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ORIGINAL PAPER

Sex-specific aortic valve calcifications in patients undergoing transcatheter aortic valve implantation

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Aims

To study sex-specific differences in the amount and distribution of aortic valve calcification (AVC) and to correlate the AVC load with paravalvular leakage (PVL) post-transcatheter aortic valve intervention (TAVI).

Methods and results

This registry included 1801 patients undergoing TAVI with a Sapien3 or Evolut valve in two tertiary care institutions. Exclusion criteria encompassed prior aortic valve replacement, suboptimal multidetector computed tomography (MDCT) quality, and suboptimal transthoracic echocardiography images. Calcium content and distribution were derived from MDCT. In this study, the median age was 81.7 (25th–75th percentile 77.5–85.3) and 54% male. Men, compared to women, were significantly younger [81.2 (25th–75th percentile 76.5–84.5) vs. 82.4 (78.2–85.9), $P \leq 0.01$] and had a larger annulus area [512 mm^2 (25th–75th percentile 463–570) vs. 405 mm^2 (365–454), $P < 0.01$] and higher Agatston score [2567 (25th–75th percentile 1657–3913) vs. 1615 (25th–75th percentile 905–2484), $P < 0.01$]. In total, 1104 patients (61%) had none-trace PVL, 648 (36%) mild PVL, and 49 (3%) moderate PVL post-TAVI. There was no difference in the occurrence of moderate PVL between men and women (3% vs. 3%, $P = 0.63$). Cut-off values for the Agatston score as predictor for moderate PVL based on the receiver-operating characteristic curve were 4070 (sensitivity 0.73, specificity 0.79) for men and 2341 (sensitivity 0.74, specificity 0.73) for women.

Conclusion

AVC is a strong predictor for moderate PVL post-TAVI. Although the AVC load in men is higher compared to women, there is no difference in the incidence of moderate PVL. Sex-specific Agatston score cut-offs to predict moderate PVL were almost double as high in men vs. women.

Keywords

transcatheter aortic valve implantation • gender • paravalvular leakage • aortic valve calcification

Introduction

The frequency of aortic stenosis (AS) increases with age and affects 3.4% of the elderly population >75 years.[1] In the Western world, degenerative aortic valve disease is the dominant cause of severe AS and characterized by leaflet stiffening and thickening by aortic valve calcification (AVC).[2] Age, hyperlipidaemia including elevated Lp(a), hypertension, obesity, diabetes, smoking, and chronic kidney disease are associated with degenerative AS.[3,4] The amount of calcification correlates with AS severity.[5]

Multidetector computed tomography (MDCT) is the cornerstone of pre-procedural planning and valve selection in patients undergoing transcatheter aortic valve intervention (TAVI).[6] MDCT is used to quantify the overall calcium load by means of the Agatston score and calcium distribution at the level of the aortic leaflets.[7] High AVC is a risk factor for cardiovascular events, conduction disturbances, and a predictor for

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Table 1 Baseline characteristics

	Total	Men	Women	P-value
n	1801	966	835	
Age	81.7 [77.5–85.3]	81.2 [76.5–84.5]	82.4 [78.2–85.9]	**<0.01**
Body mass index (BMI)	26.1 [23.6–29.6]	26.2 [24.0–29.1]	26.0 [23.0–30.1]	0.41
STS	3.4 [2.2–5.4]	3.0 [1.9–4.6]	4.0 [2.7–6.2]	**<0.01**
Medical history				
Hypertension	1482 (82.3)	789 (81.7)	693 (83.0)	0.47
Diabetes mellitus	519 (28.8)	286 (29.6)	233 (27.9)	0.31
Peripheral vascular disease	482 (26.8)	301 (31.2)	181 (21.7)	**<0.01**
History of ACS	775 (43.0)	471 (48.8)	304 (36.4)	**<0.01**
History of PCI	633 (35.1)	400 (41.4)	233 (27.9)	**<0.01**
History of CABG	208 (11.5)	169 (17.5)	39 (4.7)	**<0.01**
Prior stroke	293 (16.3)	157 (16.3)	136 (16.3)	0.99
Echocardiography				
LVEF (%)	57 [49–64]	55 [45–62]	59 [52–65]	**<0.01**
LVEDD (mm)	49 [43–55]	51 [45–57]	47 [41–52]	**<0.01**
AV mean (mmHg)	38.0 [29.0–47.9]	37.3 [28.0–47.0]	38.7 [29.0–48.7]	0.13
AV velocity (m/s)	4.0 [3.6–4.4]	4.0 [3.5–4.4]	4.1 [3.7–4.5]	**<0.01**
AVA (cm^2)	0.75 [0.60–0.90]	0.78 [0.64–0.90]	0.71 [0.60–0.86]	**<0.01**
AR > moderate	214 (13.2)	102 (11.6)	112 (15.0)	**0.04**
MR > moderate	327 (19.9)	157 (17.6)	170 (22.5)	**0.02**
TR > moderate	271 (16.6)	119 (13.6)	152 (20.1)	**<0.01**
MDCT				
Bicuspid	144 (8.0)	99 (10.2)	45 (5.3)	**<0.01**
Annulus area (mm^2)	462 [402–527]	512 [463–570]	405 [365–454]	**<0.01**
Annulus mean diameter (mm)	24.4 [22.8–26.0]	25.6 [24.4–27.1]	22.8 [21.7–24.1]	**<0.01**
Annulus perimeter (mm)	77.0 [71.9–82.3]	81.1 [77.2–85.5]	72.1 [68.6–76.2]	**<0.01**
LVOT mean diameter (mm)	23.8 [21.9–25.8]	25.1 [23.5–26.8]	22.2 [20.9–23.8]	**<0.01**
SOV mean diameter (mm)	32.6 [30.1–35.0]	34.2 [32.5–36.5]	30.4 [28.6–32.2]	**<0.01**
LCA height (mm)	13.0 [11.0–15.3]	14.0 [12.0–16.1]	12.1 [10.4–13.8]	**<0.01**
RCA height (mm)	17.0 [14.8–19.2]	18.1 [16.1–20.3]	15.6 [13.7–17.6]	**<0.01**
Agatston score	2088 [1218–3254]	2567 [1657–3913]	1615 [905–2484]	**<0.01**
NCC Agatston score	817 [443–1341]	993 [567–1543]	668 [352–1099]	**<0.01**
LCC Agatston score	571 [294–1006]	757 [394–1216]	414 [213–766]	**<0.01**
RCC Agatston score	583 [287–1001]	752 [412–1208]	437 [198–733]	**<0.01**
Indexed Agatston score	27.3 [16.2–41.7]	31.5 [20.5–47.7]	22.5 [12.8–34.0]	**<0.01**
Aortic valve calcium volume	823 [347–1916]	1046 [448–2451]	644 [247–1547]	**<0.01**
LVOT Agatston score >150	631 (38.9)	344 (39.4)	287 (38.3)	0.65
Procedural factors				
Pre-dilatation	547 (30.4)	306 (31.7)	241 (28.9)	0.20
Post-dilatation	360 (20.0)	189 (19.6)	171 (20.5)	0.62
Valve type				**<0.01**
BE	598 (33.2)	378 (39.1)	220 (26.3)	
SE	1203 (66.8)	588 (60.9)	615 (73.7)	
Procedural complications				
Valve embolization	17 (1.0)	7 (0.7)	10 (1.2)	0.31
Need for second valve	6 (0.5)	4 (0.6)	2 (0.4)	0.50

