

Online Supplementary Materials

for the following *Heart* article

TITLE: Echocardiographic Predictors of Outcomes in Adults with Aortic Stenosis

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ONLINE FIGURE LEGEND

ONLINE FIGURE: Overall Survival as a Function of Clinical Comorbidities

Legend: This figure shows the overall survival curves according to the diagnosis of hypertension (Panel A), diabetes (Panel B), coronary artery disease (CAD; Panel C), chronic obstructive pulmonary disease (COPD; Panel D) and renal failure (Panel E).

†: hazard ratio (HR) adjusted for age, gender, body surface area, stroke volume index, mean gradient, mitral regurgitation, left ventricular ejection fraction, and all clinical comorbidities. ‡: hazard ratio (HR) after further adjustment for aortic valve replacement defined as time-dependant variable. The numbers at the bottom of the graph represent the number of patients at risk at each follow time.

ONLINE TABLE 1: Patients Characteristics According to Symptomatic Status (n=919)

	Patients with Evaluation of Symptoms n=919	Asymptomatic Patients n=212 23%	Symptomatic Patients n=707 77%	p value
Clinical data				
Age, years	71 ±13	66 ±16	72 ±11	<0.0001
Male gender, %	57%	62%	55%	0.08
Height, cm	164 ±10	167 ±10	164 ±9	0.0001
Weight, kg	74 ±16	74 ±16	75 ±16	0.48
Body surface area, m ²	1.8 ±0.2	1.8 ±0.2	1.8 ±0.2	0.40
Body mass index, kg/m ²	27 ±5	26 ±5	28 ±5	0.0009
History of hypertension, %	74%	60%	78%	<0.0001
Systolic blood pressure, mm Hg	132 ±23	135 ±23	132 ±23	0.14
Diastolic blood pressure, mm Hg	72 ±11	75 ±11	71 ±11	0.0002
Diabetes, %	28%	18%	31%	0.0003
Coronary artery disease, %	59%	36%	66%	<0.0001
Prior myocardial infraction, %	33%	19%	36%	<0.0001
Atrial fibrillation, %	8%	7%	9%	0.29
Chronic obstructive pulmonary disease, %	23%	8%	27%	<0.0001
Renal Failure, %	19%	10%	21%	0.0002
Logistic EuroSCORE, %	7.9 [4.0-15.7]	4.8 [2.5-10.8]	8.6 [4.3-17.7]	<0.0001
Doppler-echocardiographic data				
<i>Standard echo variables</i>				
Bicuspid aortic valve, %	26%	37%	19%	0.01
LV outflow tract diameter, cm	2.1 ±0.2	2.2 ±0.2	2.1 ±0.2	0.0009
Stroke volume index, ml/m ²	39 ±9	42 ±9	38 ±9	<0.0001
Peak aortic jet velocity, m.s ⁻¹	3.3 ±0.9	3.2 ±0.8	3.4 ±0.9	0.006
Mean transvalvular gradient, mmHg	28 ±16	25 ±13	29 ±17	0.003
Aortic valve area, cm ²	0.99 ±0.31	1.08 ±0.26	0.96 ±0.31	<0.0001
Aortic valve area index, cm ² /m ²	0.55 ±0.17	0.60 ±0.16	0.53 ±0.17	<0.0001
Energy loss index, cm ² /m ²	0.64 ±0.23	0.70 ±0.22	0.62 ±0.23	<0.0001
Dimensionless velocity index	0.28 ±0.09	0.30 ±0.09	0.28 ±0.09	0.003
Aortic regurgitation grade	1 [0-1]	1 [0-1]	1 [0-1]	0.81
Mitral regurgitation grade	1 [0-2]	1 [0-1]	1 [0-2]	0.005
Tricuspid regurgitation grade	1 [0-2]	1 [0-2]	1 [0-2]	0.96
LV ejection fraction, %	61 ±13	64 ±10	60 ±14	<0.0001
Valvulo-arterial impedance, mmHg/ml.m ²	4.2 ±1.1	3.9 ±0.9	4.4 ±1.2	<0.001
LV end-diastolic diameter, cm	4.8 ±0.7	4.8 ±0.5	4.8 ±0.7	0.85
LV end-systolic diameter, cm	2.9 ±0.8	2.8 ±0.6	3.0 ±0.8	0.02
LV end-diastolic volume, ml	111 ±36	109 ±29	111 ±38	0.52
<i>Prevalence of patients according to threshold values defined by guidelines</i>				
Stroke volume index <35 ml/m ² , %	33%	20%	36%	<0.0001
Peak aortic jet velocity >4 m/s, %	24%	19%	25%	0.09
Mean transvalvular gradient >40 mmHg, %	21%	17%	22%	0.07
Aortic valve area <1 cm ² , %	53%	36%	58%	<0.0001
Aortic valve area index <0.6 cm ² /m ² , %	64%	51%	68%	<0.0001
Energy loss index <0.6 cm ² /m ² , %	48%	32%	52%	<0.0001
Dimensionless velocity index <0.25, %	42%	32%	45%	0.0009

