

# Severe AS With Low Valve Calcium Score: Different Prognosis?

Yeonwoo Choi, MD

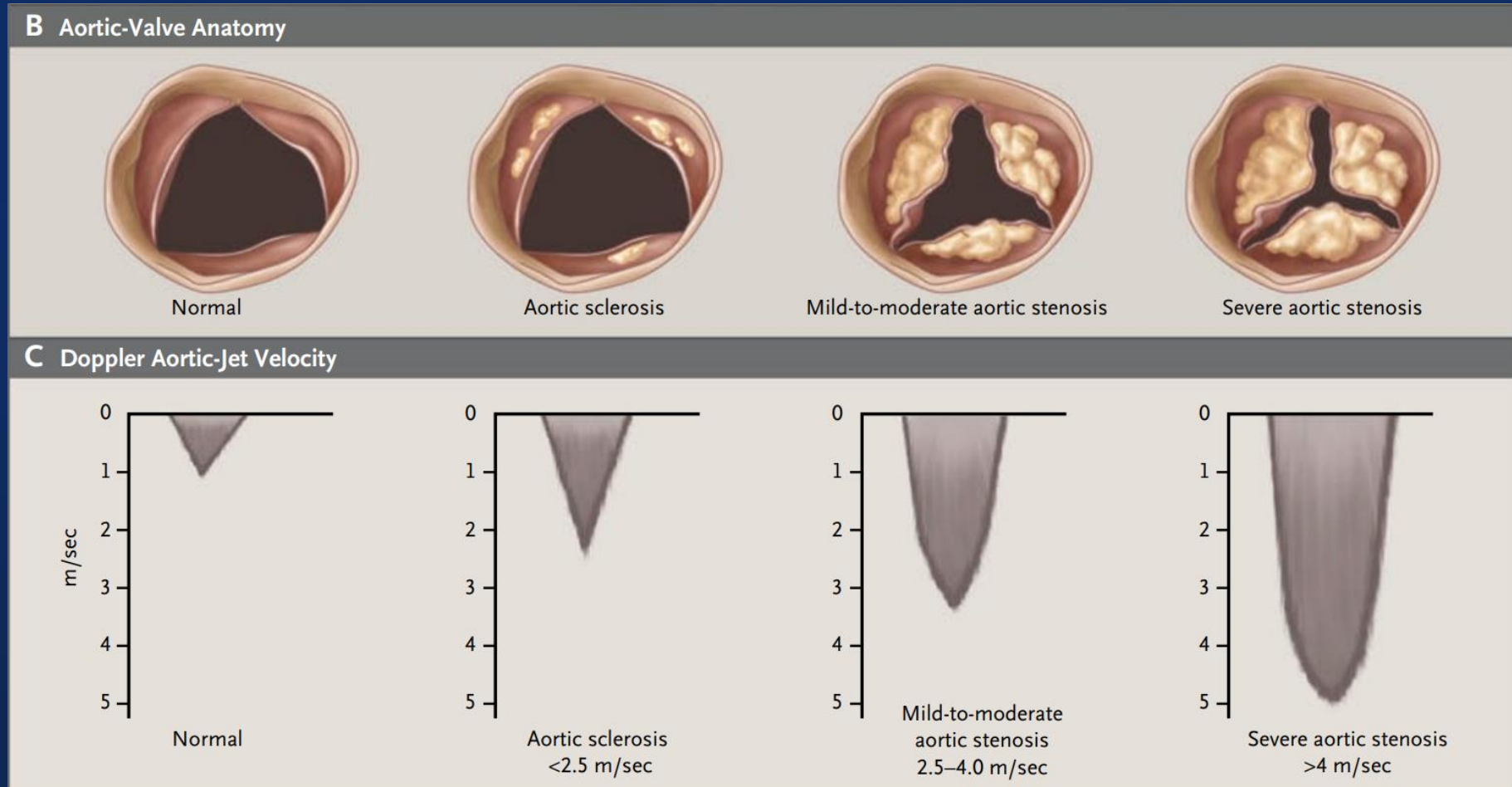
Hanyang University, Changwon Hanmaeum Hospital,  
South Korea

# Disclosure

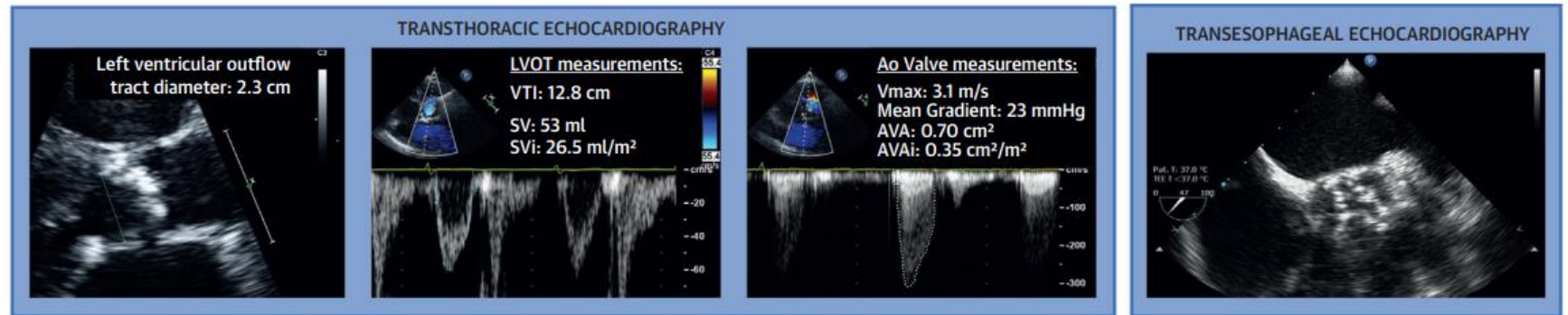
- I, Yeonwoo Choi, have NO conflict of interest related to this presentation

# Introduction

- Degenerative aortic valve stenosis is characterised by excessive valvular calcification



# Introduction



Symptomatic 84-year-old man with low-flow low-gradient aortic stenosis – Preserved Ejection Fraction – Unknown stenosis severity

