

# Supplementary File

## Outcomes in Patients with Moderate and Asymptomatic Severe Aortic Stenosis Followed Up in Heart Valve Clinics

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## **EXTENDED METHODS**

### **Follow-up**

Data collection started at the time of baseline evaluation until the last available contact or death occurrence. Follow-up organization for the Heart Valve Clinic (HVC) is described in the specific Section of the manuscript. Regarding the standard-of-care (SOC) group, most of the patients performed all the cardiological follow-ups in our hospital at the discretion of the cardiologist involved. In accordance with the clinical presentation, the cardiologists of the SOC group could request additional II-level diagnostic and laboratory tests. If the latter were requested, the patients booked them in accordance with the hospital waiting lists. In contrast, in HVC, the physicians, with the help of secretaries, directly booked the additional tests in the slots available for HVC.

In the overall population, trans-thoracic echocardiography was performed as part of routine clinical practice (see below). An exercise stress test was performed in selected patients when the symptomatic status was unclear. Aortic valve calcium score by CT was performed when clinically indicated (1). The indication for aortic valve replacement (AVR), including surgical/trans-catheter AVR (SAVR/TAVR), has been assigned following the Guidelines and confirmed during the weekly Heart Team meetings according to symptoms onset and, in case of asymptomatic patients, in presence of any among: abnormal exercise test, left ventricle ejection fraction (LVEF) < 50%, markedly elevated biomarkers, rapid progression of aortic stenosis (AS) severity, severe valve calcification assessed by CT (1).

### **Transthoracic Doppler Echocardiography**

Transthoracic echocardiography was performed as part of routine clinical practice. All Transthoracic Echocardiograms were performed using a high-quality ultrasound machine (GE Vivid E9, E95 or S70, GE Healthcare Horten, Norway or Epiq 7C, Philips Healthcare, Eindhoven, The Netherlands) and all images were stored digitally. Echocardiographic examinations were performed following the recommendations of the American Society of Echocardiography and the European Association of

Cardiovascular Imaging with the patients in the left lateral recumbent position (right lateral for the right parasternal continuous-wave Doppler flow measurements) and the use of standard views (2). The recorded images were reviewed by two cardiologists (G.V.C., M.P.) with more than 10-year experience in echocardiography and non-invasive cardiac imaging, to confirm the diagnosis and the grade of AS, according to the current Guidelines (2). Peak aortic jet velocity was derived from transaortic flow and recorded with continuous-wave Doppler using a multiwindow approach. The highest aortic velocity was used to calculate aortic time-velocity integral, mean gradients, and peak aortic valve velocity ( $V_{max}$ ). Peak and mean gradients were calculated using the simplified Bernoulli equation. The continuity equation was used to calculate the aortic valve area (AVA). The stroke volume was calculated by multiplying the area of the left ventricular outflow tract (LVOT) by the outflow tract time-velocity integral and indexed to the body surface area. If patients were in sinus rhythm, 3 cardiac cycles were averaged for all measures. For patients in atrial fibrillation, 5 cardiac cycles were averaged. LVEF was estimated by the Simpson biplane method.

### **Study endpoints**

Cardiovascular death was defined as death resulting from an acute myocardial infarction, sudden cardiac death, heart failure (HF), stroke, and other cardiovascular causes (3). Hospitalization for HF was defined as hospital admission for a primary diagnosis of HF in which the patient presented typical signs, symptoms, and diagnostic testing consistent with the diagnosis of HF and consequently received HF-directed therapy (3). Major adverse events were defined as a composite of all-cause death and non-fatal hospitalization due to worsening HF.

### **Extended Statistical Analysis**

Propensity score matching was used to reduce bias and differences in the patients' baseline characteristics (4). The propensity score was computed by a regression model, and the matching was performed using the nearest neighbor method without replacement with a 1:1 ratio. Matching criteria

were age, sex, body mass index (BMI), arterial hypertension, type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), history of cancer, previous coronary artery bypass graft surgery (CABG), previous mitral valve repair (MVR), previous HF, glomerular filtration rate (GFR), left ventricle mass index (LVMi), peak aortic valve velocity (Vmax), aortic valve area (AVA), tricuspid regurgitation gradient (TR Pmax), LVEF, use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), beta-blockers, aldosterone blockers, and statins. Caliper distance was 0.022, denoting good matching.

**REFERENCES**

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**SUPPLEMENTARY TABLES**

**Supplementary Table ST1 - Main findings and outcomes of unmatched patients with mAS and asAS, divided into HVC versus SOC.**

	<b>Total (N = 2129)</b>	<b>Heart Valve Clinic (N = 251)</b>	<b>Standard of care (N = 1878)</b>	<b>P value</b>
<b>Total cardiac consultation/year, n</b>	1.3 ± 2	1.4 ± 0.9	1.2 ± 2.4	0.074
<b>Exercise stress/year, n</b>	0.1 ± 0.4	0.2 ± 0.4	0.1 ± 0.6	0.026
<b>AVR, n (%)</b>	596 (28)	99 (39.4)	497 (26.5)	<0.001
SAVR	507 (85.1)	89 (89.9)	418 (84.1)	0.139
TAVR	89 (14.9)	10 (10.1)	79 (15.9)	
<b>HF readmission, n (%)</b>	307 (14.4)	49 (19.5)	258 (13.7)	0.019
<b>1-y all-cause death, n (%)<sup>†</sup></b>	302 (14.2)	6 (2.4)	296 (16.4)	<0.001

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

<sup>†</sup>Differences in categorical variables were analyzed using Fisher's Exact Test.

Abbreviations: AVR = aortic valve replacement; HF = heart failure; y = year.

**Supplementary Table ST2.** Univariate regression analysis of all-cause mortality between HVC vs SOC strategy stratifying the population by age.

