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Aortic valve calcification as a risk factor for major complications and reduced survival after transcatheter replacement

Francesco Pollari[a,*], Wolfgang Hitzl[b], Ferdinand Vogt[a], Michela Cuomo[a], Johannes Schwab[c], Claudius Söhn[a], Jurij M. Kalisnik[a], Christian Langhammer[d], Thomas Bertsch[d], Theodor Fischlein[a], Steffen Pfeiffer[a]

[a] Cardiac surgery, Cardiovascular Center, Paracelsus Medical University-Klinikum Nürnberg, Nuremberg, Germany
[b] Research Office (biostatistics), Research Program Experimental Ophthalmology and Glaucoma Research, Paracelsus Medical University, Salzburg, Austria
[c] Cardiology and Radiology, Cardiovascular Center, Paracelsus Medical University-Klinikum Nürnberg, Nuremberg, Germany
[d] Institute of Clinical Chemistry, Laboratory Medicine and Transfusion Medicine, Paracelsus Medical University-Klinikum Nürnberg, Nuremberg, Germany

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ABSTRACT

Background: Aortic valve calcification is supposed to be a possible cause of embolic stroke or subclinical valve thrombosis after transcatheter aortic valve replacement (TAVR). We aimed to assess the role of aortic valve calcification in the occurrence of in-hospital clinical complications and survival after TAVR.

Methods: We retrospectively analyzed preoperative contrast-enhanced multidetector computed tomography scans of patients who underwent TAVR on the native aortic valve in our center. Calcium volume was calculated for each aortic cusp, above and below the aortic annulus. Outcomes were recorded according to VARC-2 criteria.

Results: Overall, 581 patients were included in the study (SapienXT = 192; Sapien3 = 228; CoreValve/EvolutR = 45; Engager = 5; Acurate = 111). Median survival was 4.98 years (interquartile range 4.41–5.54). Logistic regression identified calcium load beneath the right coronary cusp in left ventricular outflow tract (LVOT) as significantly associated with stroke (odds ratio [OR] 1.2; 95% confidence interval [CI] 1.03–1.3; $p = 0.0019$) and in-hospital mortality (OR 1.1; 95% CI 1.004–1.2; $p = 0.04$), whereas total calcium volume of the LVOT was associated with both in-hospital and 30 day-mortality (OR 1.2; 95% CI 1.01–1.4; $p = 0.03$, and OR 1.2; 95% CI 1.02–1.43; $p = 0.029$, respectively). Cox regression identified total calcium of LVOT (hazard ratio [HR] 1.18; 95% CI 1.02–1.38; $p = 0.026$), male sex (HR 1.88; 95% CI 1.06–3.32; $p = 0.031$), baseline creatinine clearance (HR 0.96; 95% CI 0.93–0.98; $p < 0.001$), and baseline severe aortic regurgitation (HR 7.48; 95% CI 2.76–20.26; $p < 0.001$) as risk factors associated with lower survival.

Conclusion: LVOT calcification is associated with increased risk of peri-procedural stroke and mortality as well as shorter long-term survival.

1. Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative treatment to surgical aortic valve replacement for severe aortic valve stenosis in intermediate/high surgical risk or inoperable patients.[1] Despite its potential advantages (i.e. avoidance of cardiopulmonary bypass and minimally invasive access), the calcified valve is not removed as in surgical aortic valve replacement, but dilated during valvuloplasty and remaining compressed in the aortic root after deployment of the transcatheter heart valve prosthesis. This retained calcium is a possible source of embolism, during the operation or afterwards, as well as a thrombogenic material possibly causing subclinical leaflet thrombosis. Previous studies assessed the role of aortic valve calcification in the development of aortic root-related complications after TAVR, such as paravalvular leak (PVL),[2] annular rupture,[3] or conduction disturbances.[4] On the contrary, only a few studies investigated the correlation of aortic valve calcium with injury of other organs, due to embolization, and the incidence of major clinical outcomes.

The aim of this study was to assess risk factors for in-hospital major clinical complications and long-term survival after TAVR in a large single-center cohort, including also aortic valve calcification as measured by contrast-enhanced multidetector computed tomography (MDCT).

* Corresponding author. Department of Cardiac Surgery, Klinikum Nürnberg, Breslauer Strasse, 201 - 90471, Nuremberg, Germany.
E-mail address: fpollari@gmail.com (F. Pollari).

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Glossary of abbreviations

AKI	acute kidney injury
CAD	coronary artery disease
CI	confidence interval
HR	hazard ratio
HU	Hounsfield unit
LCC	left coronary cusp
LVOT	left ventricular outflow tract
MDCT	multidetector computed tomography
NCC	non-coronary cusp
OR	odds ratio
PCI	percutaneous coronary intervention
PH	proportional hazards
PVL	paravalvular leak
RCC	right coronary cusp
TA	transapical
TAVR	transcatheter aortic valve replacement
TF	transfemoral