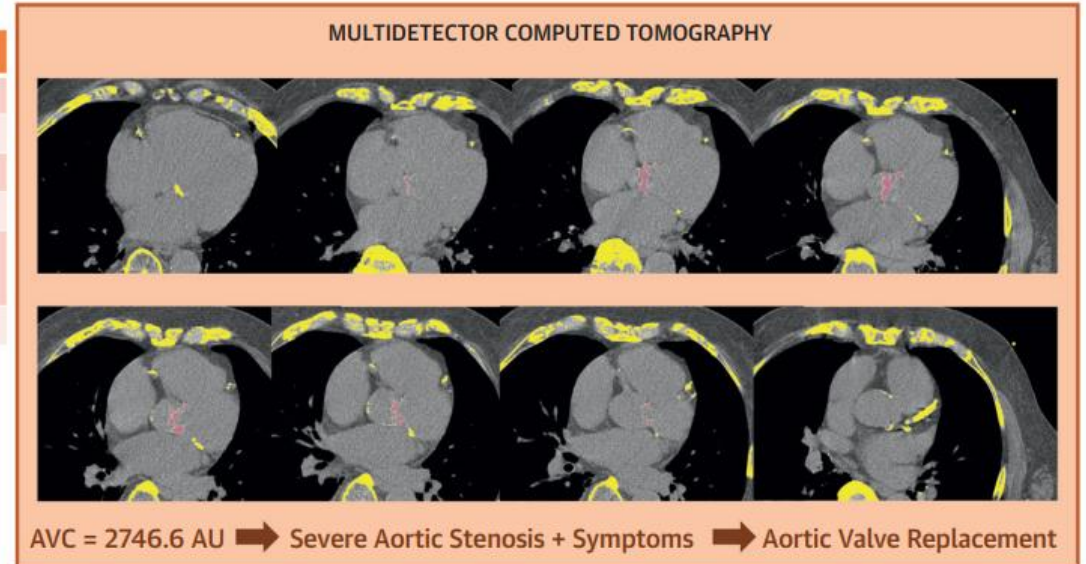
Aortic valve calcium  
(AVC) score

♀ > 1300

♂ > 2000

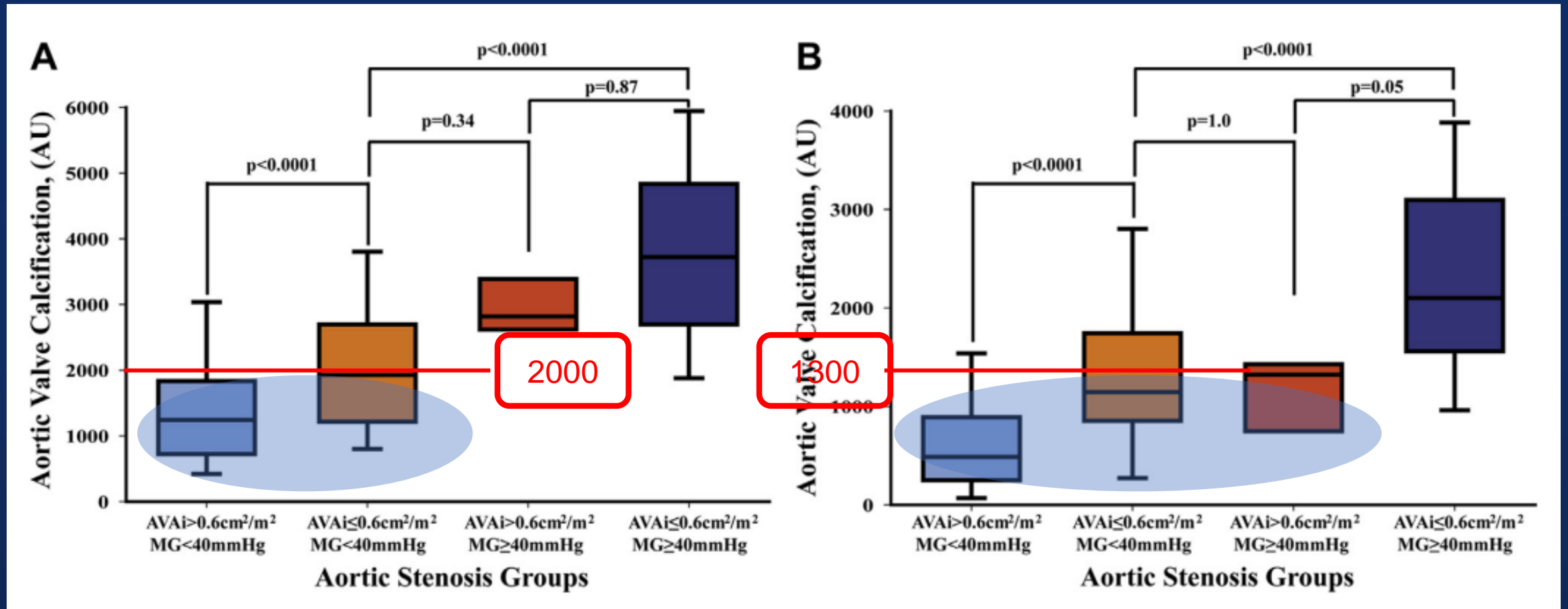
	Computed Tomography Scan protocol
kV	120-140
mAs	30-80 according to patient body weight
Acquisition	Spiral or volumetric
Pitch	0.15-0.25 according to scanner
Reconstruction placement on R-R interval	60%-80%
Slice Thickness	3 mm

	Rounded threshold identifying severe aortic stenosis
Women	AVC >1,300 AU
Men	AVC >2,000 AU

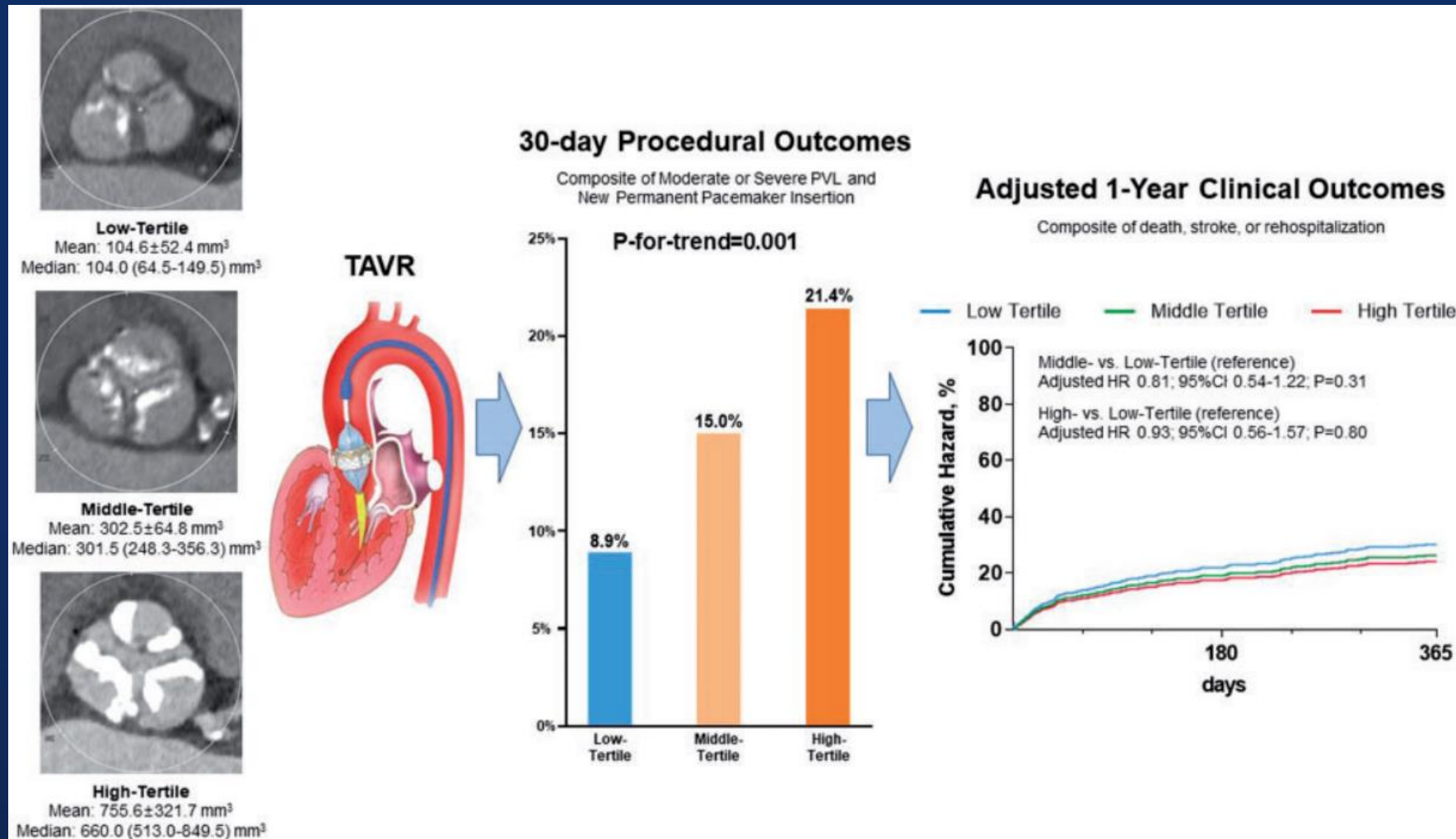


Pawade, T. et al. J Am Coll Cardiol Img. 2019;12(9):1835-48.