	<b>Coeff</b>	<b>Std Error</b>	<b>Wald</b>	<b>P value</b>	<b>HR</b>	<b>95% CI</b>
<b>Age &lt; 70 years old</b>						
HVC	-0.465	0.226	3.123	0.040	0.628	0.423 - 0.979
<b>70 &lt; Age &lt; 80 years old</b>						
HVC	-0.540	0.240	5.07	0.024	0.583	0.364 - 0.932
<b>Age &gt; 80 years old</b>						
HVC	-0.702	0.303	5.38	0.020	0.496	0.274 - 0.897

Abbreviations: HVC: Heart Valve Clinic.



**Supplementary Table ST3.** Baseline characteristics, comorbidities and medical therapy of matched and unmatched patients with mAS, divided into HVC versus SOC.

	Unmatched			Matched		
	Heart Valve	Standard of	P value	Heart Valve	Standard of	P value
	Clinic (N = 105)	Care (N = 1105)		Clinic (N = 53)	Care (N = 53)	
Age, n (%)	70 ± 13.8	77 ± 12.5	<0.001	74 ± 9.6	72 ± 12	0.370
Female Sex, n (%)	42 (40)	470 (42.5)	0.663	23 (43.4)	24 (45.3)	0.999
BMI, (Kg/m <sup>2</sup> )	27.2 [24.5-29.8]	26.4 [23.8-27.9]	0.134	27.2 [24.1-29.6]	26.5 [23.6-29.5]	0.450
HBP, n (%)	39 (37.1)	413 (37.4)	0.989	25 (47.2)	23 (43.4)	0.845
T2DM, n (%)	28 (26.7)	311 (28.1)	0.869	19 (35.8)	20 (37.7)	0.999
AF, n (%)	39 (37.1)	427 (38.6)	0.793	22 (41.5)	18 (34)	0.999
COPD, n (%)	18 (17.1)	209 (18.9)	0.716	12 (22.6)	8 (15.1)	0.456
Cancer, n (%)	16 (15.2)	184 (16.6)	0.957	7 (13.2)	7 (13.2)	0.999
CAD, n (%)	24 (22.9)	352 (31.9)	0.050	13 (24.5)	13 (24.5)	0.999
Pre-HF, n (%)	2 (1.9)	63 (5.7)	0.177	2 (3.8)	0 (0)	0.475
CABG, n (%) <sup>†</sup>	2 (1.9)	22 (2)	0.999	2 (3.8)	1 (1.9)	0.999
Pre-MVR, n (%), n (%) <sup>†</sup>	4 (3.8)	17 (1.5)	0.164	0 (0)	1 (1.9)	0.999
GFR (ml/min)	66 ± 20.6	58 ± 23	<0.001	65.6 ± 21	65.9 ± 20.4	0.947
ACE-I, n (%)	32 (30.5)	347 (31.4)	0.828	15 (28.3)	14 (26.4)	0.999
ARBs, n (%)	54 (51.4)	544 (49.2)	0.716	31 (58.5)	25 (47.2)	0.331
MRAs, n (%)	42 (40)	424 (38.4)	0.869	29 (54.7)	25 (47.2)	0.560
Beta-blockers, n (%)	56 (53.3)	633 (57.3)	0.551	31 (58.5)	33 (62.3)	0.843
Statins, n (%)	60 (57.1)	665 (60.2)	0.695	38 (71.7)	35 (66)	0.675

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

<sup>†</sup>Differences in categorical variables were analyzed using Fisher's Exact Test.

Abbreviations: BMI: body mass index; HBP: hypertension; T2DM: Type 2 Diabetes Mellitus; AF: atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CAD: coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists (aldosterone blockers).

**Supplementary Table ST4.** Baseline echocardiographic indices of matched and unmatched patients with mAS, divided into HVC versus SOC.

	Unmatched			Matched		
	Heart Valve	Standard of	P value	Heart Valve	Standard of	P value
	Clinic (N = 105)	Care (N = 1105)		Clinic (N = 53)	Care (N = 53)	
<b>LVMi, (g/m<sup>2</sup>)</b>	205 ± 73	196 ± 66	0.223	198 ± 72	200 ± 67	0.935
<b>BP LVEF, (%)</b>	56 [54-60]	55 [50-60]	0.001	55 [54-60]	55 [54-60]	0.928
<b>AVmax</b>	3.4 [3.1-3.6]	3.3 [3.1-3.6]	0.080	3.4 [3.1-3.7]	3.3 [3.1-3.6]	0.060
<b>AVA, cm<sup>2</sup></b>	1.2 [1.1-1.5]	1.1 [1.1-1.4]	0.002	1.2 [1.1-1.4]	1.1 [1.1-1.4]	0.460
<b>TR Pmax</b>	29 ± 10	32 ± 12	0.044	30 ± 11	30 ± 12	0.8258
<b>Moderate MR, n (%)</b>	5 (4.8)	58 (5.2)	0.910	3 (5.6)	5 (9.4)	0.713

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%). Abbreviations: LVMi = left ventricular mass indexed to BSA; BP LVEF: two-dimensional bi-plane left ventricular ejection fraction; AV max = aortic valve velocity max; AVA = aortic valve area; TR Pmax = tricuspid regurgitation gradient; MR = mitral regurgitation.

**Supplementary Table ST5.** Predictors of all-cause death for patients with mAS at univariable and multivariable analysis.