2. Methods

2.1. Study population

We retrospectively analyzed our center's experience with TAVR procedures between July 2009 and May 2017. All patients who underwent TAVR for symptomatic severe stenosis of the native aortic valve were included in the study. Severe aortic stenosis was defined in accordance with international guidelines[1] and indication for TAVR was discussed within a Heart Team, composed of at least a cardiologist and a cardiac surgeon. All patients with frailty factors who were judged inoperable or at high surgical risk (as defined by logistic EuroSCORE > 20%) were considered eligible for TAVR. In case of significant coronary artery disease (CAD), all patients were first treated by percutaneous intervention (PCI) and readmitted about 3 months later for TAVR. Exclusion criteria were: bicuspid aortic valve, pure aortic regurgitation, use of a cerebral protection device, and aborted procedures because of an annular diameter of > 30 mm. Overall, 760 patients were eligible for the study. However, for 172 patients the MDCT scan was not retrievable from our institutional "Picture Archiving and Communication System"; 4 patients had no preoperative contrast-enhanced MDCT because of severe renal impairment; 3 patients did not have ECG-triggered MDCT scans and were unsuitable for analysis. Thus, a total of 581 patients were evaluable (Fig. 1). Clinical, operative data and in-hospital complications were prospectively collected in our institutional database (100% completeness for all patients). Assessment of long-term survival was performed through clinical visits or phone contact. All patients provided written informed consent for the use of their data anonymously, and the study was approved by our institutional review board (IRB-2017-006). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

2.2. Outcomes

The following outcomes were recorded based on the Valve Academic Research Consortium-2 (VARC-2) recommendations[5]: perioperative (< 72 h from the index procedure) and spontaneous (> 72 h) myocardial infarction (increase of biomarkers and signs or symptoms of myocardial infarction), myocardial injury (consisting of at least one sample post-procedure with a peak value exceeding 15x the upper reference limit for troponin; if cardiac biomarkers were already increased at baseline [> 99th percentile], a further increase of at least 50% post-procedure was required with the peak value exceeding the previously stated limit. Myocardial injury was defined as an isolated biomarker increase not meeting the criteria for myocardial infarction[6]). Additional adverse events were stroke (focal or global neurological deficit > 24 h; or < 24 h if available neuroimaging documented a new hemorrhage or infarct; or the neurological deficit resulted in death), major vascular complications, bleeding, acute kidney injury (AKI), immediate procedural mortality, in-hospital mortality and 30-day mortality.

The primary aim was to assess the preoperative risk factors (clinical, echocardiographic and MDCT characteristics including calcium scoring) for the above-mentioned major in-hospital complications following TAVR. The secondary aim was to assess risk factors for survival after hospital discharge.

2.3. Procedure

The transfemoral (TF-TAVR) approach was considered as the first choice in all patients without severe peripheral arterial disease and with suitable femoral axis. Alternatively, the transapical (TA-TAVR) access was used. All procedures were conducted in a hybrid operating room under fluoroscopic control (Artis Zeego System, Siemens AG, Erlangen, Germany), general anesthesia, peri-procedural transesophageal echocardiography, and a cardiac perfusionist with ready-to-use cardiopulmonary bypass on site. All implantations were performed by a team composed of an interventional cardiologist and a cardiac surgeon. In the study period, different prostheses were implanted: SapienXT and Sapien3 (Edwards Lifesciences Inc., Irvine, CA), CoreValve/EvolutR (Medtronic, Minneapolis, MN), Engager (Medtronic, Minneapolis, MN) and Acurate TA/NeoTF (Symetis SA, Ecublens, Switzerland).

2.4. Calcium quantification and MDCT-derived measurements

All patients underwent contrast-enhanced ECG-gated MDCT (330 ms rotation, helical mode, 60–70% gating, 0.6 × 64 mm collimation, 50–100 mL of i.v. contrast agent [Solutrast 370, Bracco Imaging Deutschland GmbH] at 4 mL/s) for assessment of aortic root anatomy (suitability for TAVR) and the femoral axis (suitably for TF approach). In our center, all MDCT studies were performed with a 64-slice SOMATOM Definition AS (Siemens Healthcare GmbH, Erlangen, Germany). Calcium volume in the aortic valve was retrospectively measured using 3mensio Structural Heart software (v.7.0 SP1, Medical Imaging BV, Bilthoven, the Netherlands), as already extensively described by our group[2,4] and in line with previous studies.[3,7] Briefly, calcium volume was assessed in three different regions: (i) in the aortic valve (from basal plane up to the origin of the lower coronary ostium); (ii) in the left ventricular outflow tract (LVOT) (up to 10 mm below the basal plane)—these two regions were considered either as a whole or for each cusp separately; (iii) in the device landing zone, defined as the sum of the first two (Fig. 2). The threshold for calcium detection was

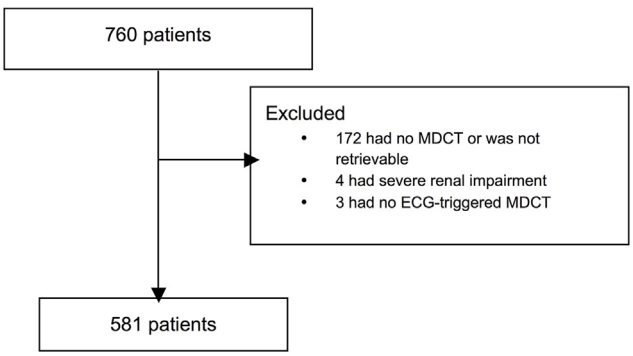

Fig. 1. Flowchart showing the selection process of the study population.

