAVR.

3.2. EAT volume

Inter- and intraobserver variability of EAT volume measurements was 4 ± 2% and 4 ± 3%, respectively. Distribution of EAT volume in our patient cohort is depicted in Fig. 1G. Overall EAT volume was 130 mm^3 (IQR: 86–177 mm^3). When indexed to BSA, EAT volume was 72 mm^3/m^2 (IQR: 47–97 mm^3/m^2). EAT volume displayed very poor correlation with BMI ($r = 0.24$; $p < 0.001$) and BSA ($r = 0.26$; $p < 0.001$). No correlation between EAT volume and age ($p = 0.630$), hyperlipidemia ($p = 0.680$), current use of lipid-lowering drugs ($p = 0.327$) or AVC was found ($p = 0.429$) (see Fig. 1H and I).

Females exhibited a significantly smaller EAT volume compared to males (women: median 126 mm^3 (IQR: 79–161 mm^3); men: median 135 mm^3 (IQR: 92–191 mm^3); $p = 0.003$). When EAT volume was indexed, no significant difference in EAT volume could be detected between females (median: 73 mm^3/m^2; IQR: 44–95 mm^3/m^2) and males (median: 71 mm^3/m^2; IQR: 48–100 mm^3/m^2) ($p = 0.348$).

3.3. EAT volume and baseline characteristics

Patients with diabetes showed a larger EAT volume (median: 144 mm^3 (IQR: 94–184 mm^3) versus 126 mm^3 (82–172 mm^3); $p = 0.037$). Furthermore, peripheral vascular disease was associated with

