TAVR for low-flow, low-gradient aortic stenosis: Prognostic impact of aortic valve calcification

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Background Compared to high gradient aortic stenosis (AS), patients with low-flow, low-gradient AS have higher mortality after transcatheter aortic valve replacement (TAVR), but distinct outcome predictors in this patient subset are yet to be determined. The present study investigated the prognostic impact of aortic valve calcification (AVC) in patients with low-flow, low-gradient AS undergoing TAVR.

Methods This retrospective single-center analysis includes all patients undergoing TAVR for severe low-flow, low-gradient AS (n = 526), ie, low EF low gradient AS (LEF-LG AS; n = 290) and paradoxical low-flow, low-gradient AS (PLF-LG AS; n = 236), in whom AVC was quantified from contrast-enhanced multislice computed tomography images. $AVC_{density}$ was defined as calcium volume per annulus area. Patients were trichotomized according to sex-specific $AVC_{density}$ tertiles in both subgroups. All-cause mortality was assessed by Kaplan-Meier analyses and independent outcome predictors were determined by multivariable analyses.

Results In both subgroups, patients with high $AVC_{density}$ had higher mean transvalvular gradients at baseline and higher rates of PVL after TAVR. High $AVC_{density}$ was associated with lowest 1- and 3-year mortality after TAVR in the LEF-LG AS but not in the PLF-LG AS group. According to multivariable analysis $AVC_{density}$ was independently associated with better survival in LEF-LG AS patients (HR 0.73 [0.60-0.88], P = .0011), but not in those with PLF-LG AS (HR 0.91 [0.73-1.14], P = .42).

Conclusions Quantification of AVC may not only be of diagnostic but also of prognostic value, as it facilitates the selection of LEF-LG AS patients with higher probability of beneficial outcome after TAVR. (Am Heart J 2020;225:138-48.)

Patients receiving transcatheter aortic valve replacement (TAVR) for severe low-flow, low-gradient aortic stenosis (AS), especially those with low ejection fraction low gradient (LEF-LG) AS, are substantially limited in their prognosis compared to those treated for high gradient AS (HGAS).[1-3] Accordingly, clinical decision-making in patients with low-flow, low-gradient AS is often difficult and identification of distinct predictors of outcome following TAVR in this complex subset of patients is of great clinical relevance. For both, LEF-LG AS and paradoxical low-flow, low-gradient (PLF-LG) AS patients, the assessment of aortic valve calcification (AVC) by multislice computed tomography (MSCT) has gained increasing importance due to a direct correlation of the extent of valve calcification with AS severity.[4-6] In this regard, $AVC_{density}$, defined as the ratio of total AVC load to the aortic annulus area, has been shown to determine AS severity with the highest diagnostic accuracy.[4]

Although it seems to be essential for diagnosing severe AS in patients with low-flow, low-gradient AS, there is no data so far regarding the prognostic impact of $AVC_{density}$ in this subset of TAVR patients. Thus, the aim of the present study was to assess the impact of $AVC_{density}$ according to preprocedural MSCT on outcome in patients undergoing TAVR for either severe LEF-LG or PLF-LG AS.

Materials and methods

Study design and data acquisition

The study was designed as a retrospective analysis of data derived from a high-volume single-center TAVR

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registry. All clinical endpoints were adjudicated according to current valve academic research consortium 2 (VARC-2) criteria after 30 days. Echocardiographic outcome was derived from in-house TTE at discharge. Survival data were obtained from in-house information as part of clinical routine. All patients provided informed consent to the procedure and data acquisition. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Patients and procedure

Between 2008 and 2018 a total of 2758 patients were treated with TAVR at our institution. For all patients the decision to perform TAVR was made by an interdisciplinary heart team based on the established criteria.[7] After excluding patients who underwent planned valve-in-valve procedures, combined percutaneous mitral valve treatment or those treated with investigational transcatheter heart valves (THV), we identified 730 patients fulfilling the echocardiographic criteria for either severe LEF-LG AS or PLF-LG AS (definition see below). Among these, 204 patients were excluded due to insufficient MSCT data for $AVC_{density}$ quantification, leaving a total of 526 patients (n = 290 with LEF-LG AS; n = 236 with PLF-LG AS) for the analysis (Supplemental Figure 1). Median follow-up time for these patients was 3.51 (95% CI 3.06-3.93) years. THV devices used are described in detail in the supplement.

Definition of severe LEF-LG and PLF-LG AS

Severity of AS and classification in either LEF-LG or PLF-LG AS were assessed by means of resting TTE at baseline according to current ESC/EACTS guidelines.[7] Severe LEF-LG AS was defined as an effective orifice area (EOA) ≤ 1.0 cm^2, transvalvular gradient <40 mmHg, SVI ≤ 35 mL/m^2 and LVEF <50%, and severe PLF-LG AS as an EOA ≤ 1.0 cm^2, transvalvular gradient <40 mmHg, SVI ≤ 35 mL/m^2 and LVEF $\geq 50\%$. EOAs were calculated by using the continuity equation.

Assessment of $AVC_{density}$ by MSCT

Quantification of AVC was implemented by calcium volume scoring on contrast-enhanced MSCT images using a dedicated software (3mensio Structural Heart V9.1, Pie Medical Imaging, Maastricht, Netherlands) as described previously.[8] An empiric threshold of 550 Hounsfield units (HU) was used for AVC assessment in the majority of patients to adequately discriminate between calcium and contrast medium. Adjustment of the threshold was necessary only in exceptional cases. Median and mean used thresholds were 550.0 (IQR 550.0, 550.0) HU and 548.8 ± 48.6 HU, respectively. The region of interest for calcium volume quantification was defined as the composite of 2 sectors: the annular plane[1] and the LVOT[2] (Figure 1). AVC was defined as the total calcium volume detected in these 2 sectors. $AVC_{density}$ was defined as the ratio of AVC (mm^3 calcium) per aortic annulus area (cm^2) as measured in MSCT (unit of $AVC_{density}$: mm^3 calcium/cm^2). Inter- and intraclass correlation coefficients (ICC) for inter- and intra-observer variability of $AVC_{density}$ quantification in 30 randomly selected patients were 0.98 (95% CI 0.952-0.989, $P < .0001$) and 1.00 (95% CI 0.995-0.999, $P < .0001$), respectively.