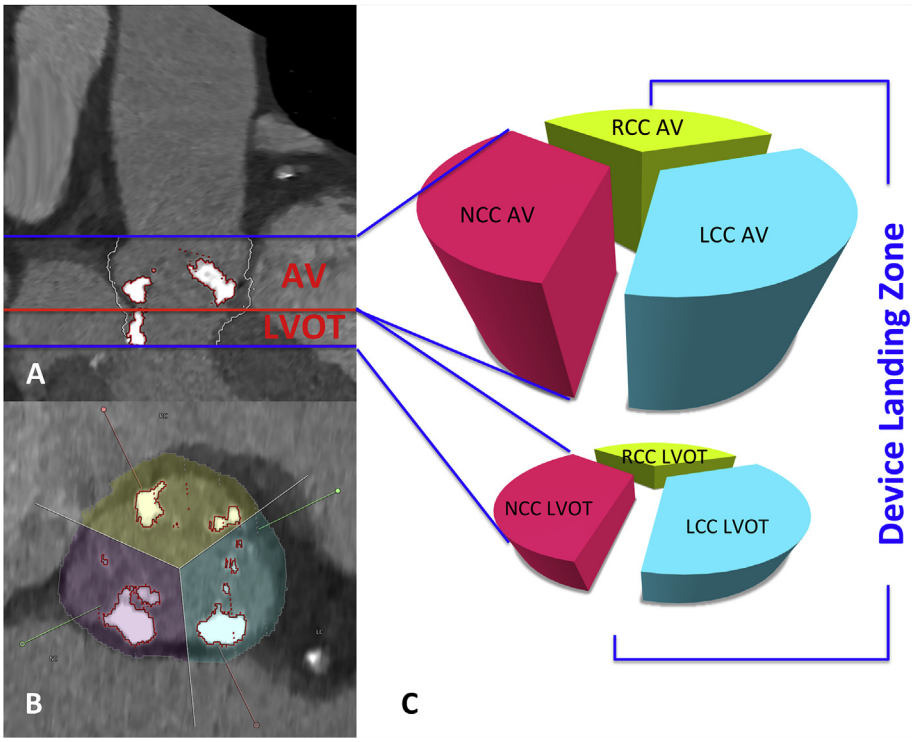

Fig. 2. Aortic calcium volume quantification on 3mensio Structural Heart. A: stretched vessel view of the aortic valve and ascending aorta with highlighting of the region of interest. The blue line identifies the upper and lower limits of the device landing zone. The red line identifies the basal plane (aortic annulus). B: transverse view of the native aortic valve with the three cusps (yellow = right coronary cusp; cyan = left coronary cusp; magenta = non-coronary cusp). C: schematic three-dimensional visualization of the examined areas. AV = aortic valve; LCC = left coronary cusp; LVOT = left ventricular outflow tract; NCC = non-coronary cusp; RCC = right coronary cusp. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

individually set to two different cut-off values depending on the average Hounsfield unit (HU) of blood in the ascending aorta. For values between 130 and 300 HU, a threshold of 500 HU was chosen, and for values between 300 and 600 HU, an empiric threshold of 800 HU was applied. The degree of over- or under-sizing was calculated as prosthesis valve area (provided by the manufacturer)/MDCT annular area. Prosthesis valve area was derived according to the geometrical rule: $A = \pi(d/2)2$, where d is the labeled prosthesis size. Aortic annulus eccentricity index was calculated as 1–(minimal diameter/maximal diameter) based on MDCT annular measurements.[3]

2.5. Statistical analysis

Dataset is published online and freely accessible (Mendeley Data, V2, doi: 10.17632/cwn4v29kkg.2). Data consistency was checked and data were screened for outliers by using quantile plots. Continuous variables were tested for normality using Kolmogorov-Smirnov test. Cross tabulation tables were computed and tested using Pearson's chi-squared, M-L test and Wilcoxon-Mann-Whitney test for two multinomials. Kruskal-Wallis ANOVA and Mann-Whitney U tests were applied. If test assumptions were not fully met, exact p-values based on Monte Carlo methods were used. Logistic regression analyses and odds ratios (OR) with corresponding 95% confidence intervals (CI) were computed. Univariate Kaplan-Meier and Cox regression models were set up, tested by using Cox's F-test, and hazard ratios (HR) with 95% CI were computed. To set up a multivariate model, only variables with univariate p-values < 0.2 were selected. The proportional hazards (PH) assumption was not met for all variables in the multivariate model, therefore a variable selection algorithm (stepwise: F-to enter $p = 0.05$, F-to remove $p = 0.15$) was applied, and the robust variance estimator was used. After applying this algorithm, the PH assumptions were met for all variables. All reported tests were two-sided, and p-values < 0.05 were considered as statistically significant. All statistical analyses in this report were performed using STATISTICA 13 (Hill, T.&Lewicki, P. Statistics: Methods and Applications. StatSoft, Tulsa, OK), NCSS 10 Statistical Software (2015) (NCSS, LLC., Kaysville, UT) and StatXact (2013), Version 10, Cytel software cooperation (Cambridge, MA, USA).