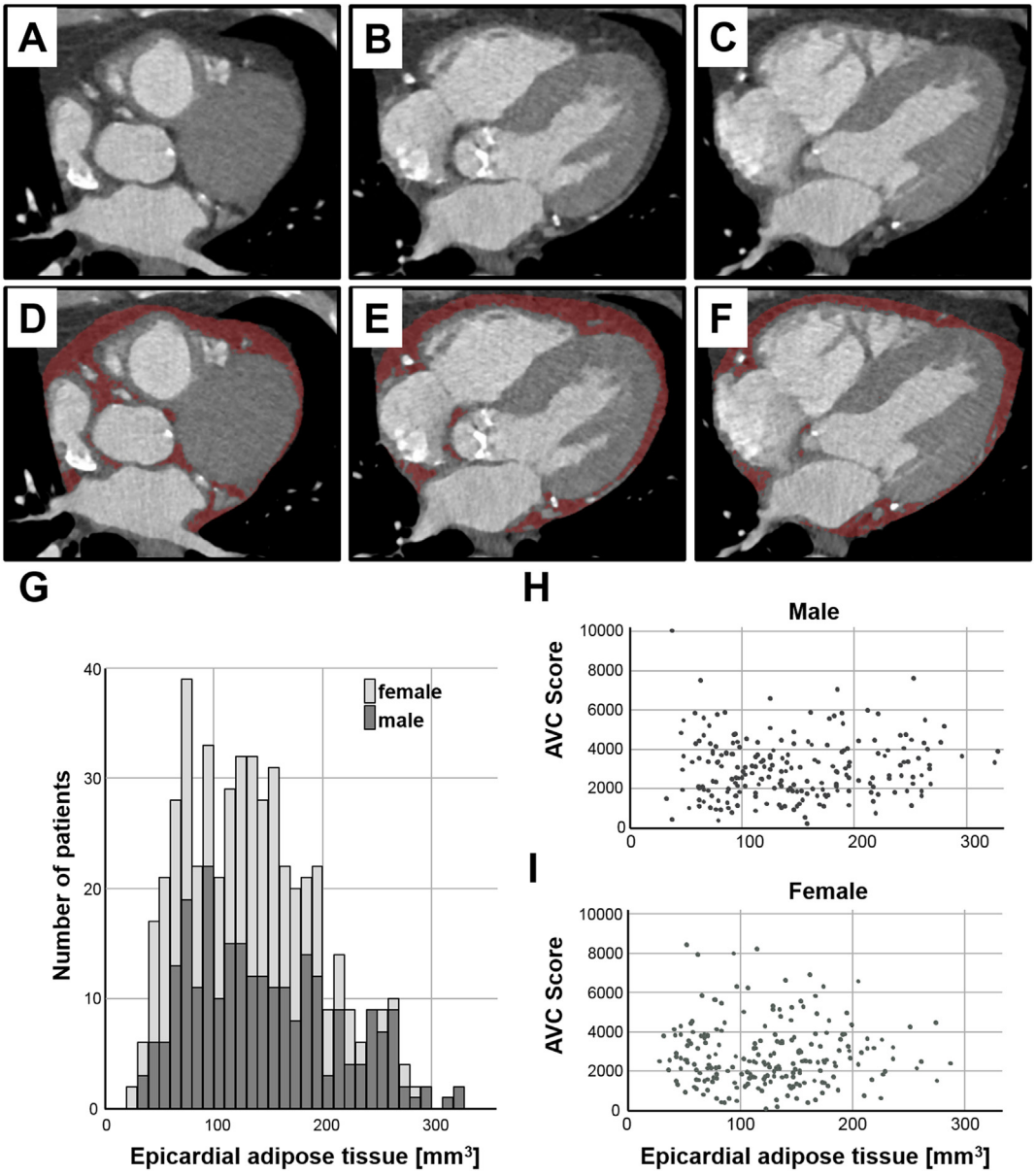

Fig. 1. Measurement of epicardial adipose tissue (EAT) (panel A-C) using semi-automated software. The pericardium was traced manually on each slice from the right pulmonary artery to the diaphragm. EAT volume was calculated automatically after fat voxels had been identified by using a threshold attenuation range of −195 to −15 HU (panel D-F). A Histogram showing the distribution of EAT volume in the patient cohort, coloured according to gender is shown as panel G. No correlation was found for EAT and aortic valve calcification score (AVC score) in males (panel H) and females (panel I).

a larger EAT volume (median: 142 mm^3 (IQR: 100–184 mm^3) versus 125 mm^3 (83–174 mm^3); p = 0.043). However, neither parameter exhibited a significant association with indexed EAT volume.

Patients with a history of previous cardiovascular interventions showed a smaller indexed EAT volume (median: 63 mm^3/m^2 (IQR: 53–80 mm^3/m^2) compared to patients without such a history (74 mm^3 (47–98 mm^3/m^2); p = 0.024)). No other associations were detected between medical history parameters or cardiac risk factors and EAT volume (Table 1).

3.4. EAT volume and short-term outcome

Patients reaching the early safety endpoint within 30 days (n = 84) after TAVR had a larger EAT volume (median: 155 mm^3 (IQR: 98–192 mm^3) versus 126 mm^3 (IQR: 82–171 mm^3); p = 0.031) as well as indexed EAT volume (median: 85 mm^3/m^2 (IQR: 56–105 mm^3/m^2) versus 70 mm^3/m^2 (46–95 mm^3/m^2); p = 0.028). Univariate (OR: 1.78; 95%CI: 1.09–2.91; p = 0.021) and multivariate (adjusted OR: 1.82; 95%CI: 1.06–3.11; p = 0.029) logistic regression analysis revealed that EAT volume ≥ 125 mm^3 independently predicted the early safety endpoint after TAVR. Similarly, logistic regression analysis with a cut-off value of 130 mm^3 (=median EAT volume; adjusted OR: 1.91; 95% CI: 1.13–3.23; p = 0.028) revealed that larger EAT volumes were associated with a higher risk for reaching the early safety endpoint. Using the median indexed EAT volume (71 mm^3/m^2) as a cut-off did not strengthen the prediction of reaching the early safety endpoint (OR: 1.71, 95%:1.02–2.88, p = 0.043).

Patients who died within 30-days after TAVR had a significantly larger EAT volume (median: 153 mm^3 (IQR: 126–188 mm^3) versus 127 mm^3 (83–188 mm^3); p = 0.042), with a strong trend towards a higher indexed EAT volume (median: 83 mm^3/m^2 (IQR: 70–97 mm^3/m^2) versus 71 mm^3/m^2 (46–97 mm^3/m^2); p = 0.062; Table 2).

Table 1
Association of EAT volume with baseline characteristics.
Gender, cardiac risk factors, previous medical history and EAT volume or EAT volume indexed to body surface area.
IQR, interquartile range; n, count.