LV ejection fraction <50%, %	16%	8%	19%	<0.0001
Valvulo-arterial impedance >4.5, %	36%	24%	65%	<0.0001

Legend: LV: left ventricle; Values are mean \pm SD or median [IQR]

ONLINE TABLE 2: Predictors of the Composite of AVR or Death and AVR alone in the subset of 565 Patients with Severe AS

Baseline variables	AVR or Death n=538 AVR or death (95%)				AVR n=386 AVR (68%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	1.00 0.95-1.06	0.95			0.87 0.82-0.92	<0.001	0.94 0.87-1.01	0.08
Male gender	1.59 1.33-1.89	<0.001	1.17 0.93-1.48	0.18	1.69 1.38-2.09	<0.001	0.97 0.73-1.27	0.81
Body surface area, m ²	2.40 1.62-3.55	<0.001	1.48 0.87-2.53	0.15	3.94 2.51-6.19	0.02	3.05 1.38-5.56	<0.001
Hypertension	0.98 0.82-1.18	0.86	–	–	0.87 0.70-1.07	0.19	–	–
Diabetes	1.22 1.00-1.47	0.05	1.09 0.88-1.35	0.42	1.17 0.93-1.47	0.17	–	–
Coronary Artery Disease	1.37 1.15-1.63	<0.001	1.45 1.20-1.74	<0.001	1.29 1.05-1.58	0.02	1.62 1.30-2.02	<0.001
COPD	1.10 0.90-1.35	0.34	–	–	0.84 0.65-1.09	0.20	–	–
Renal failure	1.52 1.22-1.89	<0.001	1.56 1.25-1.96	<0.001	1.06 0.80-1.40	0.68	–	–
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	0.98 0.93-1.03	0.46			0.90 0.85-0.95	<0.001	0.97 0.91-1.04	0.39
Peak aortic jet velocity, m/s (per 1 m/s increase)	1.63 1.47-1.80	<0.001	–	–	1.90 1.69-2.14	<0.001	–	–
Mean Gradient, mmHg (per 10 mmHg increase)	1.25 1.20-1.31	<0.001	1.28 1.21-1.34	<0.001	1.33 1.26-1.40	<0.001	1.31 1.24-1.39	<0.001
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.16 1.10-1.21	<0.001	–	–	1.13 1.07-1.19	<0.001	–	–
Aortic valve area index, cm ² /m ²	1.46	<0.001	–	–	1.47	<0.001	–	–

(per 0.1 cm ² /m ² decrease)	1.34-1.60				1.33-1.63			
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.36 1.27-1.47	<0.001	–	–	1.35 1.25-1.48	<0.001	–	–
Dimensionless velocity index (per 0.1 decrease)	1.92 1.65-2.24	<0.001	–	–	2.06 1.71-2.47	<0.001	–	–
Mitral regurgitation	1.03 0.93-1.14	0.59			0.87 0.77-0.98	0.03	1.02 0.89-1.17	–0.77
LVEF, % (per 5% decrease)	1.02 0.99-1.05	0.12	–	–	0.97 0.94-1.01	0.15	–	–
Valvulo-arterial impedance, mmHg/ml.m ²	1.08 1.00-1.17	0.046	–	–	0.98 0.89-1.08	0.68	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval.