3. Results

Baseline and procedural characteristics of the study population are shown in Table 1. Implanted prostheses were: SapienXT (n = 192), Sapien3 (n = 228), CoreValve (n = 30), EvolutR (n = 15), Engager (n = 5), and Acurate (n = 111). The immediate procedural mortality according to VARC-2 definition was 1% (7 cases). The following procedural complications were observed: conversion to surgery (n = 11, 2%), unplanned cardiopulmonary bypass (n = 11, 2%), coronary obstruction (n = 3, 1%), prosthesis valve malpositioning (n = 6, 1%), second prosthesis implantation (n = 4, 1%), unplanned intraoperative PCI (n = 1, 0.1%), and use of intra-aortic balloon pump (n = 5, 1%).

3.1. In-hospital outcomes

In-hospital complications are reported in Table 2. Notably, the incidence of myocardial injury (according to increased cardiac biomarkers but not meeting the criteria for infarction[6]) was significantly higher than peri-procedural infarction (33% versus 0.3%) after TA access, probably due to the myocardial puncture and suturing in those patients (increased biomarkers in TA-TAVR versus TF-TAVR: 71.3% versus 14%). All observed strokes were ischemic. Between prostheses, the only significant difference was noted in the incidence of myocardial injury (Supplementary Table 1) and AKI stage 3 (Supplementary Table 2). In brief, CoreValve and Sapien3 were associated with a significantly lower incidence of myocardial injury compared to both SapienXT and Acurate. Conclusions about EvolutR and Engager were not possible due to the low number of implants. Moreover, SapienXT showed a significantly higher incidence of AKI stage 3 compared with Sapien3 (6.77% vs 1.32%, $p < 0.0001$; OR 5.9, 95% CI 1.6–33). The results of multivariable logistic regression based upon all variables listed in Table 1 are shown in Table 2. On logistic regression, calcium load in LVOT beneath the right coronary cusp (RCC) was significantly associated with stroke and in-hospital mortality, whereas total calcium volume of LVOT and beneath the non-coronary cusp (NCC) was significantly associated with both in-hospital and 30-day mortality.

Table 1
Baseline and procedural characteristics of study population (N = 581).

Clinical characteristics	
Age (years)	81.71 (± 6.1)
Female gender	286 (49%)
BMI (kg/m^2)	27.11 (± 4.79)
BSA (m^2)	1.85 (± 0.21)
Creatinine (mg/dl)	1.5 (± 1.03)
Creatinine clearance (ml/min)	45.01 (± 19.59)
Chronic dialysis	23 (4%)
Extracardiac arteriopathy	161 (28%)
Poor mobility*	53 (9%)
Previous cardiac surgery	109 (20%)
-Previous CABG	100 (17%)
-Previous mitral valve repair/replacement	13 (2.2%)
Previous percutaneous valvuloplasty	11 (2%)
Previous PCI	161 (0.4%)
Chronic lung disease*	108 (19%)
Critical preoperative state*	16 (3%)
IDDM	13 (2%)
NIDDM	24 (4%)
NYHA ≥ III	501 (86.2%)
CCS class 4	3 (0.5%)
Recent myocardial infarction	17 (3%)
Urgency	42 (7.2%)
Previous PMK implantation	65 (10%)
Paroxysmal atrial fibrillation	63 (10%)
Permanent atrial fibrillation	189 (30%)
Additive EuroSCORE	10.43 (± 2.57)
Logistic EuroSCORE	23% (± 16)
EuroSCORE II	9% (± 8)
Echocardiographic parameters	
Ejection fraction (%)	52.56 (± 12.93)
Severe PHT (> 60 mmHg)	191 (33%)
Aortic valve Δmax (mmHg)	74.86 (± 24.45)
Aortic valve Δmean (mmHg)	44.58 (± 15.66)
Aortic valve effective orifice area (cm^2)	0.7 (± 0.16)
Aortic regurgitation ≥ mild	385 (70%)
Aortic regurgitation ≥ moderate	118 (20%)
Mitral regurgitation ≥ mild	448 (80%)
Mitral regurgitation ≥ moderate	190 (30%)
MDCT characteristics and calcium volume	
Annulus diameter Max (mm)	27 [24.9–28.9]
Annulus diameter Min (mm)	21.8 [20.3–23.2]
Annulus area (cm^2)	4.62 [3.9–5.3]
Annulus perimeter (mm)	77.8 [71.5–83.5]
Distance annulus-RCA (mm)	15.2 [13–18]
Distance annulus-LCA (mm)	13.3 [11.6–15]
Oversizing (%)	0.11 [0.03–0.22]
Eccentricity index	0.19 [0.14–0.23]
DLZ calcium (mm^3)	777.5 [465–1197]
Total calcium AV (mm^3)	714.2 [419–1099]
LCC calcium AV (mm^3)	192.7 [96–329]
RCC calcium AV (mm^3)	188.6 [96–321]
NCC calcium AV (mm^3)	298.1 [169–466]
Total calcium LVOT (mm^3)	20.4 [1.5–91]
LCC calcium LVOT (mm^3)	2.5 [0–36]
RCC calcium LVOT (mm^3)	0.0 [0–1.6]
NCC calcium LVOT (mm^3)	2.2 [0–25]
Procedural characteristics	
Transfemoral access	389 (70%)
Prosthesis's size	
23 mm	185 (30%)
25 mm	37 (6.4%)
26 mm	209 (36%)
27 mm	39 (6.7%)
29 mm	89 (15.3%)
31 mm	22 (3.8%)
Valvuloplasty pre-implant	563 (97%)
Implant rapid pacing	436 (75%)
Balloon dilation post-implant	195 (34%)