		EAT volume [mm^3]	p-value	Indexed EAT volume [mm^3/m^2]	p-value
	[n, %]	[median; IQR]		[median; IQR]	
Gender	Female (n = 250; 50%)	126; 79–161	**0.003**	73; 44–95	0.348
	Male (n = 253; 50%)	135; 92–191		71; 48–101	
Cardiovascular risk factors					
Diabetes mellitus	No (n = 381; 76%)	126; 82–172	**0.037**	70; 46–98	0.445
	Yes (n = 122; 24%)	144; 94–184		79; 53–95	
Hyperlipidaemia	No (n = 277; 55%)	128; 83–183	0.680	72; 46–100	0.856
	Yes (n = 225; 45%)	132; 91–173		73; 50–93	
Hypertension	No (n = 106; 21%)	123; 79–168	0.198	69; 43–100	0.427
	Yes (n = 396; 79%)	133; 89–178		73; 47–96	
Previous medical history					
Coronary artery disease	No (n = 225; 45%)	129; 81–175	0.568	73; 47–98	0.637
	Yes (n = 277; 55%)	131; 89–178		73; 49–96	
Cerebrovascular disease	No (409; 81%)	129; 86–177	0.991	73; 49–96	0.610
	Yes (93; 19%)	132; 88–172		70; 47–91	
Previous kidney transplantation	No (483; 96%)	129; 86–178	0.147	72; 47–97	0.344
	Yes (19; 4%)	153; 125–167		78; 68–90	
Peripheral vascular disease	No (397; 79%)	125; 83–174	**0.043**	70; 46–96	0.104
	Yes (105; 21%)	142; 100–184		80; 53–98	
NYHA III or NYHA IV	No (442; 88%)	128; 86–174	0.066	71; 46–96	0.070
	Yes (61; 12%)	149; 94–195		82; 55–106	
Chronic obstructive pulmonary disease	No (n = 409; 81%)	130; 86–175	0.777	73; 47–97	0.852
	Yes (n = 93; 19%)	130; 91–189		70; 46–96	
Previous coronary artery bypass graft	No (n = 412; 82%)	128; 82–174	0.122	72; 46–96	0.477
	Yes (n = 91; 18%)	135; 95–189		76; 53–97	
Previous aortic valve replacement	No (n = 487; 97%)	130; 86–178	0.258	73; 47–97	0.392
	Yes (n = 16; 3%)	119; 94–141		63; 53–80	
Previous cardiovascular intervention	No (436; 87%)	133; 87–183	0.052	74; 47–98	**0.024**
	Yes (67; 13%)	121; 79–158		62; 43–86	

3.5. EAT volume and mid- or long-term outcome

Patients with an EAT volume larger than 125 mm^3 exhibited a significantly higher 3-year mortality (log-rank p = 0.001) in the Kaplan-Meier analysis (Fig. 2A). This difference was observed shortly after TAVR and was maintained throughout the observation period (Fig. 2B). Univariate and multivariate Cox regression analyses revealed that an EAT volume > 125 mm^3 independently predicted

Table 2
Outcome within 30 days after TAVR.
Differences in baseline EAT volume or EAT volume indexed to body surface area.
IQR, interquartile range; n, count.

Outcome parameter		EAT volume [mm^3]	p-value	Indexed EAT volume [mm^3/m^2]	p-value
	[n, %]	[median; IQR]		[median; IQR]	
Periprocedural mortality (≤72 h)	No (n = 488; 97%)	129; 86–177	0.493	72; 47–97	0.551
	Yes (n = 13; 3%)	141; 131–171		81; 70–90	
All-cause mortality (≤30 days)	No (n = 470; 94%)	127; 83–188	**0.042**	71; 46–97	0.062
	Yes (n = 32; 6%)	153; 126–188		83; 70–97	
Cardiovascular mortality (≤30 days)	No (n = 472; 94%)	128; 83–177	0.092	71; 46–97	0.114
	Yes (n = 30; 6%)	147; 125–187		82; 70–96	
Periprocedural myocardial infarction (≤72 h)	No (n = 498; 99%)	130; 86–176	0.139	72; 47–97	0.180
	Yes (n = 3; 1%)	177; 138–244		84; 79–148	
Myocardial infarction (≤30 days)	No (n = 498; 99%)	130; 86–176	0.139	72; 47–97	0.180
	Yes (n = 3; 1%)	177; 138–244		84; 79–148	
Stroke (≤30 days)	No (n = 487; 97%)	130; 86–176	0.893	73; 47–96	0.946
	Yes (n = 14; 3%)	115; 87–195		64; 46–113	
Bleeding (≤30 days)	No (n = 370; 74%)	130; 86–175	0.883	71; 47–96	0.694
	Yes (n = 131; 26%)	132; 87–183		77; 46–98	
Major or life threatening bleeding (≤30 days)	No (n = 482; 96%)	130; 86–176	0.418	72; 47–96	0.273
	Yes (n = 19; 4%)	146; 92–190		83; 51–103	
Acute kidney injury (≤30 days)	No (n = 574; 94%)	129; 85–174	0.067	73; 47–96	0.135
	Yes (n = 28; 6%)	153; 104–209		82; 60–105	
New permanent pacemaker implantation (≤30 days)	No (n = 415; 83%)	130; 87–175	0.901	73; 48–96	0.856
	Yes (n = 84; 17%)	126; 81–187		68; 45–102	
Valve related dysfunction requiring repeat procedure (≤30 days)	No (n = 493; 98%)	129; 86–177	0.452	71; 47–97	0.625
	Yes (n = 9; 2%)	145; 135–175		82; 74–90	
Early safety endpoint	No (n = 419; 83%)	126; 82–171	**0.031**	70; 46–95	**0.028**
	Yes (n = 84; 17%)	155; 98–192		85; 56–105	