# Introduction



# Introduction



# Methods

## ■ ASAN-AVR Registry

- Prospective, single-center, real-world registry
  - All consecutive patients who had undergone surgical or transcatheter AVR
- 
- Patients
    - Duration : July 2010 ~ December 2019
    - A total of 1002 patients with symptomatic degenerative AS who underwent AVR with or without concomitant percutaneous or surgical coronary revascularization
    - Exclusion criteria : AV Vmax <4.0m/s, concomitant procedures such as aorta replacement, other valvular surgery, atrial ablation, and bicuspid or rheumatic disease

# Methods

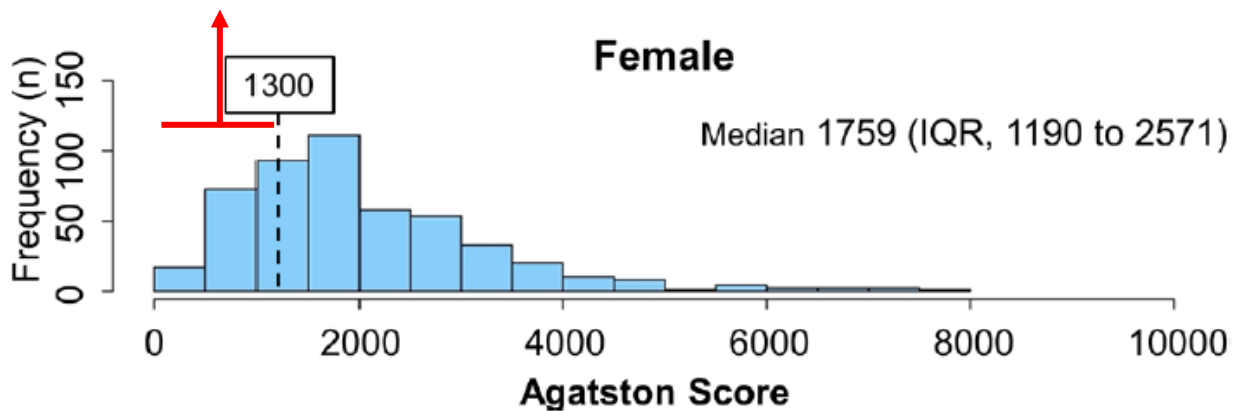
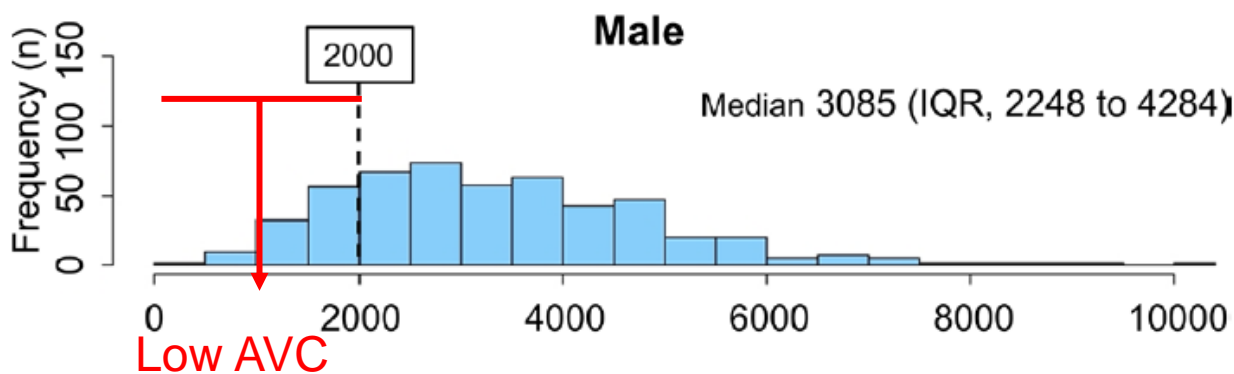
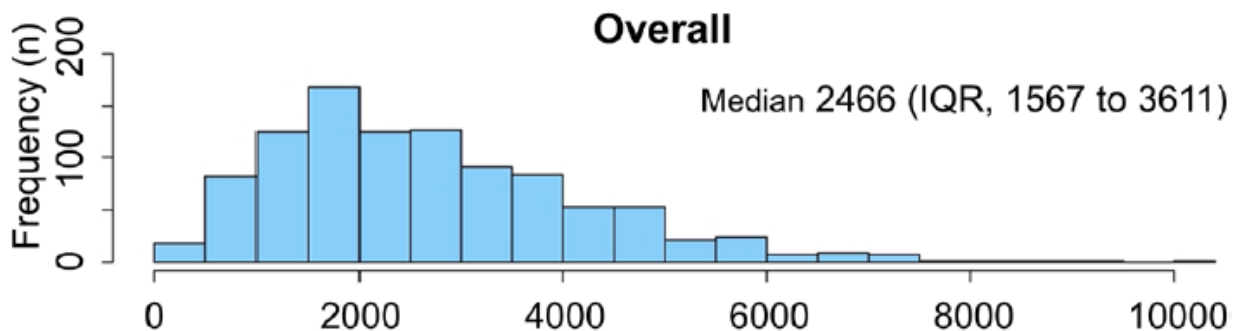
- AVC measurement
  - Electrocardiogram-gated multi-slice CT angiography before AVR
  - Calcium detection set at 130 Hounsfield Units and 3-mm slice thickness
- Aortic valve calcium (AVC) score
  - Male <2000AU and female <1300 AU → Low AVC



# Methods

- Endpoint
  - Primary outcome : death from any cause
    - Death; CV death or Non-cardiac death
    - Myocardial infarction
    - Stroke
    - MACE; composite of death from any cause and MI, stroke
  - Median f/u : 3.8 years
  - Low AVC vs High ACV

# Results



# Results

**Table 1** Clinical characteristics

Characteristics	Low AVC (N=242)	High AVC (N=760)	P value
Age (years)	73.5±8.7	76.3±7.5	<0.001
Female sex	144 (59.5%)	343 (45.1%)	<0.001
Body mass index (kg/m <sup>2</sup> )	25.0±3.4	24.7±3.6	0.31
Hypertension	187 (77.3%)	600 (78.9%)	0.64
Diabetes mellitus	96 (39.7%)	306 (40.3%)	0.93
Dyslipidaemia	169 (69.8%)	548 (72.1%)	0.55
Smoking	18 (7.4%)	66 (8.7%)	0.63
Atrial fibrillation or flutter	31 (12.8%)	80 (10.5%)	0.39
Peripheral artery disease	7 (2.9%)	23 (3.0%)	>0.99
Previous PCI	42 (17.4%)	142 (18.7%)	0.71
Previous congestive heart failure	22 (9.1%)	78 (10.3%)	0.68
Previous myocardial infarction	6 (2.5%)	20 (2.6%)	>0.99
Previous cerebrovascular accident	31 (12.8%)	85 (11.2%)	0.57
CKD*	63 (26.0%)	176 (23.2%)	0.41
CKD stage 3	45 (18.6%)	147 (19.3%)	
CKD stage 4	5 (2.1%)	15 (2.0%)	
CKD stage 5	13 (5.4%)	14 (1.8%)	
Dialysis	13 (5.4%)	14 (1.8%)	0.006

# Results

**Table 1** Clinical characteristics

Characteristics	Low AVC (N=242)	High AVC (N=760)	P value
CKD*	63 (26.0%)	176 (23.2%)	0.41
CKD stage 3	45 (18.6%)	147 (19.3%)	
CKD stage 4	5 (2.1%)	15 (2.0%)	
CKD stage 5	13 (5.4%)	14 (1.8%)	
Dialysis	13 (5.4%)	14 (1.8%)	0.006
Previous CABG	2 (0.8%)	6 (0.8%)	>0.99
AVR			0.009
SAVR	150 (62.0%)	396 (52.1%)	
TAVR	92 (38.0%)	364 (47.9%)	
Concomitant revascularisation	26 (10.7%)	70 (9.2%)	0.56
Aortic valve calcium score			
All patients	1118 (810 to 1463)	2935 (2143 to 396)	<0.001
Male patients	1566 (1241–1807)	3562 (2824–4551)	<0.001
Female patients	925 (679–1125)	2191 (1704–2959)	<0.001

# Results

**Table 2** Echocardiographic variables

Characteristics	Low AVC (N=242)	High AVC (N=760)	P value
Aortic valve peak velocity (m/s)	4.6±0.5	5.1±0.7	<0.001
Aortic valve peak pressure gradient (mm Hg)	84.6±20.1	107.4±30.0	<0.001
Aortic valve mean pressure gradient (mm Hg)	49.1±13.1	64.7±18.9	<0.001
Aortic valve area (cm <sup>2</sup> )	0.69±0.16	0.59±0.14	<0.001
AR grade ≥moderate grade			0.012
Moderate	36 (14.9)	129 (17.0)	
Severe	7 (2.9)	40 (5.3)	
End diastolic volume (mL/m <sup>2</sup> )	105.9±43.8	110.3±41.9	0.16
End systolic volume (mL/m <sup>2</sup> )	43.9±29.6	47.4±29.5	0.11
Stroke volume (mL/m <sup>2</sup> )	38.4±13.4	38.2±12.3	0.86
LV ejection fraction (%)	60.6±9.5	59.0±10.4	0.035
LV mass (g/m <sup>2</sup> )	119.4±29.5	138.0±37.0	<0.001
LVH*	161 (66.5)	611 (80.4)	<0.001

Values are means±SD, n (%).