Values are presented as mean (± standard deviation), Number (%), or median [interquartile range].
AV = aortic valve; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; DLZ = device landing zone; IDDM = insulin-dependent diabetes mellitus; LCA = left coronary artery; LCC = left coronary cusp; LVOT = left ventricular outflow tract; MDCT = multidetector computed tomography; NCC = non-coronary cusp; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PHT = pulmonary hypertension; RCA = right coronary artery; RCC = right coronary cusp. *) according to EuroSCORE II definition.

3.2. Survival outcome

A follow-up was possible in 95.7% of the whole study population (556/581 patients). Supplementary Fig. 1 shows the overall survival of the study population. Median survival was 4.98 years (interquartile range: 4.41–5.54). Univariate and multivariate Cox regression analysis for survival based on the variables listed in Table 1 is shown in Supplementary Table 3. Total calcium volume of LVOT (HR 1.18; 95% CI 1.02–1.38; p = 0.026; HR rescaled to 100 mm^3) correlated with higher death rates during follow-up, with a hazard of dying 1.18 times higher if total calcium in LVOT increased by 100 mm^3. Overall survival according to the degree of LVOT calcification is depicted in Fig. 3. Additionally, male sex (HR 1.88; 95% CI 1.06–3.32; p = 0.031), baseline creatinine clearance (HR 0.96; 95% CI 0.93–0.98; p < 0.001), and baseline severe aortic regurgitation (HR 7.48; 95% CI 2.76–20.26; p < 0.001) were found to be associated with lower survival at follow-up.

4. Discussion

The main findings of this study can be summarized as follows: (i) calcium load beneath the RCC is correlated with peri-procedural stroke; (ii) calcium load beneath the NCC and total calcium of LVOT are associated with in-hospital and 30-day mortality as well as with lower survival at follow-up.

Stroke is a major complication following TAVR and its incidence at 30 days across studies ranges between 3.4% in the SURTAVI trial,[8] 4.5% in the PARTNER 1 trial,[9] and 5.5% in the PARTNER 2 trial,[10] increasing at follow-up. As well known, clinically detectable stroke is merely the tip of the iceberg, since observational studies with diffusion-weighted magnetic resonance imaging (DWMRI) could show the presence of ischemic brain lesion in the majority of patients who underwent TAVR.[11,12] Aggarwal and colleagues were the first to correlate the presence of solid emboli through transcranial Doppler signal to the amount of baseline aortic valve calcification on MDCT.[13] Spaziano and colleagues found a correlation between aortic calcification and a composite outcome (i.e. all-cause mortality or stroke at 1 year) in a multicenter registry including only women.[14] To the best of our knowledge, ours is the first study to demonstrate a significant correlation between baseline regional aortic valve calcification and clinically relevant stroke. Prediction of peri-procedural stroke is crucial as it may support the heart team in selecting those patients who could benefit most from cerebral protection devices, whose indiscriminate use did not provide better results up to date.[12] Although TAVR is nowadays increasingly offered to intermediate and also low-risk patients,[15,16] several trials excluded patients with extreme calcifications of LVOT from enrollment making their findings complex to translate into the real world.[16] The correlation of sole calcifications beneath the RCC with stroke has two possible explanations. The first one relates to the friable calcifications in this LVOT region, in that calcium deposit on the interventricular septum could be more susceptible to embolization. Nguyen-Kim and colleagues performed an up to date unique analysis of valve calcification before and after prosthesis deployment, noting a reduction of volume and mass in all patients.[17] Although such a “loss” of calcification volume and mass (that anyway could depend on compression, and not only on embolization) was significant in all cusps, though more prominent in the RCC (mass = −38.5%; volume = −41.7%). The second hypothesis, derived from our surgical experience, regards the blood flow pattern in the ascending aorta. The RCC is located near the greater curvature. of the ascending aorta and blood stream lapping this point might favor the supra-aortic branches as targets for emboli. In this case,

Table 2
In-hospital outcomes. Multivariate logistic regression showing baseline risk factors that are significantly associated with each of the analyzed outcome. The incidence (as absolute number and %) is showed near each outcome.