Continued

Table 1 Continued

	Total	Men	Women	*P*-value
PVL				0.63
None/trace	1104 (61.3)	583 (60.4)	521 (62.4)	
Mild	648 (36.0)	357 (37.0)	291 (34.9)	
Moderate	49 (2.7)	26 (2.7)	23 (2.8)	

STS, Society of Thoracic Surgeon's Predicted Risk of Mortality; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimensions; AV, aortic valve; AVA, aortic valve area; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; LVOT, left ventricular outflow tract; SOV, sinus of Valsalva; LCA, left-coronary artery; RCA, right-coronary artery; NCC, non-coronary cusp; LCC, left-coronary cusp; RCC, right-coronary cusp.

the severity of paravalvular leakage (PVL) post-TAVI.[8,9] More than mild, PVL has been associated with an increased risk of cardiovascular death, rehospitalizations, and reinterventions.[10]

Men are more prone to calcium deposition and higher calcium load in the aortic valve than women.[7] Men may have a higher incidence of significant PVL after TAVI than women.[11] Whether this is caused by the higher AVC load is uncertain. Therefore, the aim of this study is to investigate sex-specific associations between AVC load with PVL post-TAVI using contemporary transcatheter heart valves (THVs).

Methods

Study population

This registry included all patients who underwent a successful TAVI procedure with a balloon-expandable (BE) or self-expandable (SE) supra-annular functioning THV for severe AS between February 2014 and August 2021 in two tertiary care centres. Patients with a history of failing bioprosthesis were excluded (see Supplementary data online, *Figure S1*).

Patient eligibility for TAVI was as per multidisciplinary heart team consensus. A dedicated prospective database captured relevant patient demographics, medical history and comorbidities, electrocardiogram (ECG), transthoracic echocardiography (TTE), MDCT, and procedural and clinical outcome data. Exclusion criteria included prior aortic valve replacement, suboptimal MDCT quality to address calcium load and distribution, and suboptimal TTE images to assess PVL post-TAVI. All patients provided written consent for the TAVI procedure and use of anonymous individual data for research purposes. The study was conducted in accordance with the declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects Act as per Institutional Review Boards' review (MEC-2021-0349).

MDCT analysis

Contrast-enhanced cardiac MDCT studies were performed prior to the TAVI procedure. Imaging included an ECG-gated contrast-enhanced scan with multiple phases reconstructed during systole (at every 5% between 20% and 50% of the R-R interval). MDCT was analysed by three mensio structural heart package (Pie Medical Imaging, Maastricht, The Netherlands). The aortic valve and root were automatically reconstructed from the ECG-gated contrast scan. Dimensions of the aortic valve, left ventricular outflow tract (LVOT), and sinus of Valsalva were determined. Transcatheter valve oversizing was calculated relative to the annulus perimeter with the following formula: [(prosthesis perimeter/annulus perimeter) − 1] × 100.