\*LVH is defined as a left ventricular mass indexed to a body surface area of >115 g/m<sup>2</sup> for men and >95 g/m<sup>2</sup> for women.

AR, aortic valve regurgitation; AVC, aortic valve calcification; LV, left ventricle; LVH, left ventricular hypertrophy.

# Results

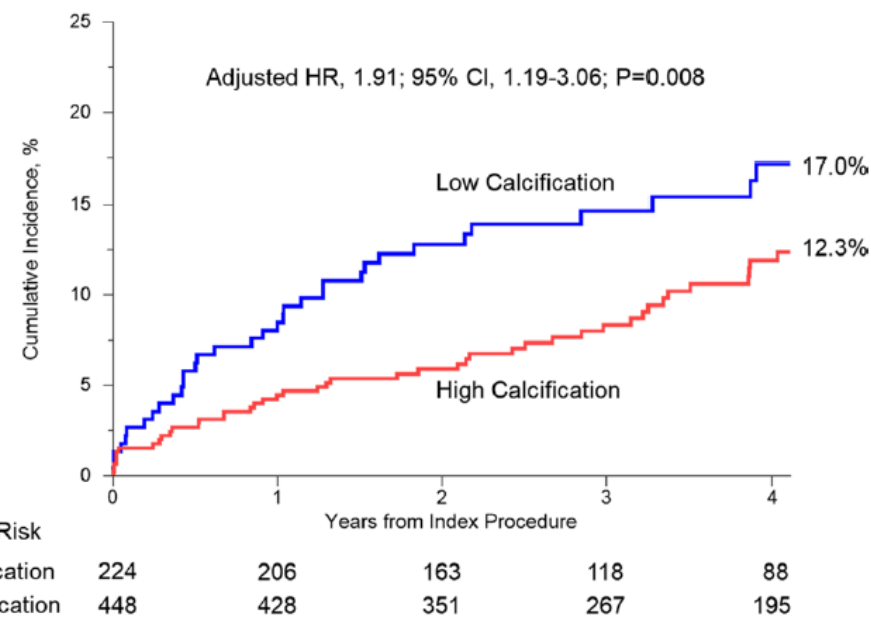
**Table 3** Clinical outcomes

\*Age and sex matching

at a 1:2 ratio.

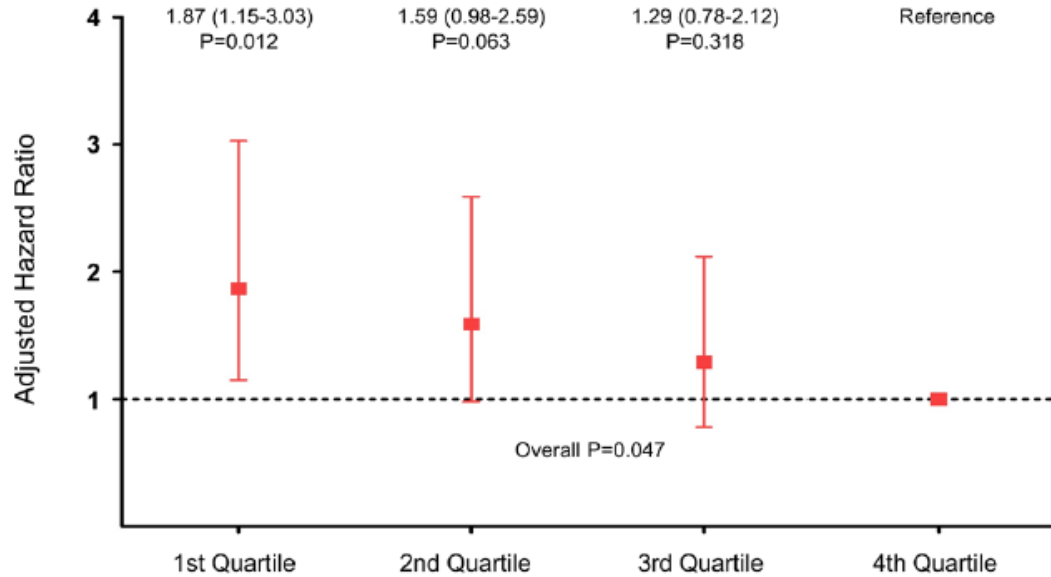
Adjusted HR\*

	Low AVC n (%)	High AVC	Unadjusted HR (95% CI)	P value	Adjusted HR* (95% CI)	P value
<b>Overall population</b>	<b>N=242</b>	<b>N=760</b>				
Death	41 (16.9)	102 (13.4)	1.32 (0.92 to 1.90)	0.14	1.91 (1.19 to 3.06) <sup>†</sup>	0.008
CV death	28 (11.6)	80 (10.5)	1.15 (0.74 to 1.76)	0.54	1.57 (0.90 to 2.74)	0.11
Non-cardiac death	13 (5.4)	22 (2.9)	1.96 (0.99 to 3.89)	0.055	3.21 (1.26 to 8.19)	0.015
Cancer	6 (2.5)	15 (2.0)				
Pneumonia	2 (0.8)	3 (0.4)				
Septic shock	3 (1.2)	2 (0.3)				
Peritonitis	1 (0.4)	1 (0.1)				
Ischaemic colitis	1 (0.4)	1 (0.1)				
Myocardial infarction	2 (0.8)	10 (1.3)	0.66 (0.14 to 3.02)	0.59	1.69 (0.23 to 12.2)	0.61
Stroke	10 (4.1)	30 (3.9)	1.08 (0.53 to 2.22)	0.83	1.08 (0.42 to 2.76)	0.87
MACE	47 (19.4)	119 (15.7)	1.30 (0.92 to 1.82)	0.13	1.76 (1.14 to 2.71)	0.011
<b>TAVR population</b>	<b>N=92</b>	<b>N=364</b>				
Death	24 (26.1)	67 (18.4)	1.64 (1.03 to 2.62)	0.039	2.12 (1.09 to 4.14)	0.028
Myocardial infarction	2 (2.2)	7 (1.9)	1.48 (0.33 to 6.69)	0.61	1.16 (0.19 to 7.03)	0.88
Stroke	2 (2.2)	17 (4.7)	0.49 (0.11 to 2.13)	0.34	0.27 (0.03 to 2.22)	0.22
MACE	25 (27.2)	73 (20.1)	1.52 (0.96 to 2.39)	0.074	1.50 (0.82 to 2.76)	0.19
<b>SAVR population</b>	<b>N=150</b>	<b>N=396</b>				
Death	17 (11.3)	35 (8.8)	1.33 (0.75 to 2.38)	0.33	1.95 (0.95 to 4.21)	0.089
Myocardial infarction	0 (0.0)	3 (0.8)	NA		NA	
Stroke	8 (5.3)	13 (3.3)	1.69 (0.70 to 4.08)	0.24	1.87 (0.54 to 6.50)	0.33
MACE	22 (14.7)	46 (11.6)	1.32 (0.80 to 2.20)	0.28	1.92 (0.98 to 3.77)	0.058