Statistical analysis

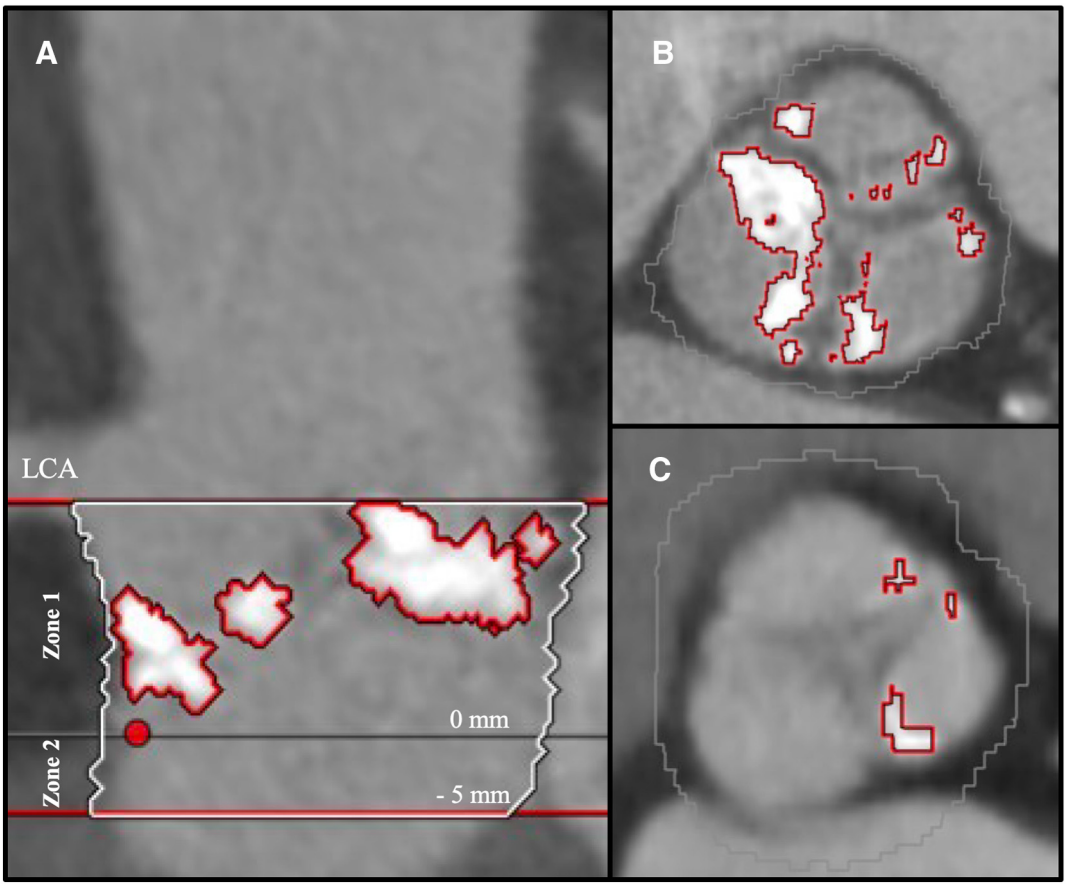
Patients were divided into sex-specific tertiles according to $AVC_{density}$ in the subgroups of LEF-LG AS and PLF-LG AS. ICC estimates and their 95% CI were calculated based on a mean-rating (k = 2 raters), absolute-agreement, 2-way model. For between-group comparisons the Mann-Whitney *U* test was used for continuous variables and the χ^2 test for binary variables. Survival curves were produced using the Kaplan-Meier method. Survival curve differences were tested using the log-rank test. For the uni- and multivariable analyses, performed for each subgroup, the following set of variables was used: age, male sex, BMI in the categories underweight (≤ 18.5 kg/m^2), normal weight (>18.5-25 kg/m^2, reference) and overweight (>25 kg/m^2), diabetes, COPD, atrial fibrillation, impaired glomerular filtration rate (GFR) <60 mL/min, prior stroke, prior myocardial infarction, SVI, non-TF access, log-transformed $AVC_{density}$, and LVEF <30% (only for LEF-LG AS subgroup). Variables that showed p-values <0.25 in the univariable Cox regression analyses were used in a forward selection process based on Akaike Information Criteria. Spline analyses were performed using the resulted models of the forward selection process. All statistical analyses were performed using *R version 3.5.2*.

Results

LEF-LG AS versus PLF-LG AS patients

Compared to patients with PLF-LG AS, those with LEF-LG AS were younger, more often male and presented more frequently in NYHA stage IV. Moreover, the rate of prior myocardial infarction and coronary artery bypass surgery was higher in these patients. The higher comorbidity of LEF-LG patients translated into higher estimated surgical risk according to EuroSCORE II and STS PROM compared to PLF-LG AS patients. Baseline echocardiography revealed lower mean transvalvular gradients and SVI in patients with LEF-LG AS. Furthermore, MSCT prior to TAVR showed lower $AVC_{density}$ in LEF-LG AS compared to PLF-LG AS patients. A detailed comparison of LEF-LG AS and PLF-LG AS patients regarding baseline characteristics is given in Supplemental Table I.

Figure 1



AVC quantification based on contrast-enhanced MSCT. A, AVC volume quantification in pre-defined zones: Zone 1 (=*annular plane;* basal plane to the coronary ostia) and Zone 2 (=*LVOT;* basal plane to 5 mm deep in the LVOT). **B**, Example for high AVC. **C**, Example for low AVC. Abbreviations: LCA = left coronary artery.

Baseline characteristics according to $AVC_{density}$ tertiles

Baseline characteristics according to sex-specific $AVC_{density}$ tertiles for patients presenting with LEF-LG AS and PLF-LG AS are given in Table I and Table II, respectively. Patients treated for LEF-LG AS (n = 290) and PLF-LG AS (n = 236) were trichotomized according to sex-specific $AVC_{density}$ tertiles in those with low, moderate and high $AVC_{density}$ for each subgroup. Boundaries of tertiles are given in Supplemental Table II. Figure 2 displays boxplots of $AVC_{density}$ according to female or male sex demonstrating overall higher $AVC_{density}$ in men than in women. Patients with high $AVC_{density}$ were older and had lower BMI compared to patients with lower $AVC_{density}$ (significant for LEF-LG AS, non-significant trend for PLF-LG AS patients). No significant differences regarding comorbidities were present among $AVC_{density}$ tertiles despite a higher rate of diabetes in patients with low $AVC_{density}$. Accordingly, there was no difference regarding EuroSCORE II and STS PROM in between the tertiles, neither for LEF-LG AS nor PLF-LG AS patients. Regarding echocardiography at baseline, mean transvalvular gradients were higher and EOA was smaller in patients with higher $AVC_{density}$ for both AS subtypes. In contrast, no difference was found by means of SVI between $AVC_{density}$ tertiles.