Variables	Unmatched cohort						Matched cohort					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
<b>Age, years</b>	1.08	1.07 - 1.09	<0.001	1.04	1.03 - 1.06	<0.001	1.08	1.03 - 1.12	0.001	1.06	1.02 - 1.11	0.006
<b>Gender, female</b>	1.25	1.09 - 1.43	0.001	-	-	-	1.20	0.62 - 2.34	0.584	-	-	-
<b>BMI</b>	1.00	0.99 - 1.01	0.337	-	-	-	1.06	0.99 - 1.13	0.096	-	-	-
<b>HBP</b>	0.99	0.86 - 1.14	0.899	-	-	-	1.50	0.77 - 2.93	0.230	-	-	-
<b>T2DM</b>	1.20	1.03 - 1.39	0.016	-	-	-	1.86	0.96 - 3.61	0.068	-	-	-
<b>AF</b>	1.68	1.47 - 1.93	<0.001	-	-	-	1.35	0.69 - 2.64	0.382	-	-	-
<b>COPD</b>	1.57	1.34 - 1.83	<0.001	1.56	1.23 - 1.98	0.001	2.54	1.24 - 5.19	0.011	2.74	1.26 - 6	0.011
<b>Cancer</b>	1.11	0.93 - 1.32	0.254	-	-	-	1.20	0.50 - 2.89	0.687	-	-	-
<b>CAD</b>	1.18	1.02 - 1.37	0.024	-	-	-	1.77	0.89 - 3.52	0.103	-	-	-
<b>Pre-HF</b>	2.06	1.49 - 2.86	<0.001	-	-	-	1.61	0.22 - 11.8	0.639	-	-	-
<b>CABG</b>	1.16	0.71 - 1.90	0.558	-	-	-	3.18	0.97 - 9.99	0.057	-	-	-
<b>Pre-MVR</b>	0.50	0.22 - 1.11	0.090	-	-	-	1.00	0.01 - 9.99	0.997	-	-	-
<b>GFR</b>	0.97	0.97 - 0.98	<0.001	0.98	0.97 - 0.99	<0.001	0.98	0.96 - 0.99	0.004	0.98	0.96 - 0.99	0.041
<b>ACE-I</b>	0.89	0.76 - 1.03	0.108	-	-	-	1.30	0.64 - 2.66	0.470	-	-	-
<b>ARBs</b>	0.79	0.69 - 0.90	0.001	0.75	0.61 - 0.92	0.006	1.67	0.84 - 3.31	0.145	-	-	-
<b>MRAs</b>	1.55	1.35 - 1.77	<0.001	-	-	-	2.05	1.02 - 4.13	0.044	-	-	-

<b>Beta-blockers</b>	0.70	0.61 - 0.80	<0.001	0.64	0.52 - 0.79	<0.001	0.80	0.41 - 1.56	0.505	-	-	-
<b>Statins</b>	0.65	0.57 - 0.75	<0.001	0.79	0.64 - 0.98	<0.001	1.12	0.55 - 2.30	0.756	-	-	-
<b>AVmax</b>	0.94	0.84 - 1.04	0.217	-	-	-	0.86	0.24 - 3.06	0.821	-	-	-
<b>AVA</b>	0.98	0.90 - 1.06	0.566	-	-	-	1.07	0.83 - 1.35	0.965	-	-	-
<b>TR P max</b>	1.03	1.03 - 1.04	<0.001	1.04	1.01 - 1.04	<0.001	1.01	0.99 - 1.04	0.329	-	-	-
<b>LV Mass</b>	1.00	1.00 - 0.99	0.672	-	-	-	1.00	0.99 - 1.01	0.949	-	-	-
<b>LVEF</b>	0.96	0.95 - 0.97	<0.001	0.97	0.96 - 0.98	<0.001	1.00	0.96 - 1.94	0.958	-	-	-
<b>Moderate MR</b>	1.41	1.30 - 1.52	<0.001	-	-	-	1.39	1.23 - 1.84	0.032	-	-	-
<b>HeartValveClinic</b>	0.35	0.27 - 0.47	<0.001	0.39	0.22 - 0.69	0.001	0.35	0.17 - 0.72	0.004	0.38	0.11 - 0.50	<0.001

Abbreviations: BMI = body mass index; HBP = hypertension; T2DM = type 2 diabetes mellitus; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = ACE inhibitors; ARBs = angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists (aldosterone blockers); AV Vmax = aortic valve velocity max; AVA = aortic valve area; TR = tricuspid regurgitation; LV = left ventricle; LVEF = left ventricular ejection fraction; MR: mitral regurgitation.

**Supplementary Table ST6.** Baseline characteristics, comorbidities and medical therapy of matched and unmatched patients with asAS, divided into HVC versus SOC.

	Unmatched			Matched		
	Heart Valve	Standard of	P value	Heart Valve	Standard of	P value
	Clinic (N = 146)	Care (N = 773)		Clinic (N = 61)	Care (N = 61)	
Age, n (%)	72.4 ± 13.2	77.8 ± 11.6	<0.001	74.7 ± 11.3	75.8 ± 13.1	0.617
Female Sex, n (%)	59 (40.4)	373 (48.3)	0.099	23 (37.7)	23 (37.7)	0.999
BMI, (Kg/m <sup>2</sup> )	25.9 [23.3-29]	25.9 [23.3-28.9]	0.844	27 [24.6-29.4]	26.1 [23.1-29.1]	0.555
HBP, n (%)	39 (26.7)	281 (36.4)	0.032	16 (26.2)	15 (24.6)	0.999
T2DM, n (%)	26 (17.8)	195 (25.2)	0.069	11 (18)	11 (18)	0.999
AF, n (%)	41 (28.1)	248 (32.1)	0.391	18 (29.5)	17 (27.9)	0.999
COPD, n (%)	25 (17.1)	136 (17.6)	0.985	7 (11.5)	7 (11.5)	0.999
Cancer, n (%)	21 (14.4)	127 (16.4)	0.621	9 (14.8)	7 (11.5)	0.789
CAD, n (%)	29 (19.9)	196 (25.4)	0.190	14 (23)	13 (21.3)	0.999
Pre-HF, n (%)	3 (2.1)	30 (3.9)	0.398	2 (3.3)	2 (3.3)	0.999
CABG, n (%) <sup>†</sup>	2 (1.4)	8 (1)	0.999	1 (1.6)	0 (0)	0.999
Pre-MVR, n (%), n (%) <sup>†</sup>	2 (1.4)	6 (0.8)	0.824	1 (1.6)	1 (1.6)	0.999
GFR (ml/min)	68.3 ± 18.8	60 ± 21.7	<0.001	64.7 ± 19	63.5 ± 19	0.729
ACE-I, n (%)	44 (30.1)	229 (29.6)	0.980	20 (32.8)	18 (29.5)	0.845
ARBs, n (%)	69 (47.3)	352 (45.5)	0.770	29 (47.5)	28 (45.9)	0.999
MRAs, n (%)	45 (30.8)	309 (40)	0.046	24 (39.3)	22 (36.1)	0.852
Beta-blockers, n (%)	90 (61.6)	434 (56.1)	0.254	39 (63.9)	34 (55.7)	0.460
Statins, n (%)	92 (63)	467 (60.4)	0.619	40 (65.6)	41 (67.2)	0.999

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

<sup>†</sup>Differences in categorical variables were analyzed using Fisher's Exact Test.