Calcium quantification

The calcium scoring was determined on a prospectively ECG-triggered non-contrast-enhanced scan acquired at a time delay of 280 ms after the R-peak and reconstructed at a slice thickness of 3 mm or on a prospectively ECG-triggered contrast-enhanced scan. For the non-contrast-enhanced scan, a threshold of 130 Hounsfield units (HUs) was used to define calcifications and for the contrast-enhanced scans a minimum attenuation threshold of 650 HU was used. The density score was determined as follows: a weighting factor of 1 was assigned for an area of 130–199 HU with the non-contrast scan or 650–850 HU for the contrast scan, a factor 2 for an area of 200–299 HU or 850–1050 HU, factor 3 for an area of 300–399 HU or 1050–1250 HU, and factor 4 for an area of >400 HU or >1250 HU. The density score was multiplied by the area and the sum of all weighted areas in the region of interest generated the total Agatston score. The (two-way mixed) intraclass correlation coefficient (ICC) between the two methods (non-contrast vs. contrast) was 0.91 (95% confidence interval (CI) 0.78–0.97, $P < 0.01$).

The aortic valve region was defined as the aortic valve leaflets and the (virtual) annulus defined by the leaflet hinge points. The calcium volume and Agatston score were determined for the total aortic valve and for each leaflet separately. For the bicuspid aortic valves (BAVs) Sievers 1, we assumed three commissures and used the raphe to separate two cusps. For the BAV Sievers 0, we divided the valve into two leaflets and documented the leaflet-specific Agatston score based on the location of the ostium of the coronary arteries. To correct for the annulus size, an indexed Agatston score was calculated with the following formula: (Agatston score/annulus perimeter). Calcium volume was also determined in the LVOT. LVOT calcium was defined by an Agatston score of >150.

Clinical outcomes and event screening

The main endpoint was the amount of calcium in the aortic valve and the occurrence of PVL post-TAVI for men and women. PVL post-TAVI was assessed by TTE before discharge conform VARC3-criteria.[12]

Statistical analysis

Distribution of continuous variables was tested for normality with the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation or median (25th–75th percentile) and analysed with a student's *t*-test, Analysis of Variance (ANOVA), Mann Whitney U-, or Kruskal–Wallis-test as appropriate. Categorical variables were reported as percentage and compared with χ^2 or Fishers exact test. Receiver-operating characteristic (ROC) curves were generated to find the optimal cut-off values for moderate PVL based on the Agatston score (Youden index criteria). Additional analysis of moderate PVL predictors was assessed by multivariate analysis, using backward-stepwise logistic regression. The following parameters were included in the model: annulus area, Agatston score, LVOT calcification, valve oversizing, and valve platform. A