Procedural data and 30-day clinical and functional outcome according to $AVC_{density}$ tertiles

Procedural data as well as 30-day VARC-2 outcome according to $AVC_{density}$ tertile for LEF-LG AS and PLF-LG AS patients is presented in Supplemental Tables III and IV, respectively. There was no difference between $AVC_{density}$ tertiles with respect to access site and use of balloon or self-expandable THV types. However, mechanically expandable THVs were more frequently used in patients with high $AVC_{density}$ (non-significant trend for LEF-LG AS, significant for PLF-LG AS patients). Moreover, the rate of predilation was higher in patients with high $AVC_{density}$ compared to those with low $AVC_{density}$. VARC-

Table I. Baseline characteristics (LEF-LG AS)

	All (N = 290)	Low $AVC_{density}$ (1st tertile) (N = 96)	Moderate $AVC_{density}$ (2nd tertile) (N = 96)	High $AVC_{density}$ (3rd tertile) (N = 98)	*P*
Clinical baseline parameters					
Age (years)	79.9 (75.7, 84.2)	79.6 (75.0, 83.0)	79.1 (73.7, 83.7)	81.4 (77.5, 85.3)	.0034
Male sex	190 (65.5)	63 (65.6)	63 (65.6)	64 (65.3)	1.00
BMI (kg/m^2)	25.9 (23.5, 29.7)	26.8 (24.1, 30.7)	26.3 (23.8, 29.6)	24.7 (22.4, 28.4)	.0044
EuroSCORE II (%)	9.7 ± 7.7	9.2 ± 7.8	9.4 ± 6.7	10.4 ± 8.6	.51
STS PROM (%)	6.9 ± 5.5	7.0 ± 5.9	6.5 ± 4.7	7.1 ± 5.9	.77
Diabetes	103 (35.5)	41 (42.7)	38 (39.6)	24 (24.5)	.018
Atrial fibrillation	131 (45.5)	42 (44.2)	45 (46.9)	44 (45.4)	.93
Peripheral artery disease	107 (36.9)	34 (35.4)	40 (41.7)	33 (33.7)	.48
GFR (CKD-EPI) ($mL/min/1.73m^2$)	55.1 (38.7, 72.9)	55.7 (37.9, 69.5)	55.6 (39.5, 75.2)	54.5 (38.5, 73.3)	.76
Prior PCI	131 (45.2)	48 (50.0)	46 (47.9)	37 (37.8)	.19
Prior CABG	70 (24.1)	25 (26.0)	26 (27.1)	19 (19.4)	.40
Prior MI	72 (24.8)	23 (24.0)	25 (26.0)	24 (24.5)	.94
Prior stroke	58 (20.0)	20 (20.8)	20 (20.8)	18 (18.4)	.88
COPD	63 (21.8)	21 (22.1)	23 (24.0)	19 (19.4)	.74
Echocardiographic baseline parameters					
P mean (mmHg)	22.0 (17.0, 28.1)	18.0 (14.0, 21.6)	21.0 (17.0, 27.6)	28.0 (22.9, 35.0)	<.001
EOA (cm^2)	0.8 (0.6, 0.9)	0.9 (0.7, 1.0)	0.8 (0.6, 0.9)	0.7 (0.6, 0.8)	<.001
SVI (mL/m^2)	26.9 (22.9, 30.6)	26.5 (22.7, 30.7)	27.0 (21.6, 30.7)	26.9 (23.7, 30.6)	.69
MR ≥Grad 2	127 (44.1)	40 (42.1)	37 (38.5)	50 (51.5)	.17
LVEF <30%	112 (38.6)	37 (38.5)	34 (35.4)	41 (41.8)	.66
MSCT baseline parameters					
CT Threshold (HU)	552.4 ± 44.1	550.5 ± 43.8	555.2 ± 43.2	551.5 ± 45.7	.74
Annulus perimeter derived diameter (mm)	25.5 (24.0, 26.9)	25.3 (24.1, 26.8)	25.8 (24.0, 27.0)	25.5 (23.6, 27.0)	.76
Annulus area (cm^2)	495.7 (438.3, 548.2)	483.6 (438.3, 538.7)	501.1 (443.9, 554.1)	494.1 (420.8, 549.2)	.76
Total AVC (mm^3 calcium)	368.4 (219.6, 691.6)	161.5 (105.8, 231.2)	374.9 (304.5, 498.9)	834.5 (611.5, 1136.6)	<.001
Calcification annular plane (mm^3 calcium)	359.4 (215.3, 622.8)	157.2 (100.2, 226.3)	365.7 (293.3, 472.3)	798.6 (554.0, 1114.4)	<.001
Calcification LVOT (mm^3 calcium)	0.8 (0, 12.6)	0 (0, 1.1)	1.3 (0, 12.3)	6.1 (0, 83.3)	<.001
$AVC_{density}$ (mm^3 calcium/cm^2)	780.3 (448.6, 1363.6)	361.5 (239.2, 447.0)	772.8 (635.9, 907.7)	1672.9 (1354.9, 2167.6)	<.001

Data presented are the number (percentage) of patients for categorical variables or median values (25th percentile, 75th percentile) for continuous variables.
Abbreviations:
AVC, Aortic valve calcification; *BMI*, body mass index; *CABG*, coronary artery bypass graft; *COPD*, chronic obstructive pulmonary disease; *EOA*, effective orifice area; *GFR*, glomerular filtration rate; *HU*, Hounsfield units; *LEF-LG AS*, low LVEF low gradient aortic stenosis; *LVEF*, left ventricular ejection fraction; *LVOT*, left ventricular outflow tract; *MI*, myocardial infarction; *MR*, mitral valve regurgitation; *MSCT*, multislice computed tomography; *PCI*, percutaneous coronary intervention; *P mean*, mean transvalvular pressure gradient; *STS PROM*, Society of Thoracic Surgeons predicted risk of mortality; *SVI*, stroke volume index.

2 device success was high for both AS subtypes without significant differences in between $AVC_{density}$ tertiles.