Abbreviations: BMI: body mass index; HBP: hypertension; T2DM: Type 2 Diabetes Mellitus; AF: atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CAD: coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers. MRAs = mineralocorticoid receptor antagonists (aldosterone blockers).

**Supplementary Table ST7.** Baseline echocardiographic indices of matched and unmatched patients with asAS, divided into HVC versus SOC.

	Unmatched			Matched		
	Heart Valve	Standard of	P value	Heart Valve	Standard of	P value
	Clinic (N = 146)	Care (N = 773)		Clinic (N = 61)	Care (N = 61)	
<b>LVMi, (g/m<sup>2</sup>)</b>	206.5 ± 69	206 ± 66	0.924	209 ± 72	208 ± 61	0.938
<b>BP LVEF, (%)</b>	55 [54-65]	55 [52-60]	0.014	55 [54-65]	58 [55-65]	0.199
<b>AVmax</b>	4.5 [4.2-4.9]	4.5 [4.2-4.8]	0.726	4.4 [4.2-4.9]	4.5 [4.3-4.9]	0.342
<b>AVA, cm<sup>2</sup></b>	0.8 [0.65-0.9]	0.75 [0.6-0.9]	0.016	0.8 [0.65-0.9]	0.8 [0.63-0.9]	0.451
<b>TR Pmax</b>	31 ± 11	33 ± 13	0.077	32 ± 12	31 ± 10	0.800
<b>Moderate MR, n (%)</b>	5 (3.4)	34 (4.4)	0.768	1 (1.6)	2 (3.2)	0.999

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%). Abbreviations: LVMi = left ventricular mass indexed to BSA; BP LVEF: two-dimensional bi-plane left ventricular ejection fraction; AV max = aortic valve velocity max; AVA = aortic valve area; TR Pmax = tricuspid regurgitation gradient; MR = mitral regurgitation.

**Supplementary Table ST8.** Predictors of all-cause death for patients with asAS at univariable and multivariable analysis.

Variables	Unmatched cohort						Matched cohort					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
<b>Age, years</b>	1.10	1.08 - 1.11	<0.001	1.08	1.06 - 1.11	<0.001	1.11	1.06 - 1.16	<0.001	1.10	1.06 - 1.16	<0.001
<b>Gender, female</b>	1.37	1.11 - 1.70	0.003	-	-	-	1.63	0.88 - 3.04	0.121	-	-	-
<b>BMI</b>	0.96	0.94 - 0.98	0.001	-	-	-	0.95	0.88 - 1.02	0.174	-	-	-
<b>HBP</b>	0.96	0.77 - 1.21	0.747	-	-	-	0.79	0.37 - 1.73	0.561	-	-	-
<b>T2DM</b>	1.27	1.00 - 1.60	0.048	-	-	-	0.93	0.41 - 2.11	0.871	-	-	-
<b>AF</b>	2.14	1.73 - 2.65	<0.001	-	-	-	1.18	0.60 - 2.33	0.633	-	-	-
<b>COPD</b>	1.39	1.08 - 1.79	0.011	1.40	1.01 - 1.95	0.03	0.85	0.30 - 2.40	0.759	-	-	-
<b>Cancer</b>	1.23	0.94 - 1.61	0.136	-	-	-	1.77	0.86 - 3.63	0.120	-	-	-
<b>CAD</b>	1.19	0.94 - 1.50	0.139	-	-	-	0.88	0.42 - 1.85	0.739	-	-	-
<b>Pre-HF</b>	3.83	2.50 - 5.88	<0.001	2.09	1.19 - 3.69	0.01	5.32	1.62 - 17.5	0.006	-	-	-
<b>CABG</b>	3.33	1.65 - 6.74	0.001	-	-	-	1.00	0.01 - 9.99	0.996	-	-	-
<b>Pre-MVR</b>	1.01	0.32 - 3.14	0.991	-	-	-	1.00	0.01 - 9.99	0.997	-	-	-
<b>GFR</b>	0.97	0.97 - 0.98	<0.001	0.98	0.98 - 0.99	<0.001	0.97	0.96 - 0.98	0.004	-	-	-
<b>ACE-I</b>	0.94	0.75 - 1.19	0.632	-	-	-	0.32	0.14 - 0.77	0.011	0.23	0.09 - 0.62	0.003
<b>ARBs</b>	0.85	0.68 - 1.05	0.126	-	-	-	0.47	0.24 - 0.90	0.024	-	-	-
<b>MRAs</b>	1.66	1.35 - 2.05	<0.001	0.72	0.54 - 0.97	0.028	2.03	1.09 - 3.78	0.025	-	-	-