Variable	p-value	OR	95%CI
Periprocedural myocardial infarction = 2 (0.3%)			
Previously valvuloplasty	< 0.001	56.9	3.3–975
Myocardial injury (isolated increase of troponin) = 192 (33%)			
Creatinine (mg/dl)	< 0.001	1.65	1.31–2.08
Creatinine clearance (ml/min)[a]	0.004	0.98	0.97–0.99
Dialysis	< 0.001	4.96	2–12.3
Extracardiac arteriopathy	0.004	1.74	1.19–2.5
Paroxysmal atrial fibrillation	0.034	1.7	1.03–3
Permanent atrial fibrillation	0.003	0.55	0.37–0.81
Prosthesis	< 0.001	[d]	
Ejection fraction	0.01	0.98	0.97–0.996
Prosthesis's size	0.02	1.10	1.01–1.18
Spontaneous myocardial infarction = 4 (1%)			
Paroxysmal atrial fibrillation	0.016	7.7	1.07–56
Stroke = 9 (1.5%)			
Urgency	0.008	[d]	
Permanent atrial fibrillation	0.04	3.9	0.96–15.7
RCC calcium LVOT (mm^3)[b]	0.019	1.2	1.03–1.3
Life-threatening bleeding = 15 (3%)			
Severe PHT (> 60 mmHg)	0.012	0.14	0.02–0.94
Urgency	0.011	[d]	
Major bleeding = 62 (11%)			
Creatinine clearance (ml/min)	< 0.001	1.03	1.01–1.05
Annulus diameter Min (mm)	0.023	1.14	1.02–1.28
Female gender	0.004	2.18	1.2–3.8
Poor mobility	0.009	0.15	0.003–0.89
Severe PHT	0.014	1.9	1.13–3.27
Major vascular complications = 23 (4%)			
Ejection fraction	0.03	0.97	0.94–0.999
Previously valvuloplasty	0.0146	5.8	1.2–28.6
AKIN (AKIN1 = 31 [5.3%]; AKIN2 = 5 [0.9%]; AKIN3 = 22 [3.8%])			
Balloon dilation post-implant	0.002	[d]	
Prosthesis	0.016	[d]	
Creatinine (mg/dl)	0.009	[d]	
Previously valvuloplasty	0.0005	[d]	
In-hospital mortality = 36 (6%)			
Poor mobility	0.0048	3.17	1.36–7.3
NYHA class	0.0016	[d]	
Urgency	< 0.001	[d]	
Creatinine clearance (ml/min)	0.01	0.97	0.95–0.99
Aortic valve Δmax (mmHg)	0.02	0.98	0.96–0.99
Total calcium LVOT (mm^3)[c]	0.03	1.2	1.01–1.4
RCC calcium LVOT (mm^3)[b]	0.04	1.1	1.004–1.2
Additive EuroSCORE	0.03	1.14	1.01–1.3
Logistic EuroSCORE	0.01	11.12	1.78–69
EuroSCORE II	0.03	40.80	1.5–1104
30-days mortality = 32 (6%)			
Poor mobility	0.01	3.05	1.24–7.44
NYHA	< 0.001	[d]	
Urgency	< 0.001	[d]	
Creatinine clearance (ml/min)	0.027	0.98	0.95–0.99
Aortic valve Δmax (mmHg)	0.012	0.98	0.96–0.99
Total calcium LVOT (mm^3)[c]	0.029	1.2	1.02–1.43
NCC calcium LVOT (mm^3)[b]	0.029	1.05	1.005–1.09
Additive EuroSCORE	0.032	1.15	1.01–1.32
Logistic EuroSCORE	0.012	11.7	1.72–80
EuroSCORE II	0.043	35.4	1.11–1129

[a] Odds ratio was rescaled to an increase of 10 ml/min.
[b] Odds ratio was rescaled to an increase of 10 mm^3.
[c] Odds ratio was rescaled to an increase of 100 mm^3.
[d] cannot be computed because only available for 2 × 2 crosstabulation tables.

RCC-LVOT calcification could be no more prone to embolize, rather be in the better position to target the cerebral circulation. At present, no study has already investigated this hypothesis. For this reason, we are designing a study based upon computational models built from image-based computational fluid dynamics aimed to settle this question.

The second main finding of our study is the recognition of valve calcification as a risk factor for survival. Our analysis showed a significant association between the total amount of calcium volume in LVOT and 30-day mortality, as well as with survival after hospital discharge. Despite methodological differences in calcium determination (LVOT calcification was measured with a semi-quantitative method and only "as a whole"), this finding is in line with the few available studies.[14,18] Although a correlation of valve calcification with PVL has been postulated to explain the worse outcome,[18] this association with PVL has not been confirmed.[14] Our results support the hypothesis that LVOT calcium correlates with lower survival regardless of PVL. Several reasons may account for the lower survival in patients with higher amounts of LVOT calcification, including peri-procedural annular rupture, onset of conduction system disorders (i.e. atrioventricular block and/or late onset of malignant arrhythmias), or even late embolic events. In a multicenter population of 186 patients treated with a balloon-expandable prosthesis, Hansson and colleagues found that LVOT calcification, especially under the NCC, was predictive of annular rupture.[3] The risk for atrioventricular block has also been demonstrated by Spaziano et al.,[14] as well as in another subanalysis of our group.[4] The association between valve calcifications and CAD could be advocated as a confounder, but patients in our study were previously treated for any significant CAD and were discharged on standard medical therapy in case of non-significant CAD. Finally, it may also be hypothesized that valve calcification may be a marker for more advanced disease (such as atherosclerosis or degeneration) of extra-cardiac organs. Previous studies investigated the association of extra-cardiac atherosclerosis with survival post-TAVR with the implementation of new prognostic scores (e.g. the CAPRI score[19]). As aortic valve calcification and extra-cardiac arteriopathy are strongly associated,[20] this hypothesis appears to be the most plausible. Further studies with closer follow-up are needed to investigate the real causes for lower survival in patients with diffuse LVOT calcification. Moreover, LVOT calcification (in total or limited to a single cusp) may theoretically be included in prognostic scores to improve the prediction of post-procedural morbidity and mortality.[21] In an era where TAVR indication is expanded to younger and low-risk patients, and trying to prove the substantiality of early discharge through the concept of minimally invasive TAVR, the precise understanding of baseline risk factors is crucial to choose the best treatment option for every patient.