For both, LEF-LG and PLF-LG AS patients, no differences were found between patients with low, moderate or high $AVC_{density}$ regarding the rate of disabling stroke, major or life-threatening bleeding, acute renal failure, myocardial infarction or 30-day mortality. However, there was a non-significant trend towards a higher rate of permanent pacemaker implantation (PPI) in patients with lower $AVC_{density}$.

Echocardiographic outcome at discharge is displayed in Figure 3. Patients with high $AVC_{density}$ had higher rates of more-than-mild paravalvular leakage (PVL) compared to those with low $AVC_{density}$ (significant for LEF-LG AS, non-significant trend for PLF-LG AS patients). Supplemental Table V demonstrates echocardiographic outcome according to THV types for the whole study population. More-than-mild PVL and Pmean were significantly higher in patients with high $AVC_{density}$ treated with self-expandable THV, but not in those treated with balloon- or mechanically-expandable THV.

Association of $AVC_{density}$ and mortality

After 1-year follow-up all-cause death occurred in 100 patients (high, moderate, low $AVC_{density}$: 24, 38, 38) of the LEF-LG AS group and in 54 patients (18, 16, 20) of the PLF-LG AS group.

Figure 4 shows Kaplan-Meier estimates for 1- and 3-year all-cause mortality according to sex-specific $AVC_{density}$ tertiles for patients with LEF-LG AS (**A, B**) and PLF-LG AS (**C, D**). Among LEF-LG AS patients those with high $AVC_{density}$ had a lower mortality rate 1 year after TAVR (24.9%) compared to those with moderate (40.0%) and low $AVC_{density}$ (40.2%) ($P = .041$ for comparison of all tertiles). This finding was consistent after 3 years (high, moderate, low $AVC_{density}$: 44.1%, 61.7%, 56.3%, $P =$

Table II. Baseline characteristics (PLF-LG AS)

	All (N = 236)	Low $AVC_{density}$ (1st tertile) (N = 79)	Moderate $AVC_{density}$ (2nd tertile) (N = 78)	High $AVC_{density}$ (3rd tertile) (N = 79)	*P*
Clinical baseline parameters					
Age (years)	82.2 (78.5, 85.4)	81.9 (77.3, 84.5)	81.9 (78.4, 85.8)	83.0 (79.7, 87.1)	.11
Male sex	113 (47.9)	38 (48.1)	37 (47.4)	38 (48.1)	1.00
BMI (kg/m^2)	26.7 (24.1, 30.6)	27.8 (23.8, 31.2)	27.4 (24.2, 30.7)	26.2 (24.2, 29.4)	.35
EuroSCORE II (%)	5.7 ± 6.0	6.3 ± 5.9	6.1 ± 8.0	4.8 ± 3.4	.29
STS PROM (%)	5.2 ± 3.4	5.3 ± 3.4	5.4 ± 4.0	5.0 ± 2.8	.73
Diabetes	82 (34.7)	33 (41.8)	29 (37.2)	20 (25.3)	.081
Atrial fibrillation	109 (47.8)	37 (48.7)	40 (54.1)	32 (41.0)	.27
Peripheral artery disease	68 (28.8)	33 (41.8)	16 (20.5)	19 (24.1)	.0069
GFR (CKD-EPI) ($mL/min/1.73m^2$)	57.8 (42.5, 74.6)	59.5 (42.8, 78.9)	55.4 (41.0, 72.6)	57.8 (43.8, 78.5)	.44
Prior PCI	89 (37.9)	33 (41.8)	32 (41.0)	24 (30.8)	.28
Prior CABG	35 (14.8)	14 (17.7)	12 (15.4)	9 (11.4)	.53
Prior MI	32 (13.6)	12 (15.2)	15 (19.2)	5 (6.3)	.054
Prior stroke	37 (15.7)	13 (16.5)	14 (17.9)	10 (12.7)	.64
COPD	50 (21.2)	15 (19.0)	15 (19.2)	20 (25.3)	.54
Echocardiographic baseline parameters					
P mean (mmHg)	27.0 (20.0, 32.6)	20.5 (16.0, 27.0)	29.0 (21.0, 32.0)	31.0 (26.0, 36.8)	<.001
EOA (cm^2)	0.7 (0.6, 0.9)	0.8 (0.7, 1.0)	0.7 (0.6, 0.8)	0.6 (0.5, 0.8)	<.001
SVI (mL/m^2)	29.6 (26.0, 32.2)	30.0 (26.4, 32.7)	29.5 (25.9, 32.2)	29.0 (25.5, 31.8)	.36
MR ≥ Grad 2	87 (37.3)	27 (34.6)	35 (44.9)	25 (32.5)	.23
MSCT baseline parameters					
CT Threshold (HU)	544.1 ± 53.1	546.2 ± 58.2	541.0 ± 55.1	544.9 ± 45.7	.82
Annulus perimeter derived diameter (mm)	24.4 (22.8, 26.0)	24.8 (23.1, 25.7)	24.3 (22.8, 25.8)	24.4 (22.8, 26.2)	.87
Annulus area (cm^2)	449.4 (393.7, 505.2)	460.5 (406.3, 498.9)	449.4 (397.0, 502.4)	438.0 (386.7, 522.1)	.85
Total AVC (mm^3 calcium)	438.5 (237.8, 698.4)	175.5 (100.8, 261.9)	425.2 (297.4, 553.2)	821.9 (659.8, 1022.2)	<.001
Calcification annular plane (mm^3 calcium)	387.4 (225.1, 640.9)	170.2 (98.4, 256.4)	393.8 (268.7, 524.2)	714.5 (558.2, 960.8)	<.001
Calcification LVOT (mm^3 calcium)	2.0 (0, 41.7)	0 (0, 1.9)	2.0 (0, 26.4)	44.6 (2.0, 164.5)	<.001
$AVC_{density}$ (mm^3 calcium/cm^2)	936.1 (530.0, 1565.5)	404.4 (226.8, 549.4)	936.1 (753.3, 1125.0)	1745.5 (1562.9, 2377.0)	<.001

Abbreviations:
PLF-LG AS, paradoxical low-flow, low-gradient aortic stenosis.
All other abbreviations as in Table I.

.029). In contrast, in PLF-LG AS patients there were no significant differences regarding 1- and 3-year mortality following TAVR between $AVC_{density}$ tertiles (high, moderate, low $AVC_{density}$: 1-year: 23.0%, 20.6%, 25.4%, *P* = .73; 3-year: 36.2%, 40.3%, 42.6%, *P* = .65).