Table 2 Baseline characteristics as per PVL grade

	Total cohort			Men			Women		
	≤ Mild PVL	Moderate PVL	*P*-value	≤ Mild PVL	Moderate PVL	*P*-value	≤ Mild PVL	Moderate PVL	*P*-value
n									
Age	81.7 [77.5–85.3]	81.7 [77.0–87.5]	0.41	81.2 [76.5–84.5]	81.6 [77.0–85.6]	0.51	82.4 [78.2–85.9]	83.0 [76.7–88.3]	0.58
BMI	26.2 [23.6–29.6]	24.7 [23.0–28.5]	0.09	26.2 [24.1–29.2]	25.1 [23.4–29.1]	0.47	26.1 [23.1–30.1]	24.4 [21.5–28.0]	0.09
STS	3.4 [2.2–5.3]	3.6 [2.3–7.6]	0.26	3.0 [1.9–4.6]	2.9 [1.7–4.5]	0.9	4.0 [2.7–6.1]	5.2 [2.9–12.1]	0.06
Medical history									
Hypertension	1446 (82.5)	36 (73.5)	0.1	769 (81.8)	20 (76.9)	0.53	677 (83.4)	16 (69.6)	0.08
Diabetes mellitus	511 (29.2)	8 (16.3)	0.21	283 (30.1)	3 (11.5)	0.22	228 (28.1)	5 (21.7)	0.44
PVD	469 (26.8)	13 (26.5)	0.97	293 (31.2)	8 (30.8)	0.97	176 (21.7)	5 (21.7)	0.99
History of ACS	757 (43.2)	18 (36.7)	0.37	462 (49.1)	9 (34.6)	0.14	295 (36.3)	9 (39.1)	0.78
History of PCI	623 (35.6)	10 (20.4)	**0.03**	394 (41.9)	6 (23.1)	0.05	229 (28.2)	4 (17.4)	0.25
History of CABG	204 (11.6)	4 (8.2)	0.45	166 (17.7)	3 (11.5)	0.42	38 (4.7)	1 (4.3)	0.94
Prior stroke	282 (16.1)	11 (22.4)	0.24	151 (16.1)	6 (23.1)	0.34	131 (16.1)	5 (21.7)	0.47
Echocardiography									
LVEF (%)	57 [50–64]	58 [45–66]	0.99	55 [45–62]	58 [45–66]	0.38	59 [53–65]	55 [44–67]	0.33
LVEDD (mm)	49 [43–55]	48 [44–54]	0.91	51 [45–57]	50 [45–55]	0.76	47 [41–52]	47 [40–53]	0.99
AV mean (mmHg)	38 [29–47]	44 [34–57]	**0.01**	37 [28–47]	44 [33–58]	0.06	39 [29–48]	40 [34–56]	0.11
AV velocity (m/s)	4.0 [3.6–4.4]	4.2 [3.7–5.0]	0.18	4.0 [3.5–4.4]	4.0 [3.4–4.9]	0.46	4.1 [3.6–4.5]	4.4 [3.7–5.0]	0.22
AVA (cm^2)	0.75 [0.60–0.90]	0.65 [0.50–0.80]	**<0.01**	0.78 [0.64–0.90]	0.76 [0.63–0.90]	0.6	0.71 [0.60–0.87]	0.52 [0.47–0.68]	**<0.01**
AR > moderate	201 (12.7)	13 (28.3)	**<0.01**	97 (11.4)	5 (19.2)	0.22	104 (14.3)	8 (40.0)	**<0.01**
MR > moderate	314 (19.6)	13 (28.3)	0.15	151 (17.5)	6 (23.1)	0.46	163 (22.1)	7 (35.0)	0.17
TR > moderate	257 (16.2)	14 (30.4)	**0.01**	114 (13.4)	5 (19.2)	0.39	143 (19.5)	9 (45.0)	**<0.01**
MDCT									
Bicuspid	139 (7.9)	5 (10.2)	0.56	96 (10.2)	3 (11.5)	0.83	43 (5.3)	2 (8.7)	0.48
Annulus area (mm^2)	461 [401–526]	494 [435–564]	**0.01**	511 [462–568]	555 [499–606]	**<0.01**	405 [365–454]	435 [394–482]	0.15
Annulus mean diameter (mm)	24.3 [22.7–26.0]	25.3 [23.4–27.3]	**0.01**	25.6 [24.3–27.1]	26.7 [25.5–28.4]	**<0.01**	22.8 [21.7–24.1]	23.3 [22.6–24.7]	0.16
Annulus perimeter (mm)	77.0 [71.9–82.2]	79.2 [73.9–85.3]	**0.046**	81.0 [77.1–85.4]	84.6 [79.8–87.2]	0.02	72.0 [68.5–76.2]	74.2 [71.5–76.7]	0.15
LVOT mean diameter (mm)	23.7 [21.9–25.8]	24.4 [23.0–25.9]	0.1	25.1 [23.4–26.8]	25.3 [24.4–27.8]	0.13	22.2 [20.9–23.8]	22.9 [21.3–24.3]	0.27
SOV mean diameter (mm)	32.5 [30.1–34.9]	33.4 [30.5–36.7]	0.058	34.2 [32.4–36.5]	35.3 [33.4–37.3]	**0.048**	30.4 [28.5–32.1]	30.5 [29.4–33.1]	0.19
Annulus area (mm^2)	13.0 [11.0–15.3]	12.1 [10.4–14.4]	0.15	14.1 [12.0–16.2]	12.1 [10.3–13.5]	**<0.01**	12.1 [10.3–13.8]	12.4 [10.7–15.6]	0.15
Annulus mean diameter (mm)	17.0 [14.8–19.3]	17.0 [14.5–18.9]	0.69	18.1 [16.1–20.3]	18.1 [16.7–20.6]	0.76	15.6 [13.8–17.6]	14.8 [12.0–17.3]	0.28
Agatston score	2065 [1197–3194]	4342 [2406–5472]	**<0.01**	2544 [1635–3815]	4629 [3500–5547]	**<0.01**	1581 [880–2427]	3025 [1929–5453]	**<0.01**
Indexed Agatston score	26.8 [16.0–41.0]	51.5 [32.8–64.5]	**<0.01**	31.2 [20.2–46.3]	53.5 [41.5–64.1]	**<0.01**	21.9 [12.6–33.3]	45.0 [28.4–76.1]	**<0.01**
Aortic valve calcium volume	806 [342–1892]	1459 [786–3383]	**<0.01**	1018 [446–2434]	1818 [982–3742]	**<0.01**	629 [239–1529]	1363 [591–2033]	**<0.01**
LVOT Agatston score >150	601 (38.1)	30 (66.7)	**<0.01**	329 (38.7)	15 (62.5)	0.02	272 (37.3)	15 (71.4)	**<0.01**

Continued

Table 2 Continued

	Total cohort			Men			Women		
	≤ Mild PVL	Moderate PVL	*P*-value	≤ Mild PVL	Moderate PVL	*P*-value	≤ Mild PVL	Moderate PVL	*P*-value
Procedural factors									
Pre-dilatation	527 (30.1)	20 (40.8)	0.11	296 (31.5)	10 (38.5)	0.45	231 (28.4)	10 (43.5)	0.12
Post-dilatation	337 (19.2)	23 (46.9)	**<0.01**	177 (18.8)	12 (46.2)	**<0.01**	160 (19.7)	11 (47.8)	**<0.01**
Valve type			**<0.01**			**<0.01**			0.14
BE	594 (99.3)	4 (0.7)		377 (99.7)	1 (0.3)		217 (98.6)	3 (1.4)	
SE	1158 (96.3)	45 (3.7)		563 (95.7)	25 (4.3)		595 (96.7)	20 (3.3)	
Oversizing									
BE	3.4 [0.6–6.8]	−0.9 [−3.6–0.1]	**<0.01**	3.1 [0.4–6.1]	NA		4.0 [0.8–7.2]	−0.6 [−0.9–−0.1]	**0.03**
SE	19.8 [15.5–23.5]	15.7 [13.2–22.7]	**0.02**	19.9 [15.3–24.5]	15.7 [13.7–24.9]	0.18	19.6 [15.7–22.8]	15.5 [11.2–22.1]	**0.04**

STS, Society of Thoracic Surgeon's Predicted Risk of Mortality; ACS, acute coronary syndrome; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimensions; AV, aortic valve; AVA, aortic valve area; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; LVOT, left ventricular outflow tract; SOV, sinus of Valsalva; LCA, left-coronary artery; RCA, right-coronary artery; NCC, non-coronary cusp; LCC, left-coronary cusp; RCC, right-coronary cusp; NA, not applicable.