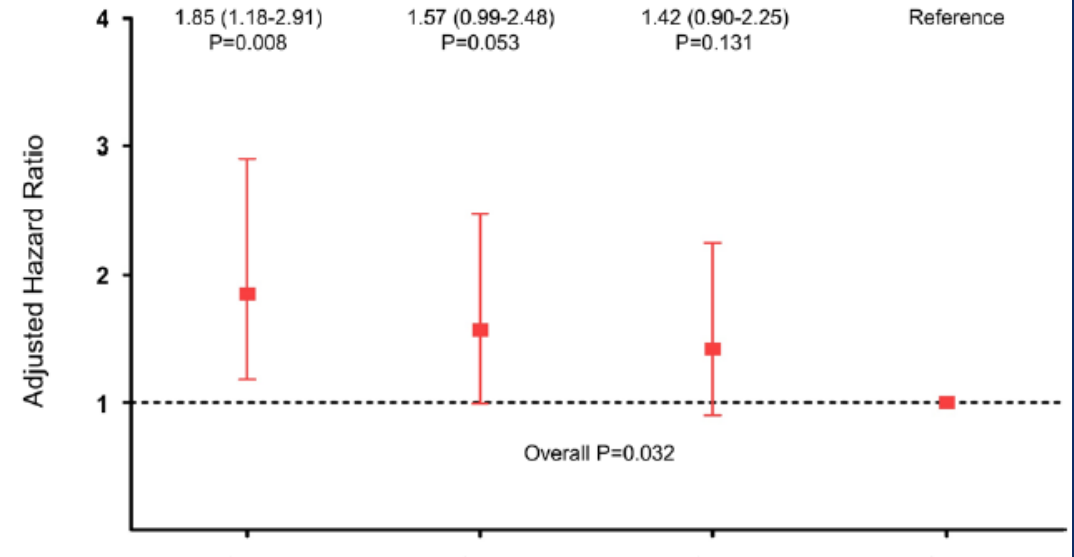
**Figure 3** Adjusted survival curves according to aortic valve calcification Kaplan-Meier curve showing rates of death from any cause in patients with low and high aortic valve calcifications.

### (A) All-cause Mortality



Amount of AVC	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Female	19-1187	1192-1759	1760-2572	2576-7669
Male	317-2246	2249-3085	3090-4289	4290-10657

### (B) MACE



Amount of AVC	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Female	19-1187	1192-1759	1760-2572	2576-7669
Male	317-2246	2249-3085	3090-4289	4290-10657

	Number (%)	Unadjusted HR (95% CI)	P value	Overall P value	Adjusted HR* (95% CI)	P value	Overall P value
<b>Death</b>				0.276			0.047
1Q (249)	41 (16.8%)	1.58 (0.97–2.55)	0.064		1.87 (1.15–3.03)	0.012	
2Q (249)	39 (15.7%)	1.48 (0.91–2.40)	0.115		1.59 (0.98–2.59)	0.063	
3Q (253)	35 (13.8%)	1.30 (0.79–2.14)	0.299		1.29 (0.78–2.12)	0.318	
4Q (251)	28 (11.2%)	1.0			1.0		
<b>MACE</b>				0.212			0.032
1Q (249)	47 (18.9%)	1.59 (1.02–2.50)	0.042		1.85 (1.18–2.91)	0.008	
2Q (249)	44 (17.7%)	1.47(0.93–2.32)	0.096		1.57 (0.99–2.48)	0.053	
3Q (253)	43 (17.0%)	1.42 (0.90–2.25)	0.131		1.42 (0.90–2.25)	0.131	
4Q (251)	32 (12.8%)	1.0			1.0		

\*Age adjusted HR

1Q = the first quartile; 2Q = the second quartile; 3Q = the third quartile; 4Q = the fourth quartile; MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval

# Discussion

- One of four of the severe degenerative AS patients
  - Lower than the proposed threshold for diagnosing severe AS (male  $\geq 2000$ , female  $\geq 1300$ )
  - Low AVC were more likely to be female, and on hamodialysis, younger and less LV remodeling, but a worse long-term survival

**Table 3. Independent Predictors of Severe Aortic Valve Stenosis with Low Aortic Calcification**

Variables	OR	95% CI	<i>P</i> value
Age	0.96	0.94-0.97	<0.001
Female sex	1.92	1.41-2.56	<0.001
Dialysis	2.32	1.05-5.17	0.039

OR = odds ratio; CI = confidence interval



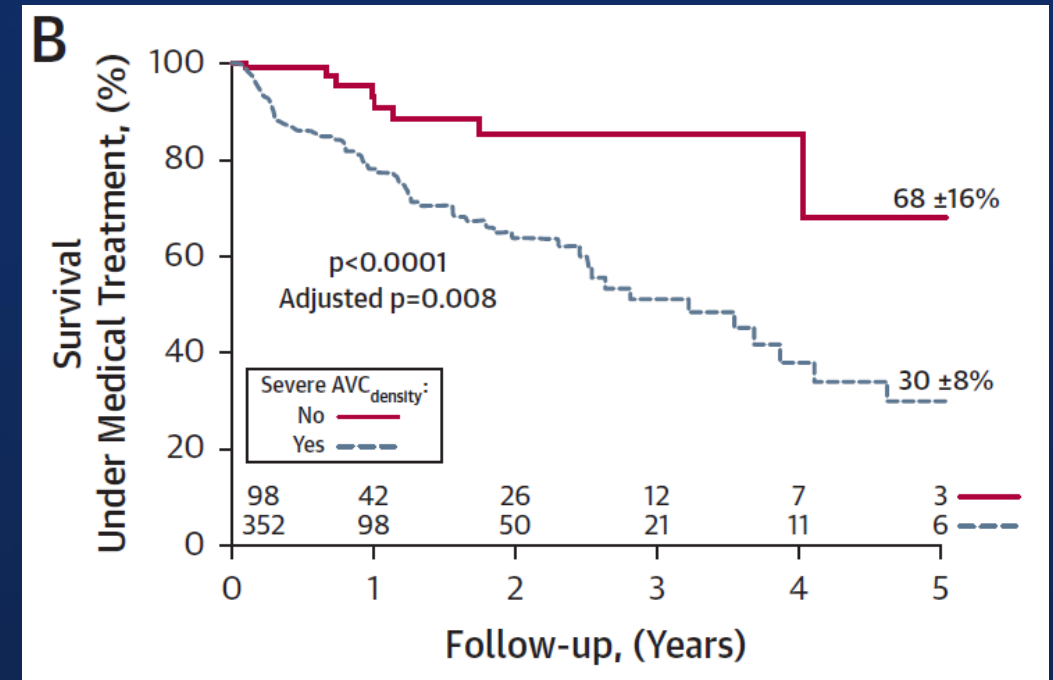
# Discussion

- Extensive valvular calcification is a hallmark of degenerative AS
  - AVC is significantly associated with the risk of mortality and need for AVR
  - Degree of AVC is associated with the progression and severity of AS
  - Quantification of AVC to assist in diagnosing severe AS