Alongside the considerations regarding calcium volume, other noteworthy aspects have emerged from our study. In this respect, the distinction in myocardial injury and infarction should not be taken lightly, especially in TA-TAVR, as this could lead to misdiagnosis.[22,23]

Surprisingly, in our analysis, PVL was not associated with lower survival at follow-up. In our opinion, this could be explained by the low incidence of PVL at discharge (12/581 patients had moderate PVL, one of those died before 30 days; none had severe PVL). Moreover, 6 of these patients received a self-expandable prosthesis, which has been demonstrated to be associated with decreasing incidence and severity of PVL over time and a significant reduction after 1 year.[24] Similarly, in our study population, PVL incidence could have reduced over time without affecting survival. Finally, it is worth noting that in a previous analysis of patients treated with CoreValve, only patients with severe PVL had a lower survival at follow-up.[24]

Age was not found to be associated with lower survival in our analysis, in line with the few studies[25,26] that investigated long-term survival during a time interval longer than 1 year. As our study population strictly conforms to the indications of international guidelines,[1] patients were of more advanced age (median 82.5 years; 25th-75th percentile 78–85.3), probably accounting for other effects on survival.

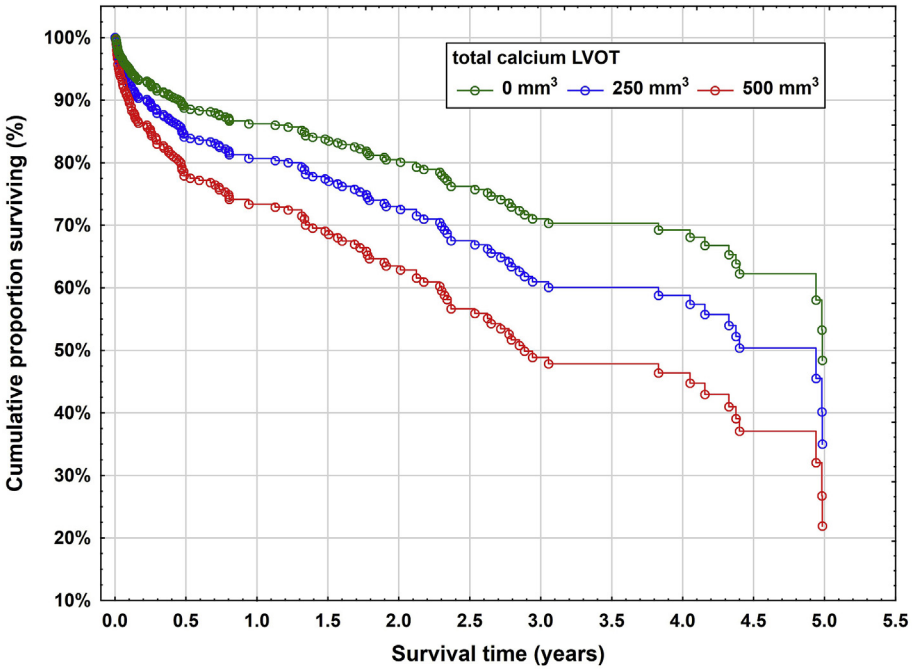

Fig. 3. Kaplan-Meier survival functions based on Cox-proportional hazard model for the study population according to the degree of total left ventricular outflow tract (LVOT) calcium volume. Green line: total LVOT calcium volume of 65 mm^3. Blue line: total LVOT calcium volume of 250 mm^3. Red line: total LVOT calcium volume of 500 mm^3. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

On the other hand, younger patients presented with multiple comorbidities that probably affected their survival as well.

The HR of baseline aortic regurgitation for death at follow-up was 7.5 (95% CI 2.8–20), which means that the hazard of dying is about 8 times higher compared to patients without baseline aortic regurgitation. Interpretation of this finding is difficult because previous studies often excluded patients with mixed aortic valve disease[8–10] or included populations with a lower incidence of ≥moderate aortic regurgitation (e.g. 8.7%,[27] 15.2%[28]). Evidence of its role in relation to survival is lacking. Given that the exact cause of death in these patients is unknown, it could be speculated that patients with combined severe pathology of the aortic valve are exposed to a higher risk of developing dilated cardiomyopathy.

4.1. Study limitations

Some limitations should be acknowledged in this study. First, the method used for assessing aortic calcification. Although previous studies investigated the reliability of contrast-enhanced MDCT in comparison with non-enhanced MDCT,[7] the results of contrast-enhanced MDCT remain strongly dependent on the selected HU threshold. On the other hand, non-enhanced MDCT for planned intervention is currently not routinely performed as it would cause an unnecessary radiation exposure for the patients. Second, the retrospective and single-center nature of our study calls for the need of multicenter randomized prospective studies in the future to validate our findings.