<b>Beta-blockers</b>	0.55	0.44 – 0.67	<0.001	0.57	0.44 – 0.75	<0.001	0.37	0.20 – 0.69	0.002	0.34	0.17 – 0.68	0.002
<b>Statins</b>	0.58	0.47 – 0.71	<0.001	-	-	-	0.64	0.34 - 1.20	0.162	-	-	-
<b>AVmax</b>	0.85	0.66 - 1.08	0.189	-	-	-	0.99	0.47 – 2.06	0.972	-	-	-
<b>AVA</b>	0.49	0.31 – 0.76	0.002	-	-	-	0.98	0.48 – 2.02	0.965	-	-	-
<b>TR P max</b>	1.03	1.03 - 1.04	<0.001	1.02	1.01 - 1.03	<0.001	1.02	1.00 - 1.04	0.034	1.04	1.02 - 1.08	0.001
<b>LV Mass</b>	1.00	1.00 – 1.00	0.770	-	-	-	1.00	0.99 – 1.01	0.424	-	-	-
<b>LVEF</b>	0.96	0.95 – 0.97	<0.001	0.97	0.96 - 0.98	<0.001	0.96	0.93 – 0.99	0.033	0.94	0.90 – 0.98	0.003
<b>Moderate MR</b>	1.40	1.32 – 1.54	<0.001	1.34	1.12 - 1.62	0.002	1.49	1.33 – 1.54	0.010	-	-	-
<b>HeartValveClinic</b>	0.41	0.29 - 0.59	<0.001	-	-	-	0.69	0.37 – 1.29	0.248	-	-	-

Abbreviations: BMI = body mass index; HBP = hypertension; T2DM = type 2 diabetes mellitus; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = ACE inhibitors; ARBs = angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists (aldosterone blockers); AV Vmax = aortic valve velocity max; AVA = aortic valve area; TR = tricuspid regurgitation; LV = left ventricle; LVEF = left ventricular ejection fraction; MR: mitral regurgitation.



**FIGURE LEGENDS**

**Supplementary Figure S1.** Covariate balance of propensity matching in patients with moderate and asymptomatic severe aortic stenosis.

**Supplementary Figure S2.** Distribution of Propensity Scores in patients with moderate and asymptomatic severe aortic stenosis.

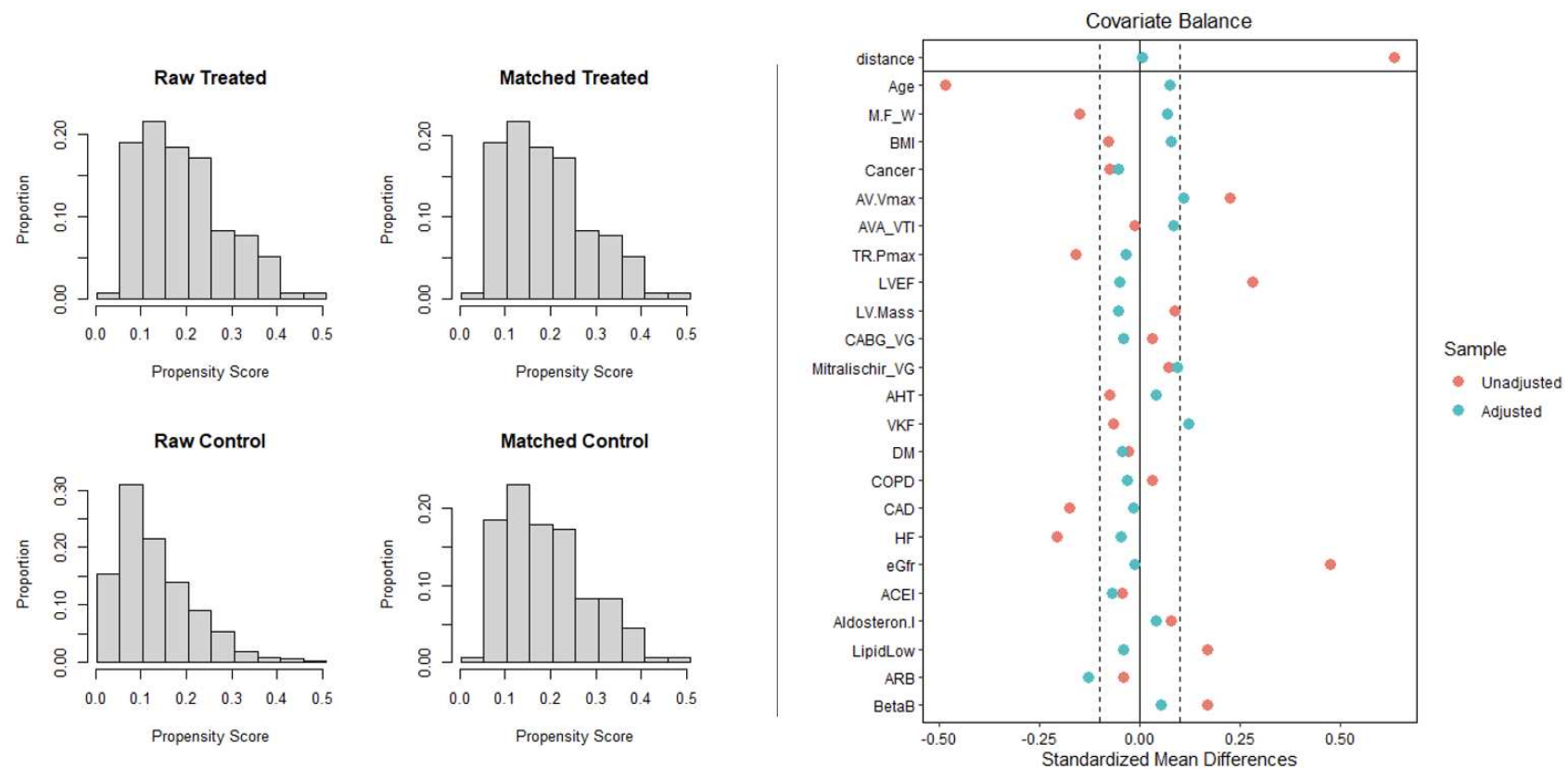
**Supplementary Figure S3.** Kaplan-Meier survival curves for all-cause death in patients with moderate and asymptomatic severe AS followed by SOC versus HVC approach, stratified in LVEF  $\geq 50\%$  and  $< 50\%$ .