Prognostic impact of $AVC_{density}$

Supplemental Tables VI and VII show the prognostic impact of $AVC_{density}$ according to multivariate analysis for patients with LEF-LG AS and PLF-LG AS, respectively. In patients with LEF-LG AS, $AVC_{density}$ was the strongest independent predictor for survival after TAVR (HR 0.73, 95% CI 0.60-0.88, *P* = .0011). Whereas a higher SVI was also protective against mortality, underweight, COPD and an LVEF <30% were independently associated with worse outcome among LEF-LG AS patients. By contrast, no independent survival benefit for $AVC_{density}$ was present for PLF-LG AS patients after multivariate adjustment (HR 0.91, 95% CI 0.73-1.14, *P* = .42). In this patient subset atrial fibrillation and impaired renal function were found to be independently associated with mortality.

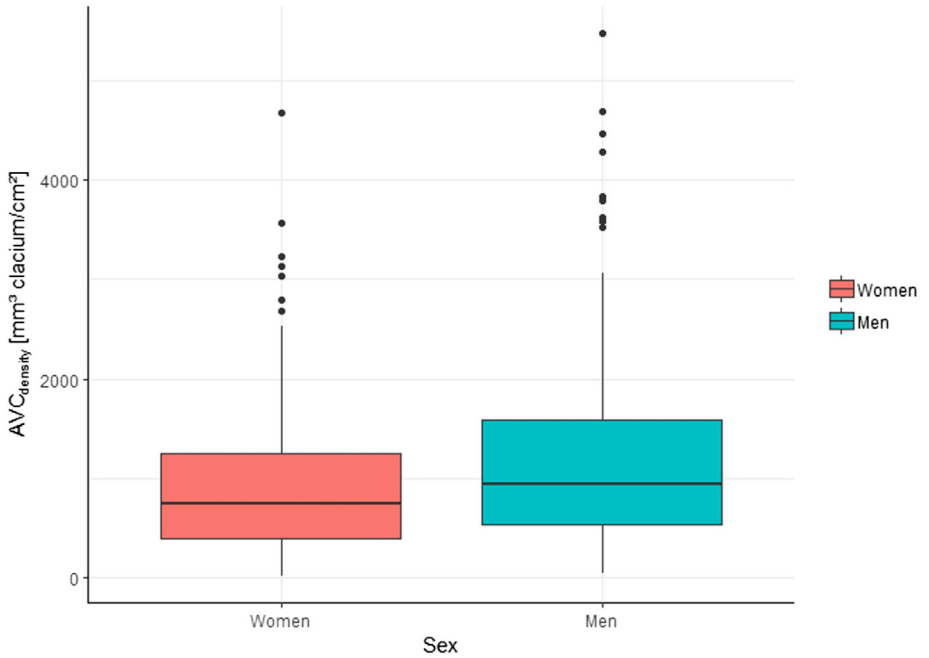
Based on HR for mortality as assessed by multivariable analyses, Figure 5 displays adjusted spline analyses demonstrating the positive impact of increasing $AVC_{density}$ on survival for (**A**) LEF-LG AS, but not for (**B**) PLF-LG AS patients.

Discussion

In the present study we assessed the prognostic impact of $AVC_{density}$ in patients with low-flow, low-gradient AS undergoing TAVR. The main findings are as follows: (i) Irrespective of the AS subtype (LEF-LG AS or PLF-LG AS), those patients with higher $AVC_{density}$ provide higher transvalvular gradients and smaller EOAs at baseline. (ii) Moreover, these patients have a higher rate of PVL compared to patients with low $AVC_{density}$. (iii) In patients with LEF-LG AS, those with high $AVC_{density}$ have lower mortality rates after TAVR compared to those with lower $AVC_{density}$. (iv) In contrast, for PLF-LG AS patients there is no difference in mortality rates according to $AVC_{density}$. (v) $AVC_{density}$ is an independent predictor of lower mortality in TAVR patients with LEF-LG AS, but not in those with PLF-LG AS.

The assessment of severe AS in patients with low mean transvalvular gradient (ie, <40 mmHg) depends on SVI

Figure 2



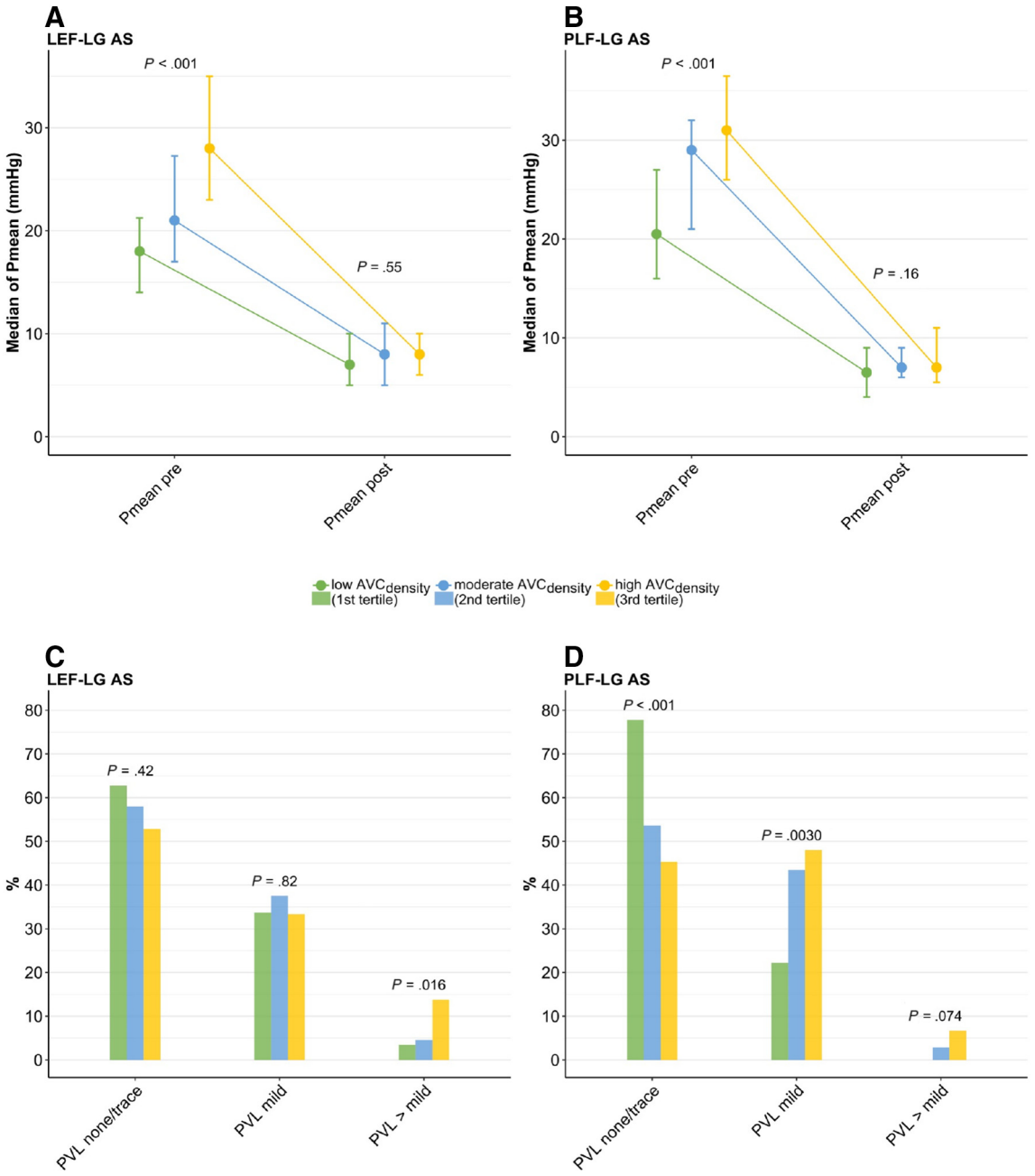
AVC$_{density}$ according to sex.