5. Conclusions

LVOT calcification is a risk factor for stroke and lower survival following TAVR. Its preoperative determination could help in predicting these outcomes and may represent a useful tool for the decision-making process of the heart team.

Declaration of competing interest

TF is consultant for LivaNova. SP is proctor for LivaNova. The other authors have no conflicts of interest to disclose. No funding was provided for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2019.12.001.

References

1. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38:2739–2791 2017.
2. Pollari F, Dell'Aquila AM, Söhn C, et al. Risk factors for paravalvular leak after transcatheter aortic valve replacement. *J Thorac Cardiovasc Surg.* 2019;157:1406–1415.e3.
3. Hansson NC, Nørgaard BL, Barbanti M, et al. The impact of calcium volume and distribution in aortic root injury related to balloon-expandable transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr.* 2015;9:382–392.
4. Pollari F, Grossmann I, Vogt F, et al. Risk factors for atrioventricular block after transcatheter aortic valve implantation: a single-centre analysis including assessment of aortic calcifications and follow-up. *Europace.* 2019;21:787–795.
5. Kappetein AP, Head SJ, Généreux P, et al. Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J.* 2012;33:2403–2418.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J.* 2019;40:237–269.
7. Jilaihawi H, Makkar RR, Kashif M, et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging.* 2014;15:1324–1332.
8. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* 2017;376:1321–1331.
9. Mack MJ, Leon MB, Smith CR, et al. PARTNER 1 Trial Investigators. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet.* 2015;385:2477–2484.
10. Leon MB, Smith CR, Mack MJ, et al. PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* 2016;374:1609–1620.
11. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation.* 2010;121:870–878.
12. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *J Am Med Assoc.* 2016;316:592–601.
13. Aggarwal SK, Delahunty Rn N, Menezes LJ, et al. Patterns of solid particle embolization during transcatheter aortic valve implantation and correlation with aortic valve calcification. *J Interv Cardiol.* 2018;31:648–654.
14. Spaziano M, Chieffo A, Watanabe Y, et al. Computed tomography predictors of mortality, stroke and conduction disturbances in women undergoing TAVR: a sub-analysis of the WIN-TAVI registry. *J. Cardiovasc. Comput. Tomogr.* 2018;12:338–343.
15. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with

a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380:1695–1705.
16. Popma JJ, Deeb GM, Yakubov SJ, et al. Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med.* 2019;380:1706–1715.
17. Nguyen-Kim TD, Sahin A, Sündermann SH, et al. Evaluation of calcium loss after transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg.* 2014;18:67–72.
18. Maeno Y, Abramowitz Y, Yoon SH, et al. Relation between left ventricular outflow tract calcium and mortality following transcatheter aortic valve implantation. *Am J Cardiol.* 2017;120:2017–2024.
19. Lantelme P, Eltchaninoff H, Rabilloud M, et al. Development of a risk score based on aortic calcification to predict 1-year mortality after transcatheter aortic valve replacement. *JACC Cardiovasc Imaging.* 2019;12:123–132.
20. Sannino A, Losi MA, Giugliano G, et al. Aortic and mitral calcification is marker of significant carotid and limb atherosclerosis in patients with first acute coronary syndrome. *Echocardiography.* 2015;32:1771–1777.
21. Pollari F, Hitzl W, Claes M, Grossmann I, Fischlein T. Machine learning for making aortic valve interventions complementary and not competitive. *JACC Cardiovasc Interv.* 2019;12:2112.
22. McCarthy C, Murphy S, Cohen JA, et al. Misclassification of myocardial injury as myocardial infarction: implications for assessing outcomes in Value-Based Programs. *JAMA Cardiol.* 2019;4:460–464.
23. Pollari F, Fischlein T, Pfeiffer S. Aortic valve and coronary artery disease in the TAVI's age: two brothers with independent destinies. *JACC Cardiovasc Interv.* 2019;12:798.
24. Oh JK, Little SH, Abdelmoneim SS, et al. Pivotal Trial Clinical Investigators. Regression of paravalvular aortic regurgitation and remodeling of self-expanding transcatheter aortic valve: an observation from the CoreValve U.S. Pivotal Trial. *JACC Cardiovasc Imaging.* 2015;8:1364–1375.
25. Overtchouk P, Guedeney P, Rouanet S, et al. Long-term mortality and early valve dysfunction according to anticoagulation use: the France TAVI Registry. *J Am Coll Cardiol.* 2019;73:13–21.
26. Levi A, Landes U, Assali AR, et al. Long-term outcomes of 560 consecutive patients treated with transcatheter aortic valve implantation and propensity score-matched analysis of early- versus new-generation valves. *Am J Cardiol.* 2017;119:1821–1831.
27. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol.* 2014;63:1972–1981.
28. Meredith IT, Walters DL, Dumonteil N, et al. 1-Year outcomes with the fully repositionable and retrievable Lotus transcatheter aortic replacement valve in 120 high-risk surgical patients with severe aortic stenosis: results of the REPRISE II study. *JACC Cardiovasc Interv.* 2016;9:376–384.