**Supplementary Figure S4.** Covariate balance of propensity matching in patients with moderate stenosis.

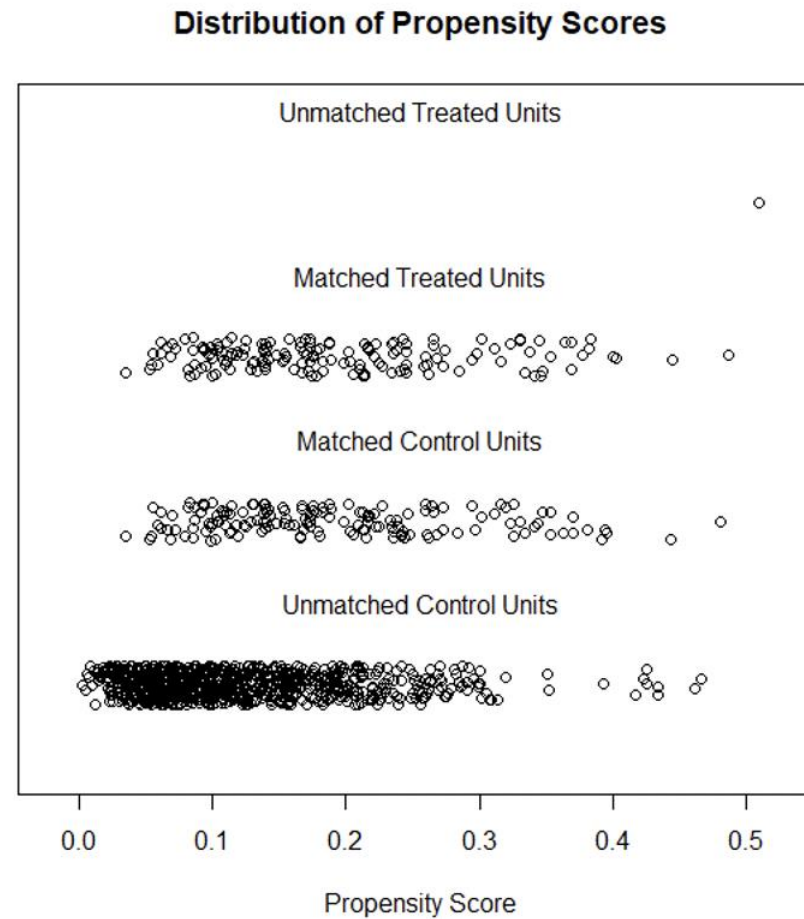
**Supplementary Figure S5.** Distribution of Propensity Scores in patients with moderate aortic stenosis.

**Supplementary Figure S6.** Covariate balance of propensity matching in patients with asymptomatic severe aortic stenosis.

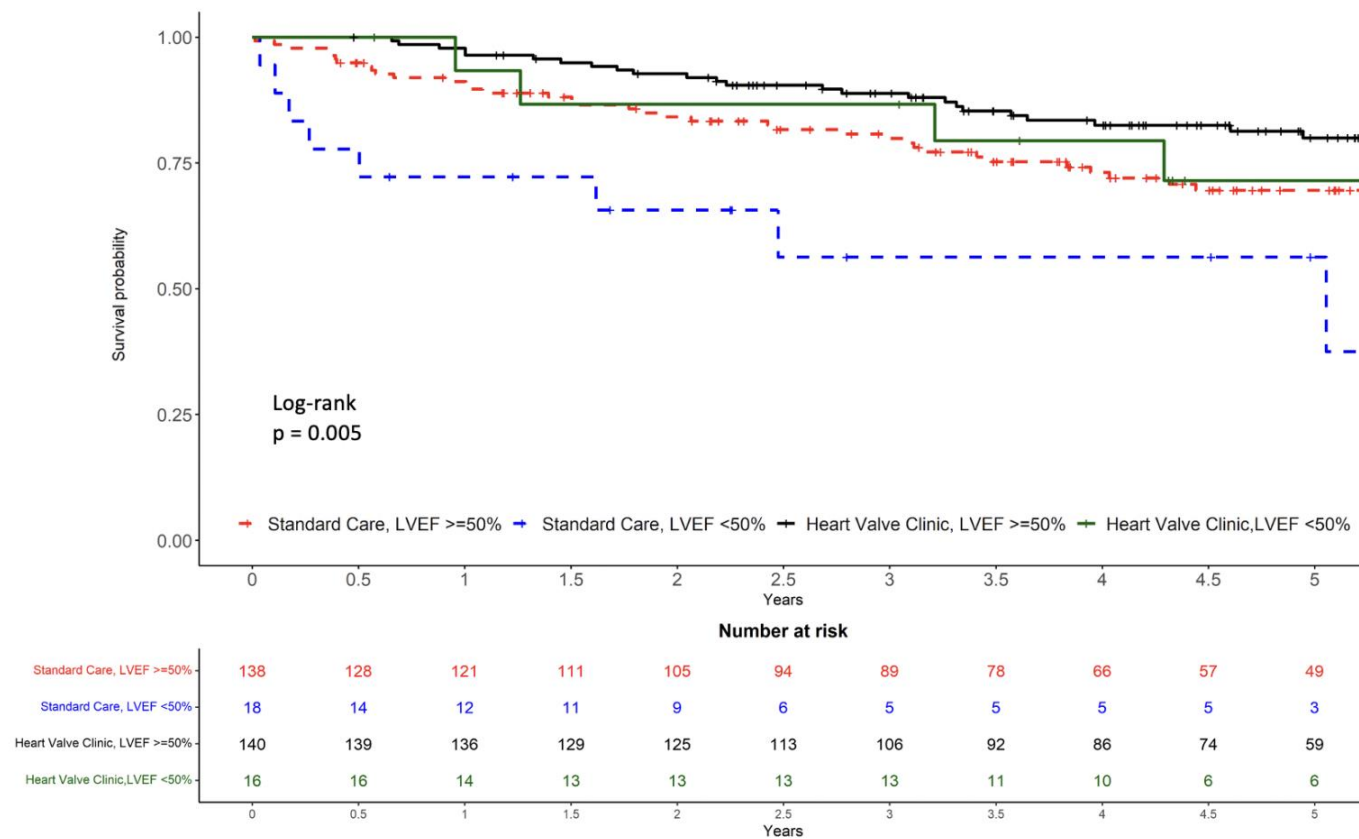
**Supplementary Figure S7.** Distribution of Propensity Scores in patients with asymptomatic severe aortic stenosis.