P-values < 0.05 are marked in bold to highlight significant p-values.

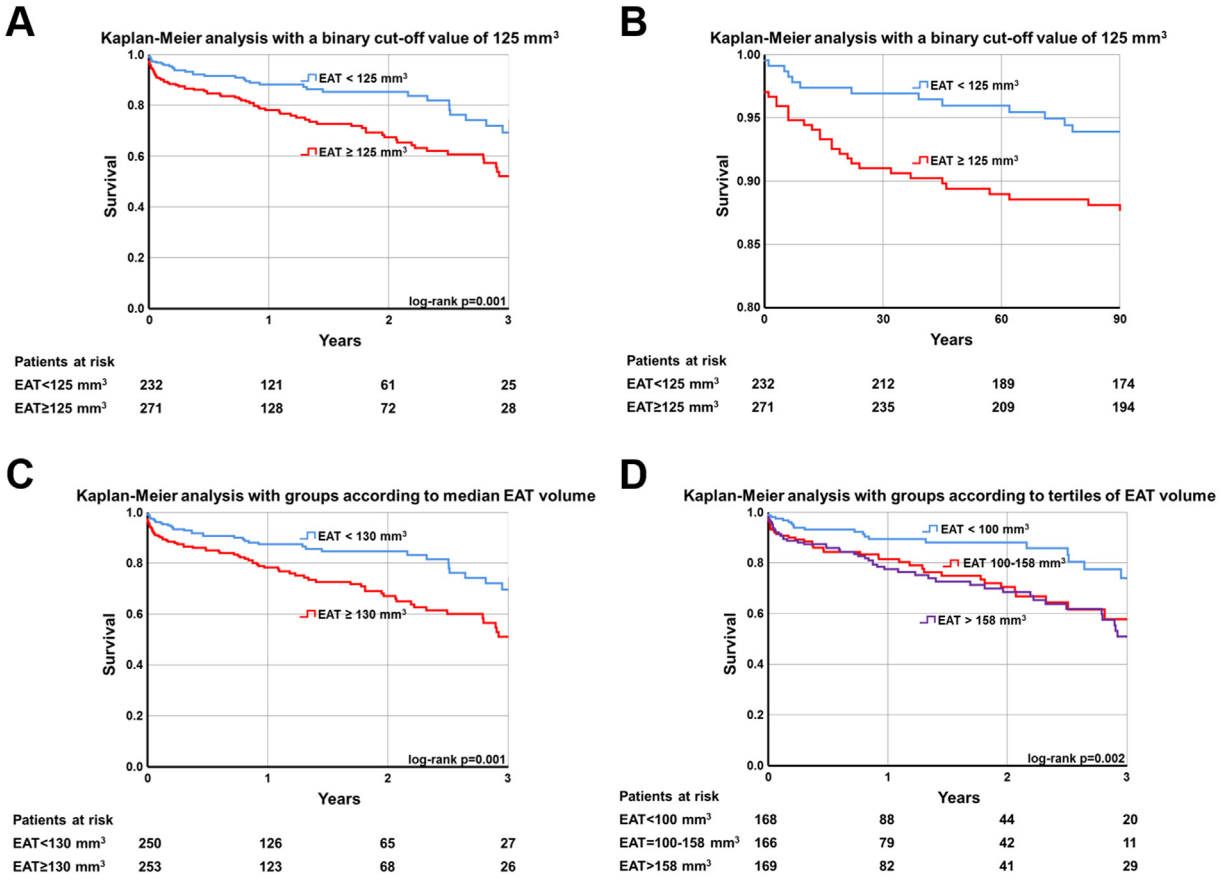

Fig. 2. Kaplan-Meier analysis of survival shows significantly higher mortality rates in patients with larger epicardial adipose tissue (EAT) volume using a cut-off of 125 mm^3 (A). Patients with an EAT volume larger than 125 mm^3 exhibited higher mortality rates immediately after TAVR (B). Patients with larger EAT volume also showed significantly higher mortality rates when patient cohorts were split according to the median EAT value (C) or according to tertiles of EAT volume (D).