and EOA. However, these echocardiographically derived parameters are associated with a certain imprecision (e.g. LVOT diameter measurement; pseudo-severe AS).[9,10] According to current guidelines, in these patients the quantification of AVC by means of MSCT should be considered to determine AS severity.[7] In fact, a strong association of AVC and AS severity has been demonstrated in previous studies.[5,11] This association between AS severity and AVC is also reflected in the present study as we demonstrate that low-flow, low-gradient AS patients with high AVC$_{density}$ provide higher transvalvular gradients and smaller EOAs at baseline. This finding was consistent for both, LEF-LG AS and PLF-LG AS.

Several previous studies have demonstrated that patients with LEF-LG AS have the worst prognosis after TAVR compared to all other AS subtypes.[3,12-14] In contrast, regarding PLF-LG AS patients, some studies revealed clinical outcomes comparable to HGAS patients,[3,14] whereas others showed that PLF-LG AS patients have a poorer prognosis after TAVR.[13] Although it is of major clinical relevance, distinct outcome predictors in TAVR patients with low-flow, low-gradient AS following TAVR have so far not been determined. In the present study we demonstrate for the first time, that a higher AVC$_{density}$ is an independent predictor of lower mortality in patients undergoing TAVR for LEF-LG AS. This finding appears to be somewhat counterintuitive, because a higher AVC load, especially if located in the LVOT, has been associated with higher age, higher rate of comorbidities and, as demonstrated in the present study, also with a higher rate of PVL after TAVR.[8,15] However, given that the severity of AS is strongly related to the AVC load, in the particular subset of TAVR patients with LEF-LG AS the adverse impact of AVC seems to be outperformed by the beneficial effect of indicating AS treatment in more severe rather than less severe AS. In fact, Clavel et al. showed that in medically treated AS patients AVC as a measure of AS severity is a strong predictor for adverse outcome.[4] Conversely, the current study demonstrates, that by eliminating AS with TAVR in the comorbid subset of LEF-LG AS patients those patients with more severe AS, reflected by higher AVC$_{density}$, experience larger benefits. On the other hand, in those with low AVC$_{density}$, ie, less severe AS, patients' prognosis seems to be less affected by the presence of AS but more determined by their comorbidities, of which severe LV dysfunction, pulmonary disease (COPD) and cachexia had the strongest adverse impact in the present study. Importantly, this does not allow the conclusion that TAVR in this patient subset is futile per se since we cannot provide data on a medically treated cohort for comparison. Still, our data emphasize the importance of preprocedural AVC quantification in LEF-LG AS patients undergoing TAVR even by using contrast-enhanced MSCT as it seems to provide not only a diagnostic, but also a prognostic value.

In contrast to patients with LEF-LG AS, we did not find a protective impact of AVC$_{density}$ for PLF-LG AS patients. This