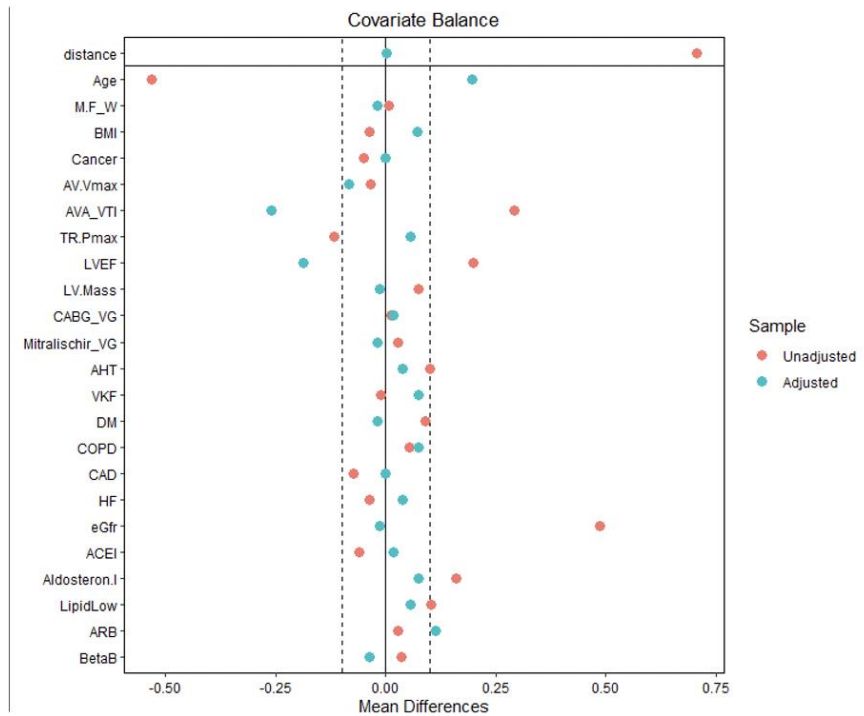
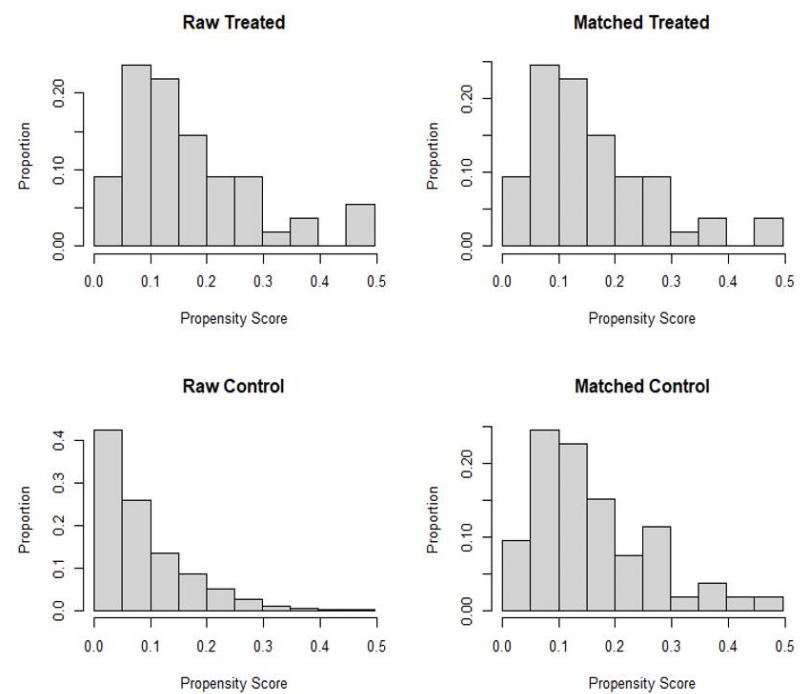
**Supplementary Figure S1.** Covariate balance of propensity matching in patients with moderate and asymptomatic severe aortic stenosis.

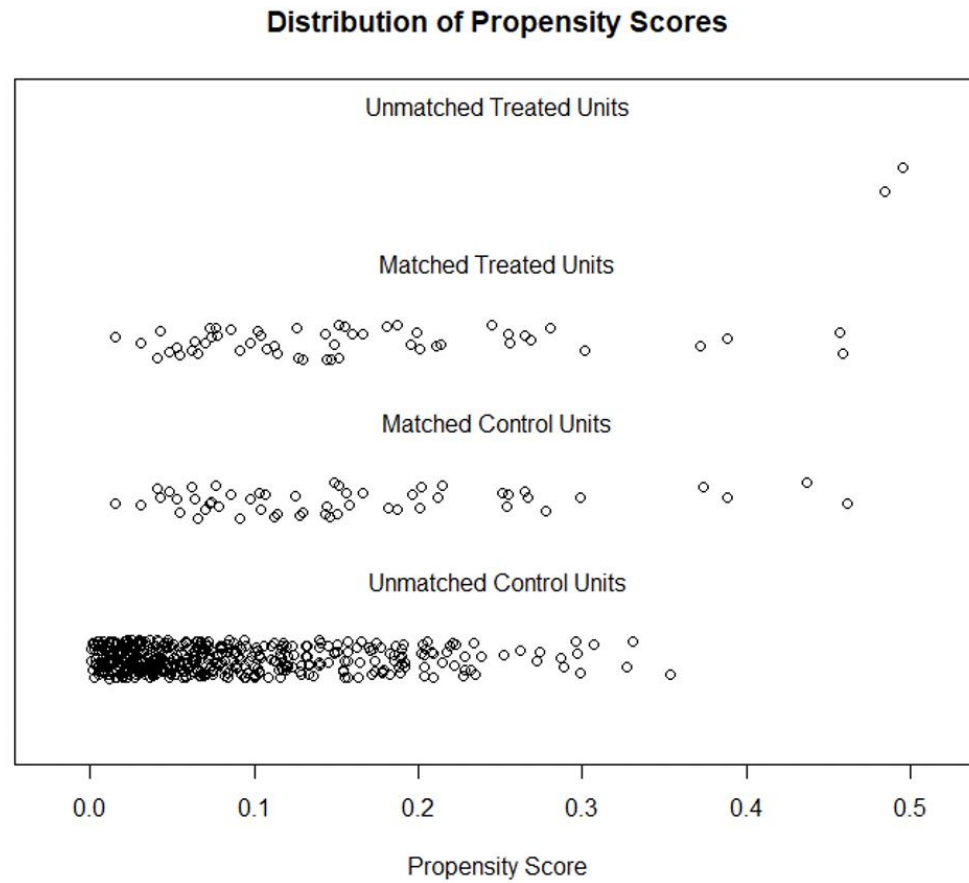
**Supplementary Figure S2.** Distribution of Propensity Scores in patients with moderate and asymptomatic severe aortic stenosis.