3-year mortality after TAVR with a univariate HR of 2.27 (95%CI: 1.44–3.57; $p < 0.001$) and an adjusted HR of 1.70 (95%CI: 1.06–2.68; $p = 0.018$). The Kaplan-Meier analysis with groups formed according to tertiles of EAT volume revealed that patients with an EAT volume < 100 mm^3 had a distinctly higher survival rate compared to patients with an EAT volume between 100 and 158 mm^3 as well as those >158 mm^3, while there was no major difference between the latter two groups (Fig. 2C). Kaplan-Meier analysis and Cox regression analysis using 100 mm^3 (log-rank $p = 0.002$) with an adjusted HR of 1.94, 95%CI: 1.15–3.26 ($p = 0.013$) and the median value of 130 mm^3 (log-rank $p = 0.001$) with a multivariate HR of 1.69, 95%CI: 1.10–2.60 ($p = 0.013$) as cut-off also showed significantly higher mortality in patients with larger EAT volumes (Fig. 2C,D). Using the median indexed EAT volume (71 mm^3/m^2) as a cut-off value did not strengthen the prediction of 3-year mortality (log-rank $p = 0.028$) with a multivariate HR of 1.39; 95%CI: 0.93–2.10 ($p = 0.112$) after TAVR.

4. Discussion

TAVR is an alternative for surgical aortic valve replacement in patients with severe aortic valve stenosis and increased surgical risk [1,2,30]. This study demonstrates that an increased EAT volume is significantly associated with mortality after TAVR. While this observation is consistent with associations of EAT volume and adverse cardiovascular outcome in the general population or in defined cohorts such as patients with HIV, acute chest pain, or atrial fibrillation [6,7,14,15,17–20,28], the association with short-, mid-, and long-term outcome after TAVR is particularly noteworthy.

Obesity has been associated with a higher mortality in the general population, but has been linked with a better outcome in patients undergoing surgical aortic valve replacement or TAVR, a finding named the obesity paradox [3,4]. EAT and visceral adipose tissue (VAT) represent unique visceral fat deposits in terms of biochemical composition and metabolic activity and share a common embryological origin [8,9,31]. Hence, EAT and VAT cannot be considered synonymous with obesity, and prognostic data associated with obesity cannot be transferred to EAT or VAT. A large EAT volume is associated with unfavorable endocrine activity and may affect the myocardium via paracrine and vasocrine mechanisms [8–10]. Moreover, EAT may foster the development of atherosclerosis, arterial stiffness, and vascular calcification [9,31,32]. VAT has recently been reported to be associated with higher mortality after TAVR in obese individuals [33]. These observations underline our findings that EAT is associated with adverse outcome in patients with severe aortic stenosis undergoing TAVR despite of the obesity paradox documented for this patient group.

In our study, increased EAT volume was a predictor of a positive early safety endpoint and mortality even after multivariate adjustment for baseline characteristics, indicating that pre-interventional measurement of EAT volume may be useful for predicting short-, mid-, and long-term mortality after TAVR. Hence, our findings may be relevant for future pre-interventional risk assessment of patients evaluated for TAVR, in particular because virtually every patient undergoes a pre-interventional CT for prosthesis sizing and access route evaluation [22]. CT measurements and signs indeed provide valuable information on post-procedural outcomes without any need for additional radiation [34], and a higher EAT volume indicates patients who should be followed more closely after TAVR.

Although EAT is associated with adverse cardiovascular outcome and peripheral vessel calcification [7,18], its association with aortic valve calcification remains somewhat controversial. On the one hand,

an association of EAT thickness with aortic valve and mitral annulus calcification was observed [35]; on the other hand, a higher AVC mass was independently associated with low BMI and low VAT in another study [33]. Our data did not reveal a correlation of EAT volume with AVC.

Similar to other studies we observed a substantial overlap in EAT values between patients developing adverse events during follow-up and patients who did not [6,7,18,36]. Nevertheless, we determined significant HR for several different cut-off values of EAT volume, indicating that the latter is a useful parameter for predicting short, mid-term, and long-term outcome after TAVR. As previously suggested, using a certain threshold such as for example 125 mm^3 would improve comparability of studies [21]; therefore, this threshold was included in our analysis. The lack of a standardized reference value also limits the application of EAT measurements in clinical routine.