**TABLE 1 Sex-Specific Aortic Valve Calcium Score Thresholds for Severe Aortic Stenosis**

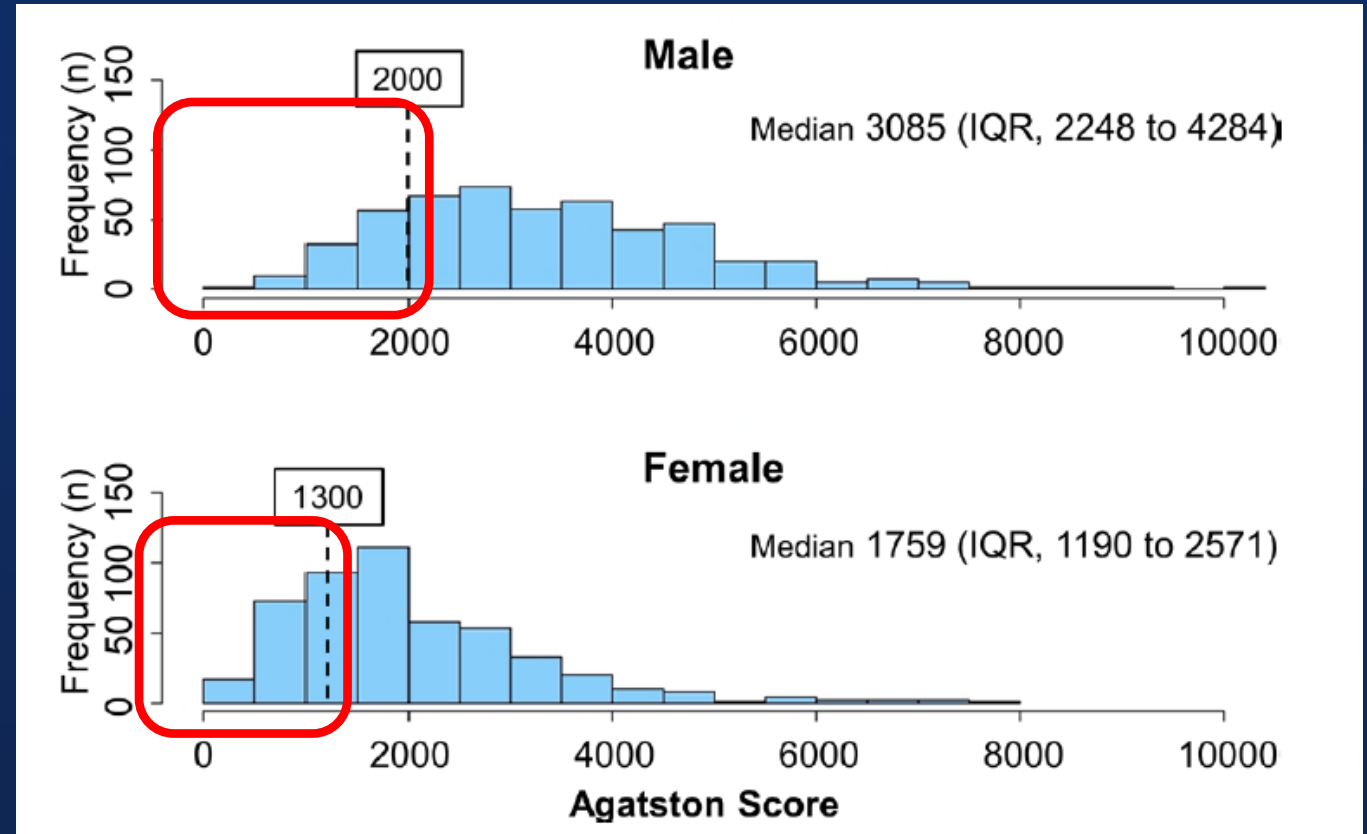
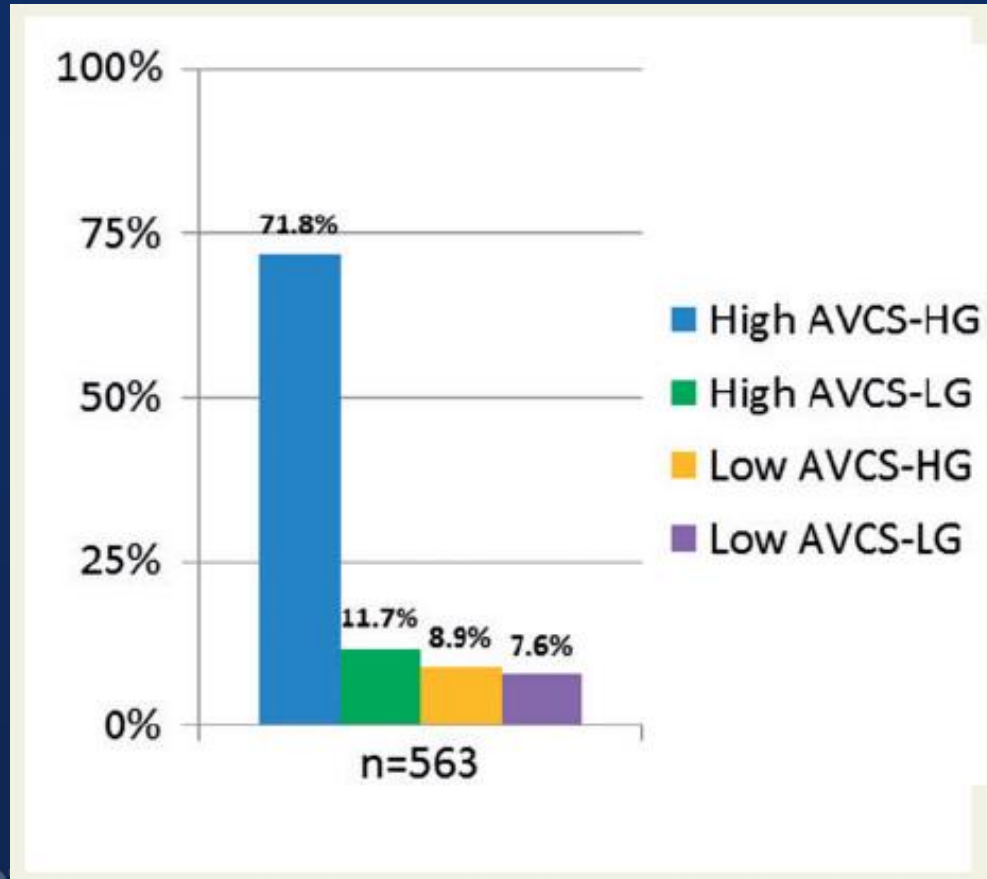
	Sex	Threshold	Sensitivity	Specificity	Ref. #
Aortic valve calcification (AU)					
	Women	1,274	89	81	(35)
		1,377	87	84	(37)
	Men	2,065	80	82	(35)
		2,062	80	82	(37)
Aortic valve calcification density (AU/cm <sup>2</sup> )					
	Women	292	96	75	(35)
		420	88	88	(37)
	Men	476	88	81	(35)
		527	83	84	(37)

AU = Agatston units (arbitrary units).



# Discussion

- However, some patients with severe degenerative AS have lower AVC  
Approximately 20% of patients with severe AS had lower AVC in previous studies  
Similarly, 24.2% of the patients had lower AVC than proposed threshold