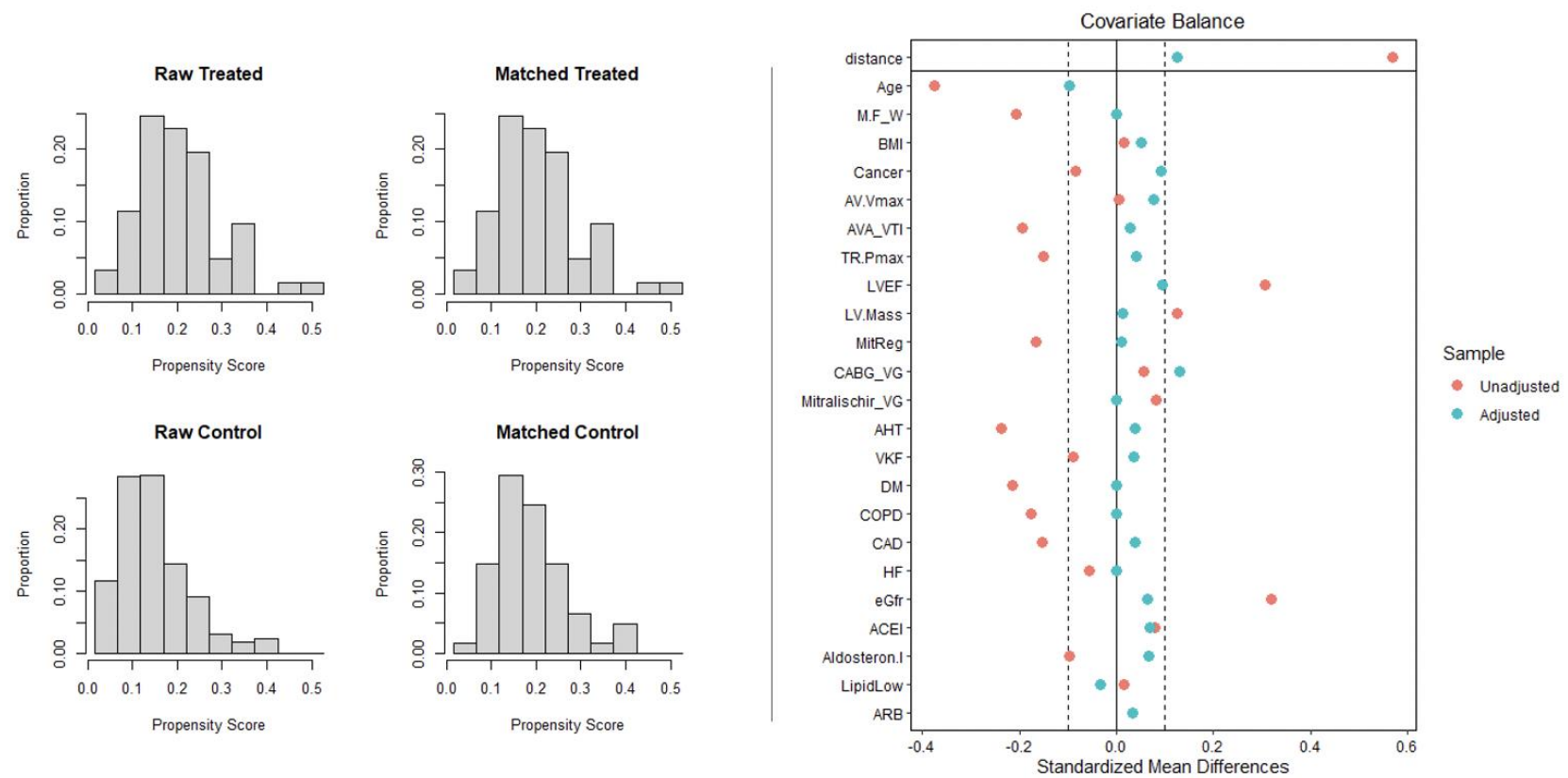


**Supplementary Figure S3.** Kaplan-Meier survival curves for all-cause death in patients with moderate and asymptomatic severe AS followed by SOC versus HVC approach, stratified in LVEF  $\geq 50\%$  and  $< 50\%$ .



**Supplementary Figure S4.** Covariate balance of propensity matching in patients with moderate aortic stenosis.

**Supplementary Figure S5.** Distribution of propensity scores in patients with moderate aortic stenosis.

**Supplementary Figure S6.** Covariate balance of propensity matching in patients with asymptomatic severe aortic stenosis.

**Supplementary Figure S7.** Distribution of propensity scores in patients with asymptomatic severe aortic stenosis.