P-value < 0.10 was pre-defined as the cut-off for inclusion of the univariate parameters into the multivariate logistic regression model. This model was further evaluated using c-statistics of the ROC curve. The interaction effect for gender was evaluated for the univariable predictors. A two-sided *P*-value < 0.05 was considered statistically significant. All statistics were performed with SPSS software version 25.0 (SPSS, Chicago, IL, USA).

Results

Study population

This study included 1801 patients [median age 81.7 years (25th–75th percentile 77.5–85.3), 54% male and the median Society of Thoracic Surgeon's Predicted Risk of Mortality (STS-PROM) was 3.4% (25th–75th percentile 2.2–5.4)]. TAVI was performed using either the BE Sapien 3 (Edwards Lifesciences, Irvine, CA) (33%) or the SE Evolut R and Pro (Medtronic, Minneapolis, MN) (67%). *Table 1* shows the differences between men and women. Men, compared to women, were younger [81.2 years (25th–75th percentile 76.5–84.5) vs. 82.4 years (78.2–85.9), $P \leq 0.01$], had a lower STS-PROM score [3.0% (25th–75th percentile 1.9–4.6) vs. 4.0% (25th–75th percentile 2.7–6.2), $P < 0.01$], and had more often peripheral vascular disease (31% vs. 22%, $P < 0.01$). Women had a higher left ventricular ejection fraction [59% (25th–75th percentile 52–65) vs. 55% (25th–75th percentile 45–62), $P < 0.01$]. Men had a larger aortic valve annulus area [512 mm^2 (25th–75th percentile 463–570) vs. 405 mm^2 (365–454), $P < 0.01$] and higher Agatston score [2567 (25th–75th percentile 1657–3913) vs. 1615 (25th–75th percentile 905–2484), $P < 0.01$] than women. The indexed Agatston score remained higher after adjustment for the annulus perimeter [31.5 (25th–75th percentile 20.5–47.7) vs. 22.5 (25th–75th percentile 12.8–34.0), $P < 0.01$]. The distribution of calcium was similar for men and women with the highest Agatston score in the non-coronary cusp. Supplementary data online, *Table S1*, depicts the differences between the BE and SE THV cohorts.

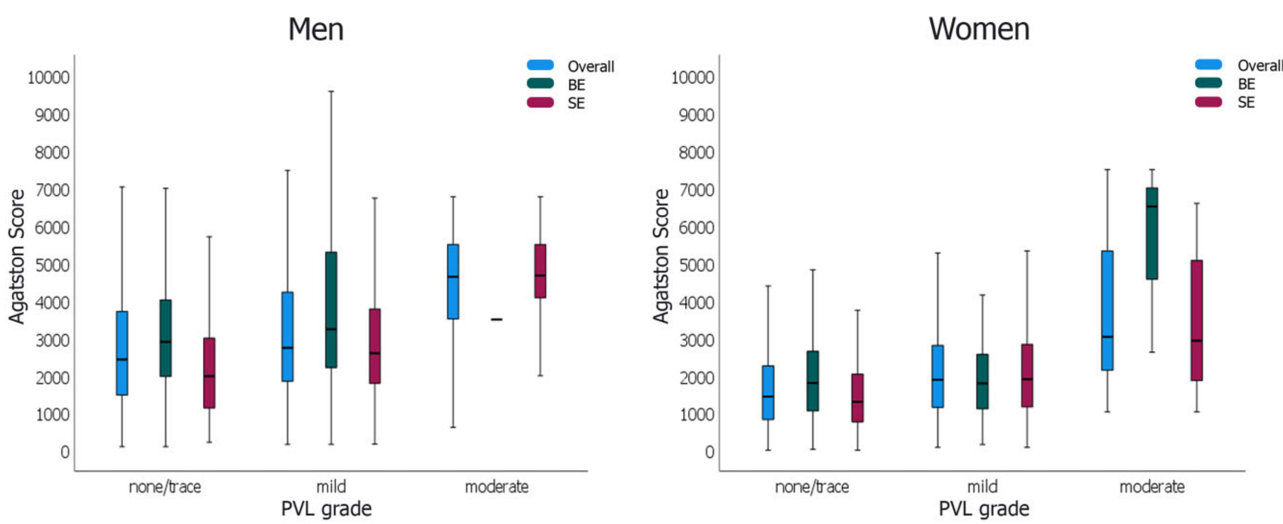
PVL

In total, 1104 patients (61%) had no or trace PVL, 648 (36%) mild PVL, and 49 patients (3%) moderate PVL post-TAVI. There was no difference in the occurrence of moderate PVL between men and women (3% vs. 3%, $P = 0.63$). *Table 2* displays the characteristics in patients with and without moderate PVL. In the entire cohort, patients with moderate PVL had a larger aortic valve annulus area [494 mm^2 (25th–75th percentile 435–564) vs. 461 mm^2 (25th–75th percentile 401–526), $P = 0.01$] and the presence of calcium in the LVOT (67% vs. 38%, $P < 0.01$). The annulus area was also significantly larger in male patients with moderate PVL [555 mm^2 (25th–75th percentile 499–606), vs. 511 mm^2 (25th–75th percentile 462–568), $P = 0.01$], but not in female patients with moderate PVL [435 mm^2 (25th–75th percentile 394–482) vs. 405 mm^2 (25th–75th percentile 365–454), $P = 0.15$]. LVOT calcium was more common in men (63% vs. 39%, $P = 0.02$) and in women with moderate PVL (71% vs. 37%, $P < 0.01$).