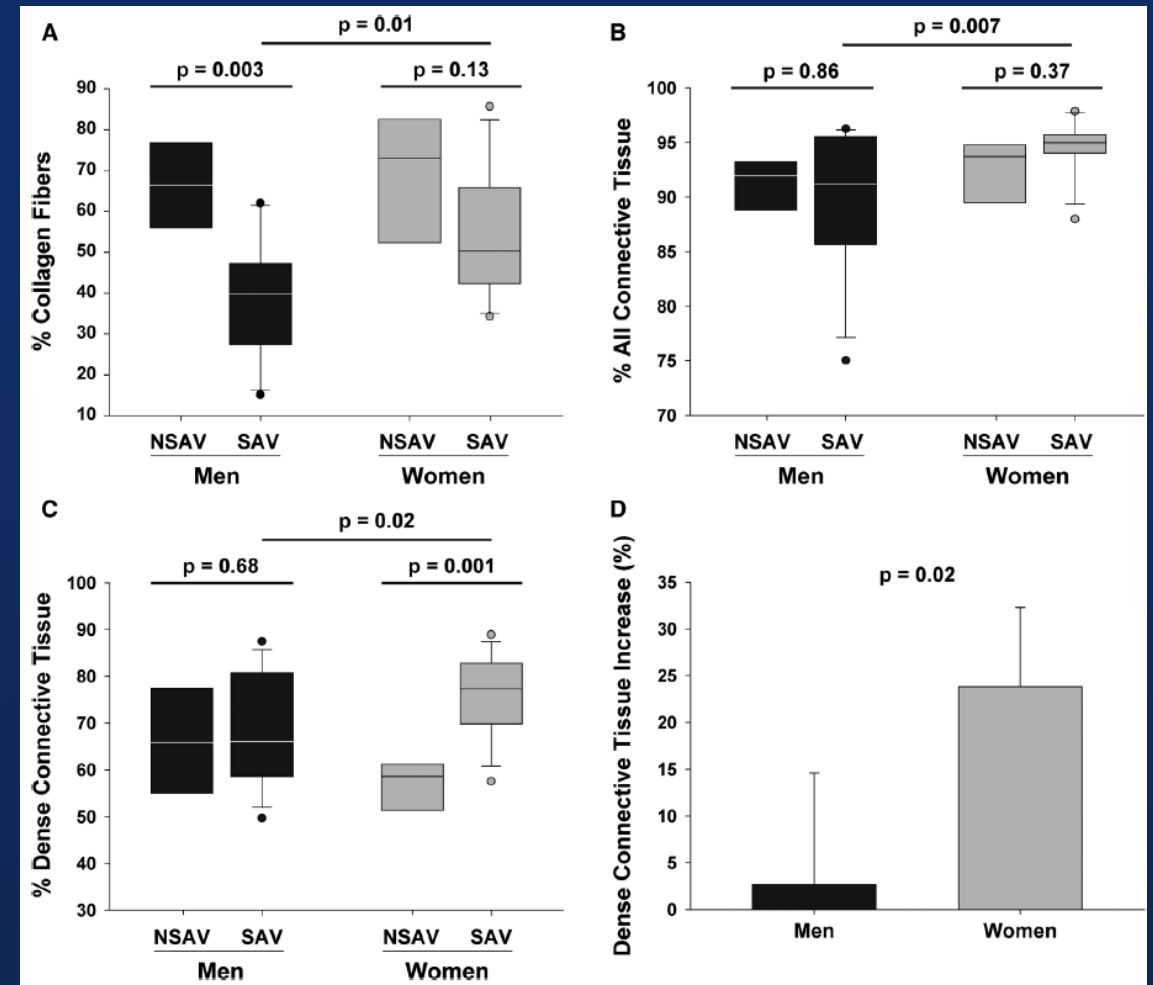
# Discussion

- Sex, age and hemodialysis were associated with severe AS with low AVC.

Women had a larger fibrotic component and a smaller calcification than men,

Non-calcified tissue (or fibrosis)

-> development and progression of AS



• Higher mortality rate in the patients with low AVC than in those with high AVC

Generally, severe AVC was considered to be associated with a higher mortality and procedural complications

However, one study that evaluate non-calcific tissue volume ~ CV events 30days, whereas calcific tissue volume did not have prognostic value

In addition, LFLG AS, or transthyretin cardiac amyloidosis

FIGURE 3 Survival Curves Based on All-Cause Mortality for Patients in the Matched Study Populations HG-AS and LFLG-AS

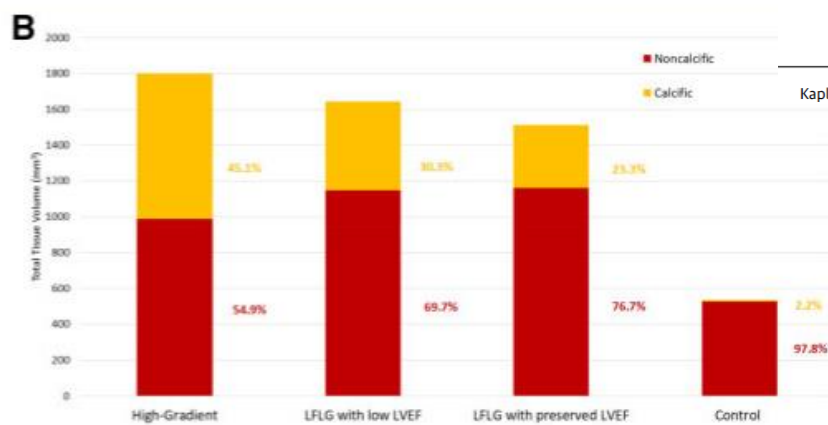
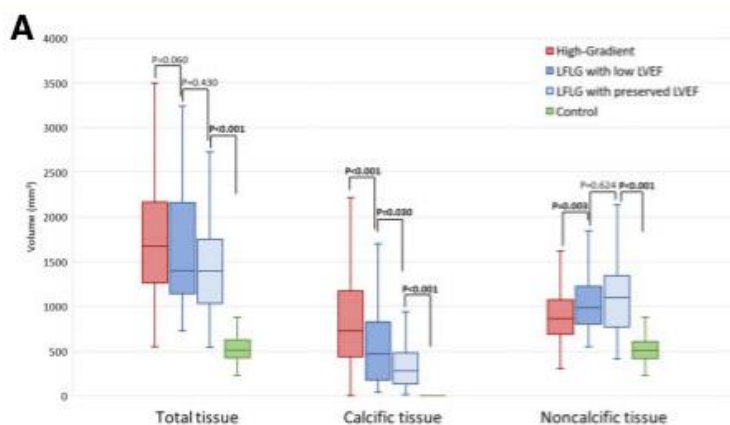
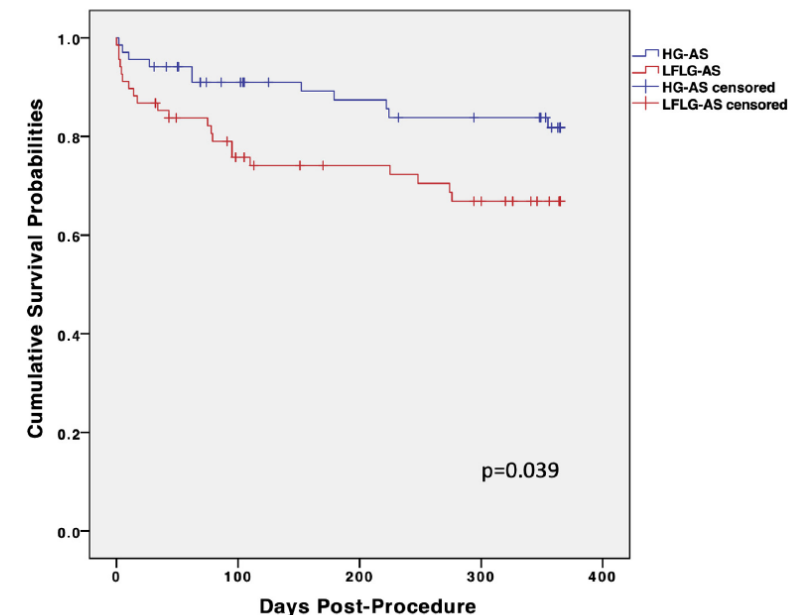


Figure 3 Comparison of (A) respective tissue volumes and (B) tissue composition between high-gradient aortic stenosis, low-flow low-gradient (LFLG) aortic stenosis and control groups.

Kaplan-Meier survival estimates for all-cause mortality. Abbreviations as in Figure 1.

# Discussion

- Sex, age and hemodialysis were associated with severe AS with low AVC.