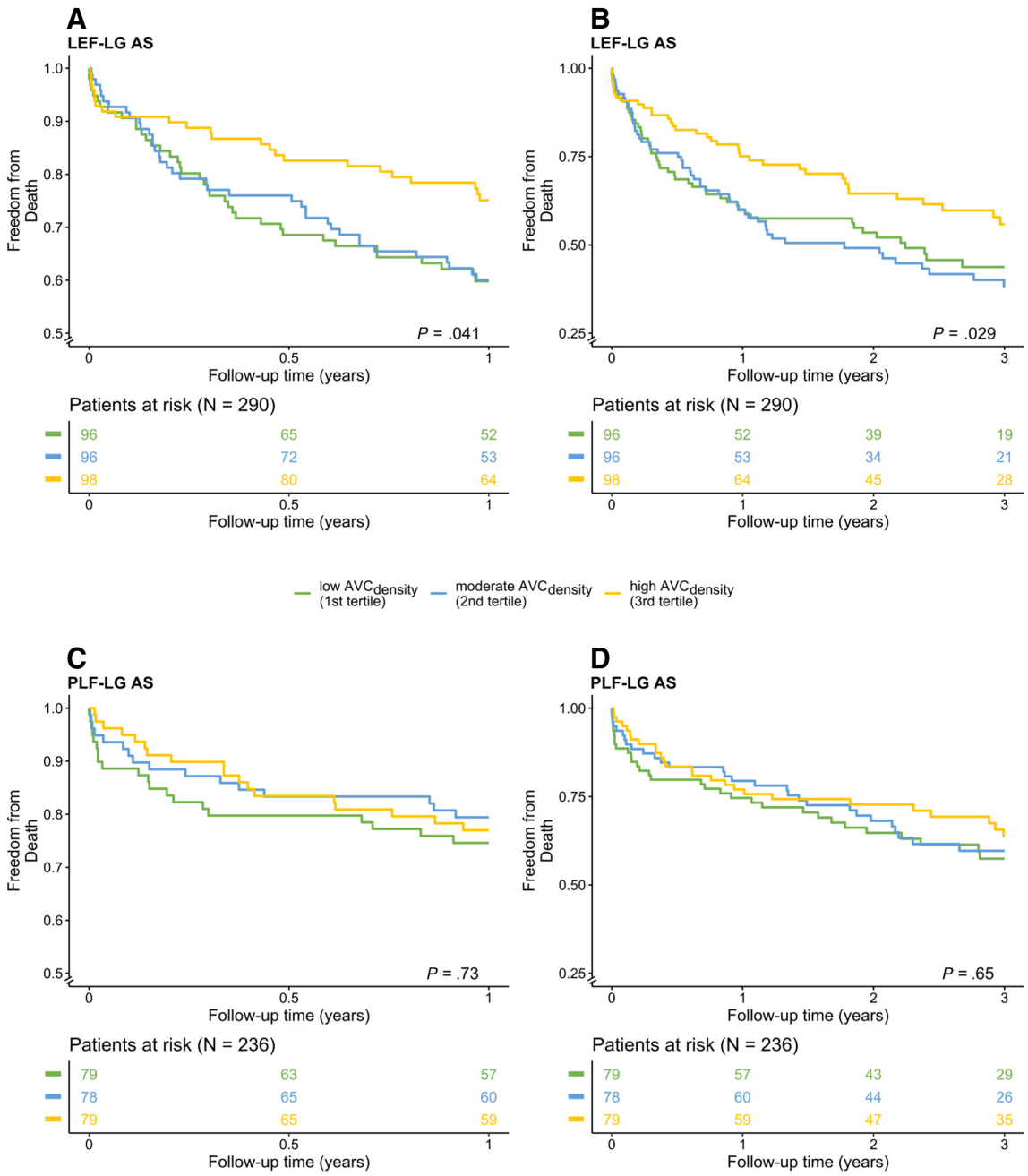
Figure 3



Echocardiographic outcome according to sex-specific $AVC_{density}$ tertiles. A, Changes in P mean before and after TAVR (LEF-LG AS). **B**, Changes in P mean before and after TAVR (PLF-LG AS). **C**, PVL after TAVR (LEF-LG AS). **D**, PVL after TAVR (PLF-LG AS). Abbreviations: P mean, mean transvalvular pressure gradient; PVL, paravalvular leakage.

finding might have several explanations. First, as dobutamine stress-echocardiography (DSE) and AVC quantification were not part of routine preprocedural assessment in our cohort, the subgroup of LEF-LG AS patients, in contrast to PLF-LG AS patients, may actually comprise subjects with pseudo-severe AS who may not have benefited from TAVR. Second, mortality rates and, thus, event rates were higher in the LEF-LG AS group increasing the likelihood of statistically significant findings in this subgroup. Third, the current spline analysis suggests that PLF-LG AS patients with moderate $AVC_{density}$ might profit most from valve replacement, as both very high and very low $AVC_{density}$ seem to have

Figure 4



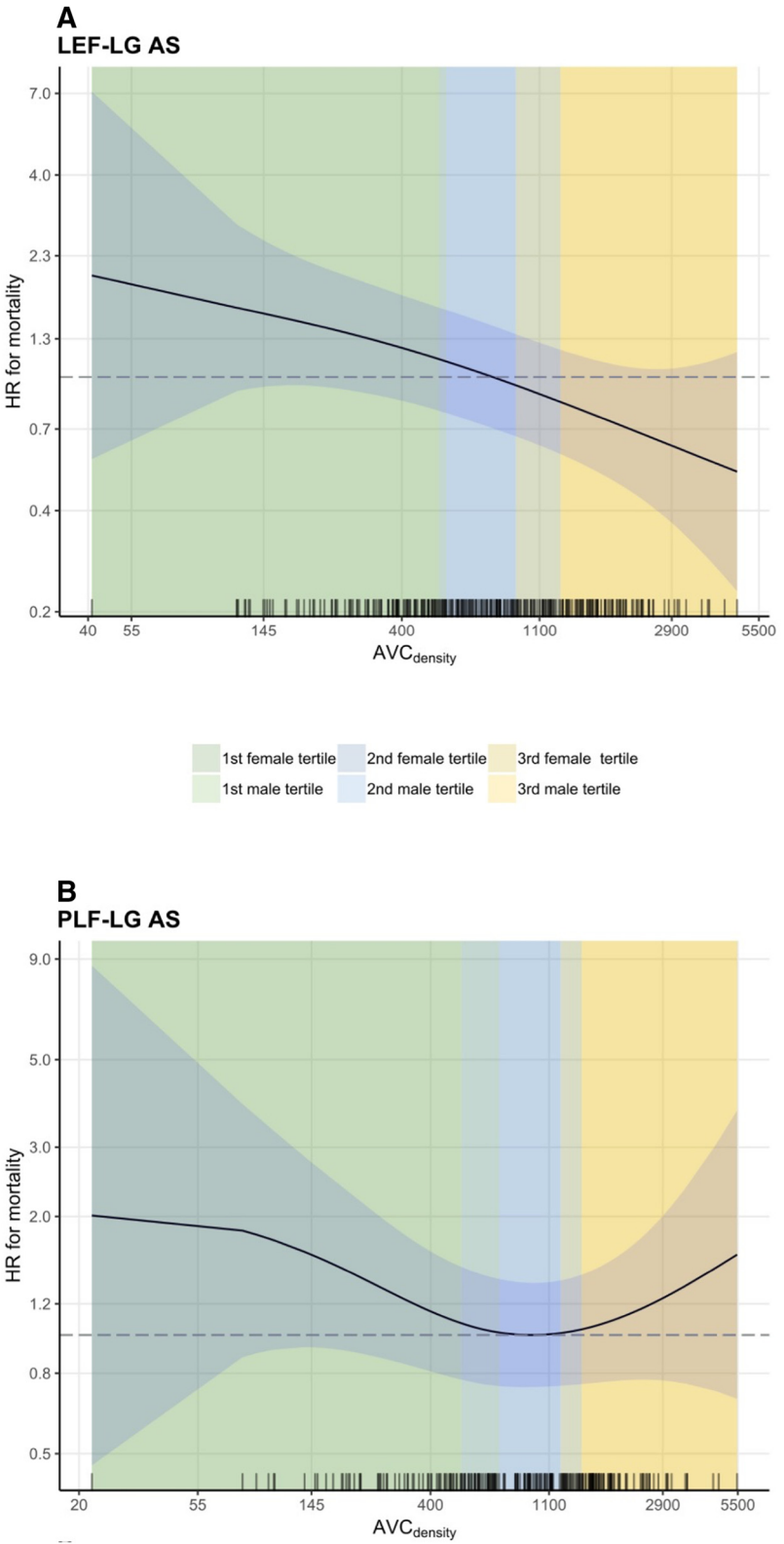
Kaplan-Meier survival curves for mortality according to sex-specific $AVC_{density}$ tertiles. A, 1-year mortality (LEF-LG AS). **B**, 3-year mortality (LEF-LG AS). **C**, 1-year mortality (PLF-LG AS). **D**, 3-year mortality (PLF-LG AS).

an adverse impact on outcome in these patients. One explanation for the adverse impact of high $AVC_{density}$ in PLF-LG AS compared to LEF-LG AS patients might be that these patients have smaller and stiffer ventricles with more severe diastolic dysfunction and, thus, a higher susceptibility to PVL, which is more frequent in patients with high $AVC_{density}$.