Our study shows that EAT volume is only weakly associated with BMI and BSA. This finding is supported by previous data revealing that EAT is associated with coronary artery disease induced events independent of BMI [6]. EAT volume might indeed be a better predictor of cardiovascular risk than BMI, since EAT volume is also associated with left ventricular mass [37]. Again, consistent with previous studies, we found significant gender differences in EAT volume, with larger volumes occurring in males [11,12]. However, after EAT volume had been indexed to BSA, no significant gender difference was detectable any longer. For this reason, we compared patient baseline characteristics as well as outcome data with both non-indexed and indexed EAT measurements. In contrast to previous studies, outcome predictions were not improved when EAT volume was indexed to BSA in our cohort [36].

There is a vast literature on the association of EAT volume with coronary artery calcification and subclinical atherosclerosis [6,11–13]. As aortic stenosis and coronary artery disease share common risk factors, the prevalence of coronary artery disease and coronary artery calcification in patients with severe aortic stenosis is high, reaching prevalence values of 40–75% for significant coronary artery disease in TAVR candidates [38]. Concomitant coronary artery disease in the setting of TAVR conveys an increased risk of ischemic events and cardiovascular mortality [39]. Nevertheless, we did not find a significant association of EAT volume with clinically established coronary artery disease or post-procedural myocardial infarction in our population, suggesting that the association of EAT volume with outcome after TAVR is not related to coronary artery disease.

4.1. Limitations

Some limitations merit consideration. This work has been designed as a single-center study. Only patients with severe aortic stenosis undergoing TAVR were included; hence, it remains to be determined whether the findings can be translated to patients undergoing surgical aortic valve replacement or medical treatment. Two different CT scanners with different scanning parameters and contrast media application protocols were used to acquire patient data, which may have increased the variability of the measurements. Finally, large-scale population studies will be required to investigate the relation between EAT volume and aortic stenosis progression.

5. Conclusions

In patients undergoing TAVR, EAT volume determined in pre-procedural CT is independently associated with all-cause 1-, 2-, and 3-year mortality as well as the early safety endpoint. Since virtually all TAVR candidates are undergoing pre-procedural CT, EAT volume quantification may add incremental prognostic value for risk assessment of TAVR candidates without the need for additional radiation.

Funding

T.N. has received a research grant “Filling the gap” from the University of Zurich.

Disclosures

F.M. is consultant for Abbott Vascular, St Jude Medical, Medtronic, ValtechCardio and receives royalties from Edwards Lifesciences.

F.R. received research grants from St Jude Medical, Novartis; personal fees for lectures from St Jude Medical, Servier, Zoll, Novartis, Bayer, and Abbott; personal fees for advisory board or steering committee clinical trial meetings from AstraZeneca, Sanofi, Cardiorentis, Amgen, BMS, Pfizer, Fresenius, Vifor, and Roche.

F.N. is consultant for Edwards Lifesciences, Abbott Vascular und Medtronic.

All other authors report no relationships that could be construed as a conflict of interest.