Differences in calcification/fibrosis ratio

Men vs Women

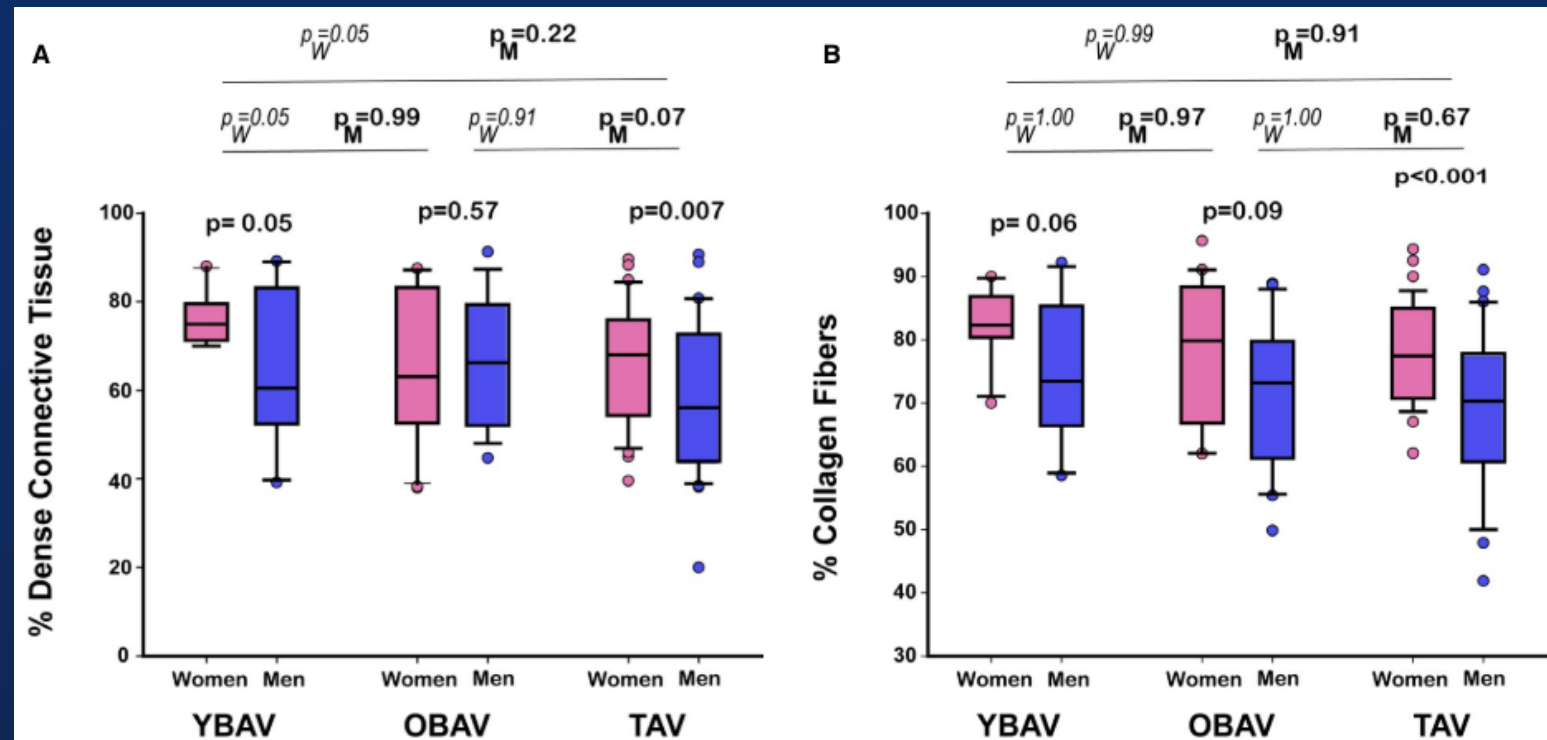
Tricuspid AV vs Bicuspid AV

Younger vs Older patients

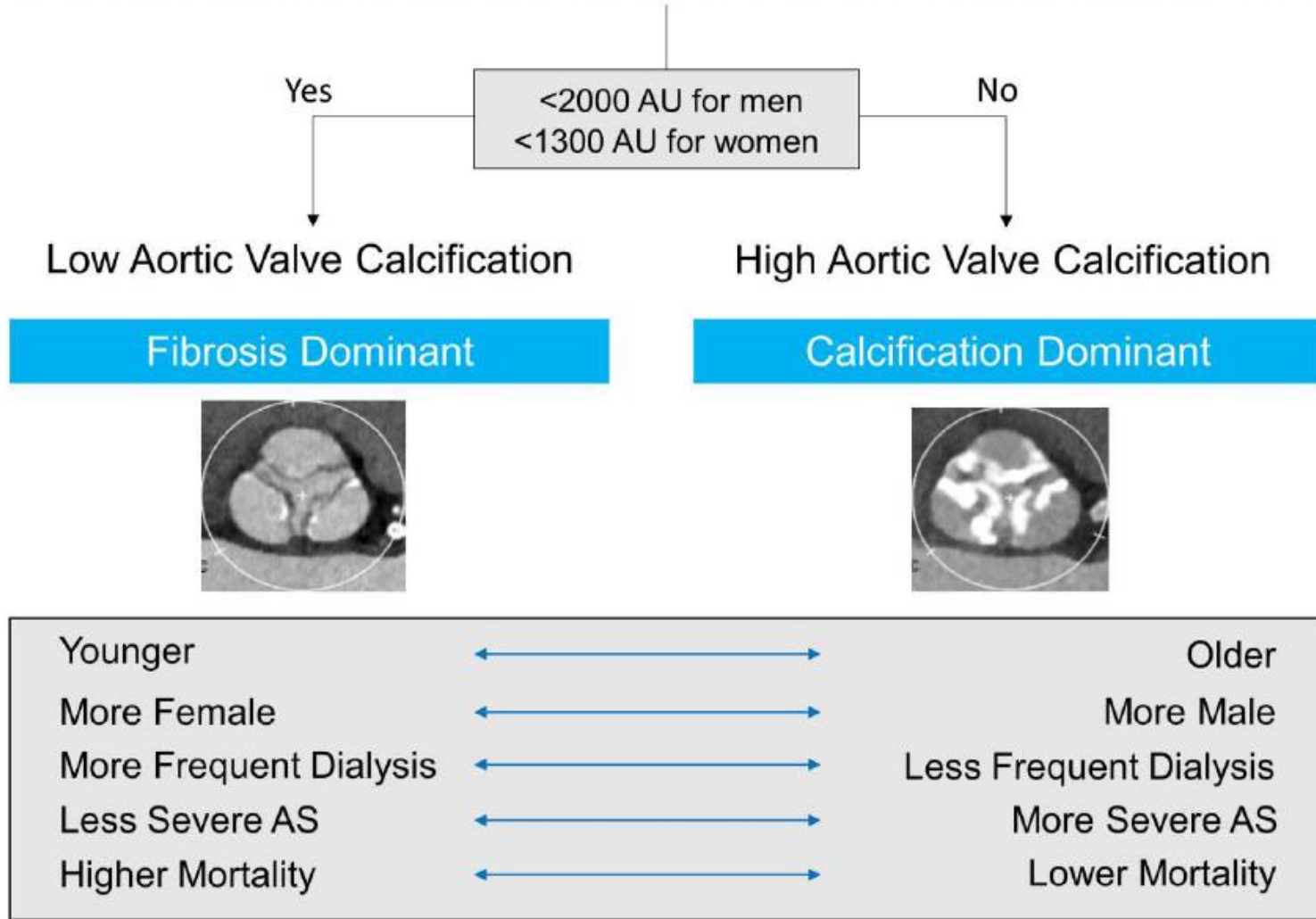
Lipid-mediated inflammation  
and insulin resistance

vs

Phosphocalcic metabolism  
and activation of the  
renin-angiotensin



## Aortic Valve **Agatston Score** for Severe Aortic Valve Stenosis ( $V_{max} > 4$ m/s)



$V_{max}$  = trans-aortic peak velocity; AS = aortic stenosis

# Discussion

- Limitation
  - Single center observational study
  - Unmeasured confounding factors, even with statistical adjustments
  - Measured only aortic valve calcification
    - > Non-calcified component or total valve volume are not available
  - Did not perform any pathological study
  - Differences between CT measured AVC and pathological calcifications

# Conclusion

- Degenerative aortic valve stenosis is characterized by excessive valvular calcification and AVC has been used for the diagnosis of AS
- However, about ¼ of patients with severe AS have an aortic valve calcium score below the sex-specific threshold.
- And, the patients with low AVC exhibit distinct clinical characteristics and higher risk of long-term mortality compared with high AVC.
- To understand the pathogenesis and progression of low AVC AS, further prospective studies focusing on this population are needed.