Limitations

This study inherits several limitations. First, it is a retrospective analysis derived from single-center data. Second, our study does not provide other outcome parameters than all-cause mortality like cardiovascular mortality, quality of life or rate of rehospitalization. Third,

Figure 5



Adjusted spline analyses for the hazard of mortality according to $AVC_{density}$. A, LEF-LG AS. B, PLF-LG AS.

DSE and non-contrast MSCT were not part of routine assessment of AS severity in the majority of patients, as both diagnostic tools were not particularly recommended until the recent guideline update and most of the patients in our study were treated prior to that. The lack of routine stress testing in the assessment of low-flow, low-gradient AS might have led to inclusion and treatment of patients with pseudo-severe AS, who would probably not have benefited from TAVR. Fourth, echocardiographic assessment of EF is associated with certain imprecision. Thus, especially in those with borderline EF, some patients might have been falsely classified regarding AS subgroups. Lastly, contrast-enhanced MSCT permits less accurate quantification of AVC load compared to non-contrast MSCT.[16] However, we did not seek to establish clear AVC cut-off values, but rather demonstrate a relation between $AVC_{density}$ and outcome in patients with low-flow, low-gradient AS.

Conclusions

The present study is the first large-scale analysis investigating the prognostic impact of $AVC_{density}$ as quantified by MSCT in patients undergoing TAVR for severe low-flow, low-gradient AS. High $AVC_{density}$ was an independent predictor of lower mortality in patients with LEF-LG AS. By contrast, there was no association of high $AVC_{density}$ with lower mortality in patients with PLF-LG AS. Hence, inclusion of $AVC_{density}$, as an indicator for AS severity, into preprocedural assessment might improve the selection of LEF-LG AS patients with a higher probability of beneficial outcome after TAVR.

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Declaration of interest

ML, ODB and LV received travel compensation (TC) from Edwards Lifesciences. FD received TC from Edwards Lifesciences, St. Jude Medical, Symetis, Boston Scientific, and Abbott, as well as speaker honoraria (SH) from Boston Scientific and Abbott. FD was a consultant for Edwards Lifesciences and is currently a full-time employee for Edwards Lifesciences. JS is a proctor for Symetis and JenaValve. HR received SH from Edwards Lifesciences. US is a consultant and proctor for Edwards Lifesciences, Abbott, Biotronik, JenaValve, Medtronic, Symetis and Boston Scientific, and received SH and TC from JenaValve, Edwards Lifesciences, Abbott, Medtronic, Symetis and Boston Scientific. MS served as consultant for JenaValve, received TC from Abbott, Edwards Lifesciences, Symetis, and Biotronik and received SH from Medtronic and Boston Scientific. LC is a proctor for and received SH as well as TC from JenaValve, Edwards Lifesciences and Boston Scientific and Medtronic and is a consultant for Edwards Lifesciences. NS received TC from Edwards Lifesciences and St. Jude Medical, as well as SH and TC from Boston Scientific. All other authors report no conflict of interest.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.03.013.

References

1. Ribeiro HB, Lerakis S, Gilard M, et al. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: The TOPAS-TAVI Registry. J Am Coll Cardiol 2018;71(12):1297-308.
2. Rodriguez-Gabella T, Nombela-Franco L, Auffret V, et al. Transcatheter aortic valve implantation in patients with paradoxical low-flow. Low-Gradient Aortic Stenosis Am J Cardiol 2018 Aug 15;122(4):625-32, https://doi.org/10.1016/j.amjcard.2018.04.044.
3. Lauten A, Figulla HR, Möllmann H, et al. TAVI for low-flow, low-gradient severe aortic stenosis with preserved or reduced ejection fraction: A subgroup analysis from the German Aortic Valve Registry (GARY). EuroIntervention 2014;10(7):850-9.
4. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: Results of an international registry study. J Am Coll Cardiol 2014;64(12):1202-13.
5. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: Correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011;97(9):721-6.
6. Pawade T, Clavel MA, Tribouilloy C, et al. Computed tomography aortic valve calcium scoring in patients with aortic stenosis. Circ Cardiovasc Imaging 2018;11(3), e007146.
7. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;2017.
8. Seiffert M, Fujita B, Avanesov M, et al. Device landing zone calcification and its impact on residual regurgitation after transcatheter aortic valve implantation with different devices. Eur Heart J Cardiovasc Imaging 2016;17(5):576-84.
9. Clavel M-A, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J 2016 Mar 31;37(34):2645-57, https://doi.org/10.1093/eurheartj/ehw096.
10. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2017;18(3):254-75.
11. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading: New insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol 2013;62(24):2329-38.
12. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: A placement of aortic transcatheter valves (PARTNER) trial analysis. Circulation 2013;127(23):2316-26.
13. Puls M, Korte KP, Bleckmann A, et al. Long-term outcomes after TAVI in patients with different types of aortic stenosis: The conundrum of

low flow, low gradient and low ejection fraction. EuroIntervention 2017;13(3):286-93.

14. Fischer-Rasokat U, Renker M, Liebetrau C, van Linden A, Arsalan M, Weferling M, et al. 1-Year survival after TAVR of patients with low-flow, low-gradient and high-gradient aortic valve stenosis in matched study populations. JACC Cardiovasc Interv 2019 Apr 22;12(8):752 LP – 763.
15. 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(11):2017-24.
16. Kim WK, Renker M, Rolf A, et al. Accuracy of device landing zone calcium volume measurement with contrast-enhanced multidetector computed tomography. Int J Cardiol 2018;263: 171-6.