References

[1] Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, A. Vahanian, O. Alfieri, F. Andreotti, M.J. Antunes, et al., Guidelines on the management of valvular heart disease (version 2012), Eur. Heart J. 33 (19) (2012) 2451–2496.
[2] R.A. Nishimura, C.M. Otto, R.O. Bonow, B.A. Carabello, J.P. Erwin 3rd, R.A. Guyton, et al., 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J. Thorac. Cardiovasc. Surg. 148 (1) (2014) e1–e132.
[3] R.M. van der Boon, A. Chieffo, N. Dumonteil, D. Tchetche, N.M. Van Mieghem, G.L. Buchanan, et al., Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation, Am. J. Cardiol. 111 (2) (2013) 231–236.
[4] M. Yamamoto, G. Mouillet, A. Oguri, M. Gilard, M. Laskar, H. Eltchaninoff, et al., Effect of body mass index on 30- and 365-day complication and survival rates of transcatheter aortic valve implantation (from the FRench Aortic National CoreValve and Edwards 2 [FRANCE 2] registry), Am. J. Cardiol. 112 (12) (2013) 1932–1937.
[5] M. Marwan, S. Achenbach, Quantification of epicardial fat by computed tomography: why, when and how? J. Cardiovasc. Comput. Tomogr. 7 (1) (2013) 3–10.
[6] A.A. Mahabadi, M.H. Berg, N. Lehmann, H. Kalsch, M. Bauer, K. Kara, et al., Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study, J. Am. Coll. Cardiol. 61 (13) (2013) 1388–1395.
[7] K.H. Cheng, C.S. Chu, K.T. Lee, T.H. Lin, C.C. Hsieh, C.C. Chiu, et al., Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease, Int. J. Obes. 32 (2) (2008) 268–274.
[8] G. Iacobellis, D. Corradi, A.M. Sharma, Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart, Nat. Clin. Pract. Cardiovasc. Med. 2 (10) (2005) 536–543.
[9] N. Gonzalez, Z. Moreno-Villegas, A. Gonzalez-Bris, J. Egido, O. Lorenzo, Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes, Cardiovasc. Diabetol. 16 (1) (2017) 44.
[10] V. Parisi, G. Rengo, G. Pagano, V. D'Esposito, F. Passaretti, A. Caruso, et al., Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis, Int. J. Cardiol. 186 (2015) 167–169.
[11] M. Dagvasumberel, M. Shimabukuro, T. Nishiuchi, J. Ueno, S. Takao, D. Fukuda, et al., Gender disparities in the association between epicardial adipose tissue volume and coronary atherosclerosis: a 3-dimensional cardiac computed tomography imaging study in Japanese subjects, Cardiovasc. Diabetol. 11 (2012) 106.
[12] J. Mancio, M. Pinheiro, W. Ferreira, M. Carvalho, A. Barros, N. Ferreira, et al., Gender differences in the association of epicardial adipose tissue and coronary artery calcification: EPICHEART study: EAT and coronary calcification by gender, Int. J. Cardiol. 249 (2017) 419–425.
[13] J. Mancio, D. Azevedo, F. Saraiva, A.I. Azevedo, G. Pires-Morais, A. Leite-Moreira, et al., Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis, Eur. Heart J. Cardiovasc. Imaging 19 (5) (2018) 490–497.
[14] A.A. Mahabadi, N. Lehmann, H. Kalsch, M. Bauer, I. Dykun, K. Kara, et al., Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: the Heinz Nixdorf Recall Study, Eur. Heart J. Cardiovasc. Imaging 15 (8) (2014) 863–869.
[15] A.M. Ansaldo, F. Montecucco, A. Sahebkar, F. Dallegri, F. Carbone, Epicardial adipose tissue and cardiovascular diseases, Int. J. Cardiol. 278 (2018) 254–260.
[16] T. Ito, H. Fujita, T. Ichihashi, N. Ohte, Impact of epicardial adipose tissue volume quantified by non-contrast electrocardiogram-gated computed tomography on ergonovine-induced epicardial coronary artery spasm, Int. J. Cardiol. 221 (2016) 877–880.
[17] P. Raggi, S. Zona, R. Scaglioni, C. Stentarelli, G. Ligabue, G. Besutti, et al., Epicardial adipose tissue and coronary artery calcium predict incident myocardial infarction and death in HIV-infected patients, J. Cardiovasc. Comput. Tomogr. 9 (6) (2015) 553–558.