Moderate PVL occurred more in patients receiving an SE THV, compared to those receiving a BE THV (3.7% vs. 0.7%, $P < 0.01$). We noted sex-specific differences in moderate PVL with the SE THV (none/trace 52%, mild 44%, and moderate PVL 4% in men vs. 59%, 38%, and 3% in women, $P = 0.04$) but not with BE THV (none/trace 74.1%, mild 25.7%, and moderate 0.3% in men vs. 72.7%, 25.9%, and 1.4% in women, $P = 0.28$) (see Supplementary data online, *Table S2*).

Agatston score

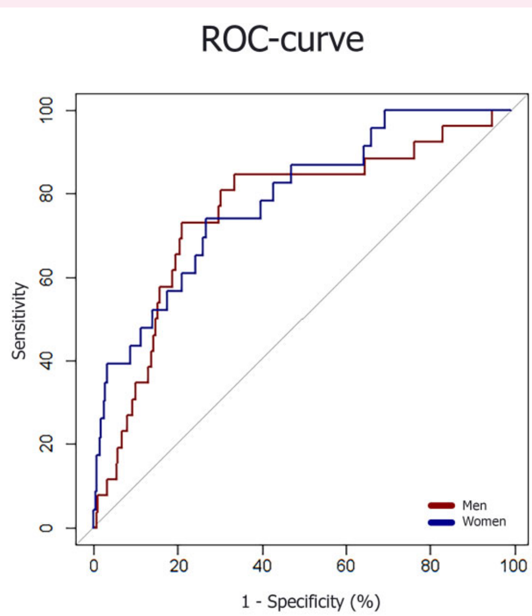
The median Agatston score was significantly higher in patients with an increased PVL grade in both male [none-trace 2420 (25th–75th percentile 1472–3702) vs. mild 2730 (25th–75th percentile 1835–4226) vs. moderate 4629 (25th–75th percentile 3500–5547), $P < 0.01$] and



	None/Trace	Mild	Moderate	P-Value
Overall	2420 [1472 - 3702]	2730 [1835 - 4226]	4629 [3500 - 5547]	<0.01
BE	2892 [1962 - 4011]	3227 [2167 - 5305]		0.11
SE	1976 [1124 - 2998]	2587 [1187 - 3771]	4664 [3788 - 5603]	<0.01

	None/Trace	Mild	Moderate	P-Value
Overall	1431 [818 - 2253]	1882 [1139 - 2825]	3025 [1929 - 5453]	<0.01
BE	1795 [1040 - 2643]	1783 [1034 - 2769]	6505 [4561 - 6998]	0.049
SE	1293 [757 - 2038]	1897 [1152 - 2842]	2923 [1825 - 5124]	<0.01

Figure 1 Agatston scores men vs. women. Agatston scores per grade PVL.



	AUC	Cut-off	Specificity	Sensitivity	Accuracy
Men	0.76 [0.66 - 0.86]	4070	0.79	0.73	0.79
Women	0.78 [0.69 - 0.88]	2341	0.73	0.74	0.73

Figure 2 ROC curves men vs. women. ROC curves to predict moderate PVL. Cut-off values calculated with the Youden index.

female patients [none-trace 1431 (25th–75th percentile 818–2253) vs. mild 1882 (25th–75th percentile 1139–2825), vs. moderate 3025 (25th–75th percentile 1929–5453), $P < 0.01$]. This trend was visible in men and women regardless of THV platform (*Figure 1*). *Figure 2* shows the ROC curves with the Agatston score as predictor for moderate PVL for males [area under the curve (AUC) 0.76 (95% CI 0.66–0.86)] and females [AUC 0.78 (95% CI 0.69–0.88)]. The cut-off value to predict moderate PVL by Agatston score in men was 4070 (sensitivity 73%, specificity 79%) and 2341 (sensitivity 74%, specificity 73%) in women. *Figure 3* illustrates MDCT and TTE images of patients with no and moderate PVL.

Multivariable analysis

Predictors for moderate PVL post-TAVI are depicted in *Table 3*. A larger annulus area [odds ratio (OR) 1.59 (95% CI 1.12–2.26), $P < 0.01$], Agatston score [OR 6.31 (95% CI 3.19–12.49), $P < 0.01$], LVOT calcium [OR 2.02 (95% CI 1.04–3.92) $P = 0.04$], and use of a SE THV [OR 8.00 (95% CI 2.57–24.90), $P < 0.01$] were associated with moderate PVL. ROC curve analysis with the predicted probabilities of the logistic regression model revealed a c-statistic of 0.82 [(95% CI 0.75–0.88), $P < 0.01$]. There was no significant difference in predictors between men and women, based on the interaction effects (see Supplementary data online, *Figure S2*).