ONLINE TABLE 3: Predictors of the Composite of AVR or Death and AVR alone in the 919 Patients with Evaluation of Symptomatic Status

Baseline variables	AVR or Death n=814 AVR or death (89%)				AVR n=513 AVR (56%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	1.11 1.05-1.16	<0.001	1.11 1.04-1.17	0.001	0.90 0.86-0.96	<0.001	1.00 0.95-1.07	0.77
Male gender	1.36 1.18-1.57	<0.001	1.37 1.12-1.65	0.002	1.57 1.31-1.88	<0.001	1.11 0.87-1.41	0.39
Body surface area, m ²	1.67 1.21-2.31	0.002	1.40 0.91-2.16	0.12	3.00 2.01-4.47	<0.001	2.76 1.65-4.61	<0.001
Symptoms (NYHA \geq 2)	1.84 1.55-2.18	<0.001	1.56 1.30-1.88	<0.001	1.58 1.29-1.95	<0.001	1.59 1.27-1.98	<0.001
Hypertension	1.21 1.04-1.42	0.02	1.25 1.04-1.49	0.02	0.96 0.80-1.16	0.69	–	–
Diabetes	1.21 1.04-1.41	0.01	1.16 0.99-1.37	0.07	1.07 0.89-1.31	0.45	–	–
Coronary Artery Disease	1.39 1.20-1.59	<0.001	1.09 0.93-1.27	0.27	1.29 1.08-1.54	0.005	1.31 1.08-1.58	0.006
COPD	1.25 1.06-1.47	0.008	0.99 0.83-1.17	0.89	0.79 0.63-1.00	0.05	0.76 0.60-0.98	0.03
Renal failure	1.60 1.34-1.90	<0.001	1.41 1.17-1.70	<0.001	0.96 0.74-1.24	0.74	–	–
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.03 0.99-1.07	0.12	1.01 0.97-1.06	0.57	0.94 0.89-0.99	0.01	0.98 0.92-1.04	0.56
Peak aortic jet velocity, m/s (per 1 m/s increase)	1.92 1.77-2.07	<0.001	–	–	2.46 2.25-2.70	<0.001	–	–
Mean Gradient, mmHg (per 10 mmHg increase)	1.38 1.32-1.43	<0.001	1.44 1.39-1.50	<0.001	1.51 1.45-1.58	<0.001	1.50 1.43-1.57	<0.001

Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.18 1.15-1.21	<0.001	–	–	1.23 1.19-1.26	<0.001	–	–
Aortic valve area index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.42 1.35-1.49	<0.001	–	–	1.61 1.51-1.72	<0.001	–	–
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.30 1.25-1.35	<0.001	–	–	1.46 1.39-1.54	<0.001	–	–
Dimensionless velocity index (per 0.1 decrease)	1.88 1.72-2.06	<0.001	–	–	2.49 2.21-2.81	<0.001	–	–
Mitral regurgitation	1.12 1.03-1.22	0.009	1.05 0.96-1.16	0.27	0.92 0.83-1.03	0.17	–	–
LVEF, % (per 5% decrease)	1.04 1.01-1.07	0.002	1.03 0.99-1.06	0.10	0.96 0.93-1.00	0.04	0.99 0.95-1.03	0.79
Valvulo-arterial impedance, mmHg/ml.m ²	1.24 1.16-1.32	<0.001	–	–	1.16 1.07-1.25	<0.001	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval.