[18] K.A. Britton, J.M. Massaro, J.M. Murabito, B.E. Kreger, U. Hoffmann, C.S. Fox, Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality, J. Am. Coll. Cardiol. 62 (10) (2013) 921–925.
[19] E. Kunita, H. Yamamoto, T. Kitagawa, N. Ohashi, T. Oka, H. Utsunomiya, et al., Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography, Atherosclerosis 233 (2) (2014) 447–453.
[20] V.Y. Cheng, D. Dey, B. Tamarappoo, R. Nakazato, H. Gransar, R. Miranda-Peats, et al., Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events, JACC Cardiovasc. Imaging 3 (4) (2010) 352–360.
[21] J.V. Spearman, M. Renker, U.J. Schoepf, A.W. Krazinski, T.L. Herbert, C.N. De Cecco, et al., Prognostic value of epicardial fat volume measurements by computed tomography: a systematic review of the literature, Eur. Radiol. 25 (11) (2015) 3372–3381.
[22] C. Storz, T. Geisler, M. Notohamiprodjo, K. Nikolaou, F. Bamberg, Role of imaging in transcatheter aortic valve replacement, Curr. Treat. Options Cardiovasc. Med. 18 (10) (2016) 59.
[23] M. Mok, R. Allende, J. Leipsic, O.A. Altisent, M. Del Trigo, F. Campelo-Parada, et al., Prognostic value of fat mass and skeletal muscle mass determined by computed tomography in patients who underwent transcatheter aortic valve implantation, Am. J. Cardiol. 117 (5) (2016) 828–833.
[24] K. Higashigaito, T. Schmid, G. Puippe, F. Morsbach, M. Lachat, B. Seifert, et al., CT angiography of the aorta: prospective evaluation of individualized low-volume contrast media protocols, Radiology 280 (3) (2016) 960–968.
[25] A.M. Bucher, U. Joseph Schoepf, A.W. Krazinski, J. Silverman, J.V. Spearman, C.N. De Cecco, et al., Influence of technical parameters on epicardial fat volume quantification at cardiac CT, Eur. J. Radiol. 84 (6) (2015) 1062–1067.
[26] M. Eberhard, M. Mastalerz, T. Frauenfelder, F.C. Tanner, F. Maisano, F. Nietlispach, et al., Quantification of aortic valve calcification on contrast-enhanced CT of patients prior to transcatheter aortic valve implantation, EuroIntervention 13 (8) (2017) 921–927.
[27] A.P. Kappetein, S.J. Head, P. Genereux, N. Piazza, N.M. van Mieghem, E.H. Blackstone, et al., Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document, J. Thorac. Cardiovasc. Surg. 145 (1) (2013) 6–23.
[28] F. Forouzandeh, S.M. Chang, K. Muhyieddeen, R.R. Zaid, A.R. Trevino, J. Xu, et al., Does quantifying epicardial and intrathoracic fat with noncontrast computed tomography improve risk stratification beyond calcium scoring alone? Circ. Cardiovasc. Imaging 6 (1) (2013) 58–66.
[29] Y. Abramowitz, Y. Kazuno, T. Chakravarty, H. Kawamori, Y. Maeno, D. Anderson, et al., Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement, Eur. Heart J. 38 (16) (2017) 1194–1203.
[30] G. Gargiulo, A. Sannino, D. Capodanno, M. Barbanti, S. Buccheri, C. Perrino, et al., Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis, Ann. Intern. Med. 165 (5) (2016) 334–344.
[31] N. Alexopoulos, D. Katritsis, P. Raggi, Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis, Atherosclerosis 233 (1) (2014) 104–112.
[32] T.E. Brinkley, F.C. Hsu, J.J. Carr, W.G. Hundley, D.A. Bluemke, J.F. Polak, et al., Pericardial fat is associated with carotid stiffness in the multi-ethnic study of atherosclerosis, Nutr. Metab. Cardiovasc. Dis. 21 (5) (2011) 332–338.
[33] J. Mancio, P. Fonseca, B. Figueiredo, W. Ferreira, M. Carvalho, N. Ferreira, et al., Association of body mass index and visceral fat with aortic valve calcification and mortality after transcatheter aortic valve replacement: the obesity paradox in severe aortic stenosis, Diabetol. Metab. Syndr. 9 (2017) 86.
[34] M. Eberhard, M. Mastalerz, J. Pavicevic, T. Frauenfelder, F. Nietlispach, F. Maisano, et al., Value of CT signs and measurements as a predictor of pulmonary hypertension and mortality in symptomatic severe aortic valve stenosis, Int. J. Card. Imaging 33 (10) (2017) 1637–1651.
[35] T.S. Alnabelsi, Y. Alhamshari, R.H. Mulki, J.N. Codolosa, N. Koshkelashvili, I. Goykhman, et al., Relation between epicardial adipose and aortic valve and mitral annular calcium determined by computed tomography in subjects aged >/=65 years, Am. J. Cardiol. 118 (7) (2016) 1088–1093.
[36] H. Shmilovich, D. Dey, V.Y. Cheng, R. Rajani, R. Nakazato, Y. Otaki, et al., Threshold for the upper normal limit of indexed epicardial fat volume: derivation in a healthy population and validation in an outcome-based study, Am. J. Cardiol. 108 (11) (2011) 1680–1685.
[37] M.J. Bakkum, I. Danad, M.A. Romijn, W.J. Stuijfzand, R.M. Leonora, I.I. Tulevski, et al., The impact of obesity on the relationship between epicardial adipose tissue, left ventricular mass and coronary microvascular function, Eur. J. Nucl. Med. Mol. Imaging 42 (10) (2015) 1562–1573.
[38] S.S. Goel, M. Ige, E.M. Tuzcu, S.G. Ellis, W.J. Stewart, L.G. Svensson, et al., Severe aortic stenosis and coronary artery disease—implications for management in the transcatheter aortic valve replacement era: a comprehensive review, J. Am. Coll. Cardiol. 62 (1) (2013) 1–10.
[39] A. Franzone, S. Stortecky, L. Raber, D. Heg, K. Yamaji, R. Piccolo, et al., Effects of coronary artery disease in patients undergoing transcatheter aortic valve implantation: a study of age- and gender-matched cohorts, Int. J. Cardiol. 243 (2017) 150–155.