Discussion

This study investigated the differences in AVC load between men and women with severe AS and the effect on PVL post-TAVI. The main findings are: (1) the AVC load was significantly higher in men than women, (2) there was no difference in PVL between men and women, and (3) the amount of AVC was a dominant predictor for PVL post-TAVI in

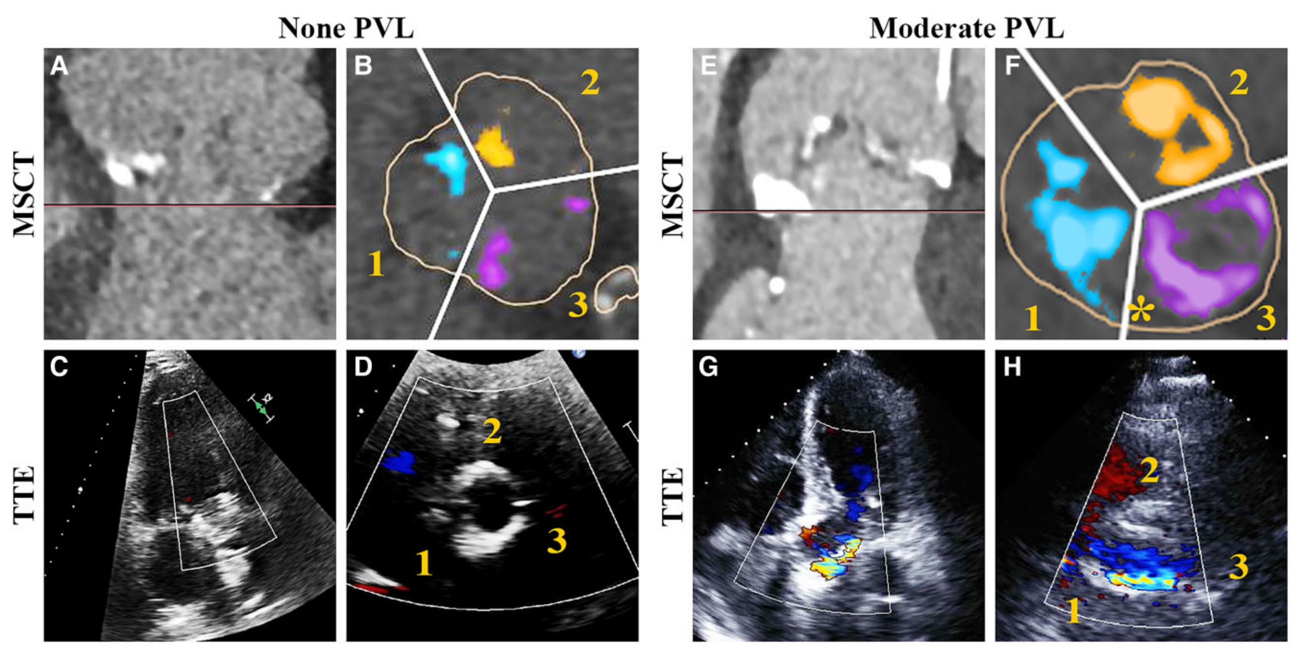


Figure 3 Graphical overview. Graphical illustration of MDCT and corresponding TTE post-TAVI. (*A and B*) MDCT of a patient with a mild-moderately calcified aortic valve. (*C and D*) TTE post-TAVI, showing no PVL. (*E and F*) MDCT of a patient with a severely calcified aortic valve. (*G and H*) TTE with a moderate-severe PVL. * corresponds with the location of the PVL. 1 = non-coronary cusp, 2 = right-coronary cusp, 3 = left-coronary cusp.

Table 3 Multivariable analysis to predict PVL

	Univariable		Multivariable	
	OR [95%CI]	***P*-Value**	**OR [95%CI]**	***P*-Value**
Annulus area (mm^2)	1.44 [1.07–1.95]	**0.02**	1.59 [1.12–2.26]	**<0.01**
Agatston score (cut-off)	8.78 [4.61–16.72]	**<0.01**	6.31 [3.19–12.49]	**<0.01**
Agatston score LVOT > 150	3.26 [1.74–6.1]	**<0.01**	2.02 [1.04–3.92]	**0.04**
Valve oversizing	1.03 [1.006–1.05]	**0.01**	1.00 [0.98–1.03]	0.78
Valve platform				
SE vs. BE	5.78 [2.07–16.12]	**<0.01**	8.00 [2.57–24.90]	**<0.01**

Multivariable analysis to predict PVL with logistic regression. The cut-off was the measured cut-off to predict PVL based on the ROC curves. PVL, paravalvular leakage; LVOT, left ventricular outflow tract; CI, confidence interval.

men and women, with higher Agatston thresholds for men than women.

In our study, men were younger, had more peripheral vascular disease, coronary artery disease, lower left ventricular ejection fraction, more often BAV, and a larger aortic annulus area compared to women. We found a higher AVC load in men than in women, also when the Agatston score was corrected for the annulus perimeter. Calcium distribution was similar in men and women with most calcium in the non-coronary cusp. We did not find a significant difference in the occurrence of >mild PVL between men and women. Calcium extent correlated with PVL in men and women. AVC was the strongest predictor for moderate PVL by multivariable analysis, after THV platform. A calcium load double to what is considered the threshold to denote severe AS identified a higher risk for more than mild PVL although the incidence of moderate PVL was relatively low (3%). Different cut-off points were identified for men and women with similar sensitivity and specificity. An Agatston score of >4070 in male patients and of >2341 in female patients was associated with an increased risk for >mild PVL.

Of note, the correlation between PVL grade and the amount of calcium was more pronounced in men and women receiving a SE THV as both men and women receiving a BE THV had a higher Agatston score and yet a lower incidence of >mild PVL. The frequency of >mild PVL was in line with what is reported for both THV platforms in the literature.[13,14] Our data suggest that in our contemporary clinical practice, THV selection is at least partially determined by AVC. More AVC triggered a preference for BE THV because of its higher radial force. Valve selection may also partly explain the fact that there was no significant difference in the occurrence of >mild PVL between men and women because more BE THV was used in men. Valve specific analysis showed that there was no difference in the prevalence of >mild PVL in patients receiving a BE THV, despite the significant difference in AVC load. However, in patients receiving an SE THV, the occurrence of mild and moderate PVL was higher in men, compared to women. In earlier studies, >mild PVL occurred more in men compared to women, suggesting that a higher AVC resulted in more PVL.[11,15,16] CT-derived computer simulations in these patients may predict amount and location of PVL after TAVI based on size, implant depth, and THV platform selection.[17,18]

Limitations

This study is a retrospective study with inherent limitations, including significant THV selection bias. THV selection was as per operator's discretion based on annulus size and calcifications and ilio-femoral artery appearance that was not controlled for. There was no independent corelab to assess MDCT and echocardiography imaging and both centres used a different methodology to assess the calcium load. However, the ICC between the two modalities was 0.91.

Conclusion

AVC is a strong predictor for moderate PVL post-TAVI. Although the AVC load in men is higher compared to women, there is no difference in the incidence of moderate PVL. Sex-specific Agatston score cut-offs to predict moderate PVL were almost double as high in men vs. women.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM *et al.* Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;**62**:1002–12.
2. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 2011;**8**:162–72.
3. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE *et al.* Clinical factors associated with calcific aortic valve disease. Cardiovascular health study. *J Am Coll Cardiol* 1997;**29**:630–4.
4. Back M, Larsson SC. Risk factors for aortic stenosis. *J Cardiol Pract* 2020;**18**(11).
5. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F *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**:721–6.
6. Cahill TJ, Chen M, Hayashida K, Latib A, Modine T, Piazza N *et al.* Transcatheter aortic valve implantation: current status and future perspectives. *Eur Heart J* 2018;**39**:2625–34.
7. Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cueff C, Malouf J, Araoz PA *et al.* Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. *Circ Cardiovasc Imaging* 2013;**6**:40–7.
8. Di Martino LFM, Soliman OII, Van Gils L, Vletter WB, Van Mieghem NM, Ren B *et al.* Relation between calcium burden, echocardiographic stent frame eccentricity and paravalvular leakage after corevalve transcatheter aortic valve implantation. *Eur Heart J* 2017;**18**:648–53.
9. Fujita B, Kutting M, Seiffert M, Scholtz S, Egron S, Prashovikj E *et al.* Calcium distribution patterns of the aortic valve as a risk factor for the need of permanent pacemaker implantation after transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1385–93.
10. Chau KH, Chen S, Crowley A, Redfors B, Li D, Hahn RT *et al.* Paravalvular regurgitation post-transcatheter aortic valve replacement in intermediate risk patients: a pooled PARTNER 2 study. *EuroIntervention* 2021;**17**:1053–60.
11. Van Mieghem NM, Reardon MJ, Yakubov SJ, Heiser J, Merhi W, Windecker S *et al.* Clinical outcomes of TAVI or SAVR in men and women with aortic stenosis at intermediate operative risk: a post hoc analysis of the randomised SURTAVI trial. *EuroIntervention* 2020;**16**:833–41.
12. VARC-3 WRITING COMMITTEE, Genereux P, Piazza N, Alu MC, Nazif T, Hahn RT *et al.* Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol* 2021;**77**:2717–46.
13. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M *et al.* Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;**380**:1695–705.
14. Manoharan G, Grube E, Van Mieghem NM, Brecker S, Fiorina C, Kornowski R *et al.* Thirty-day clinical outcomes of the evolut PRO self-expanding transcatheter aortic valve: the international FORWARD PRO study. *EuroIntervention* 2020;**16**:850–7.
15. Kodali S, Williams MR, Doshi D, Hahn RT, Humphries KH, Nkomo VT *et al.* Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. *Ann Intern Med* 2016;**164**:377–84.
16. Szerlip M, Gualano S, Holper E, Squiers JJ, White JM, Doshi D *et al.* Sex-specific outcomes of transcatheter aortic valve replacement with the SAPIEN 3 valve: insights from the PARTNER II S3 high-risk and intermediate-risk cohorts. *JACC Cardiovasc Interv* 2018;**11**:13–20.
17. de Jaegere P, De Santis G, Rodriguez-Olivares R, Bosmans J, Bruining N, Dezutter T *et al.* Patient-specific computer modeling to predict aortic regurgitation after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2016;**9**:508–12.
18. Dowling C, Gooley R, McCormick L, Firoozi S, Brecker SJ. Patient-specific computer simulation to predict long-term outcomes after transcatheter aortic valve replacement. *J Cardiovasc Comput Tomogr* 2021;**16**(3):254–61.