ONLINE TABLE 4: Receiver Operating Characteristic Curve Analyses and Cut-Point Values to predict 1-year Outcomes in AS Patients

1 YEAR	AVR					AVR or Death					All-cause Mortality					CV Mortality				
	AUC	p value*	Cut point	Sens	Spec	AUC	p value*	Cut point	Sens	Spec	AUC	p value*	Cut point	Sens	Spec	AUC	p value*	Cut point	Sens	Spec
Identification of best CPVs																				
<i>SVi</i>	0.52	0.32	–	–	–	0.54	0.03	35	37	72	0.62	<0.001	34	47	73	0.65	<0.001	36	61	64
<i>LVEF</i>	0.52	0.36	–	–	–	0.55	0.01	59	40	70	0.63	<0.001	56	51	72	0.65	<0.001	56	53	73
<i>V_{peak}</i>	0.84	<0.001	3.5	75	80	0.77	<0.001	3.5	65	80	0.49	0.81	–	–	–	0.51	0.69	–	–	–
<i>MG</i>	0.84	<0.001	31	71	84	0.77	<0.001	31	61	84	0.50	0.87	–	–	–	0.51	0.73	–	–	–
<i>AVA</i>	0.81	<0.001	1.01	84	66	0.76	<0.001	1.01	76	66	0.58	0.005	1.01	58	53	0.62	<0.001	1.05	70	48
<i>AVAi</i>	0.83	<0.001	0.55	85	68	0.77	<0.001	0.55	76	68	0.56	0.04	0.53	57	58	0.61	<0.001	0.55	66	54
<i>ELI</i>	0.83	<0.001	0.58	79	76	0.77	<0.001	0.59	73	72	0.56	0.04	0.59	55	58	0.60	0.001	0.60	64	57
<i>DVI</i>	0.82	<0.001	0.27	83	69	0.77	<0.001	0.27	73	69	0.55	0.06	–	–	–	0.59	0.006	0.27	62	53
<i>Z_{va}</i>	0.59	<0.001	4.4	62	60	0.59	<0.001	4.4	63	59	0.55	0.09	–	–	–	0.57	0.06	–	–	–
Other relevant CPVs†																				
<i>LVEF</i>	0.52	0.36	–	–	–	0.55	0.01	50	21	81	0.63	<0.001	50	43	81	0.65	<0.001	50	44	81
<i>V_{peak}</i>	0.84	<0.001	4.0	50	91	0.77	<0.001	4.0	42	91	0.49	0.81	–	–	–	0.51	0.69	–	–	–
<i>MG</i>	0.84	<0.001	40	45	93	0.77	<0.001	40	38	93	0.50	0.87	–	–	–	0.51	0.73	–	–	–
<i>AVA</i>	0.81	<0.001	0.80	56	84	0.76	<0.001	0.80	50	84	0.58	0.005	0.80	41	74	0.62	<0.001	0.80	47	74

Legend: AVR: aortic valve replacement; CPV: cut-point value; CV: cardiovascular; SVi: stroke volume index; LVEF: left ventricular ejection fraction; V_{peak}: peak aortic jet velocity; MG: mean gradient; AVA: aortic valve area; AVAi: aortic valve area index; ELI: energy loss index; DVI: dimensionless velocity index; Z_{va}: valvulo-arterial impedance; AUC: area under the curve; Sens: sensitivity; Spec: specificity. *: p value is from Receiver Operating Characteristic curve analysis. † Other CPVs that have been proposed in the guidelines or in the literature.

ONLINE TABLE 5: Predictors of All-Cause and Cardiovascular Mortality in the subset of 565 Patients with Severe AS

Baseline variables	All-cause Mortality n=300 deaths (53%)				CV Mortality n=227 CV deaths (40%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	2.14 1.86-2.45	<0.001	2.05 1.73-2.42	<0.001	2.44 2.07-2.88	<0.001	2.28 1.86-2.80	<0.001
Male gender	0.96 0.76-1.20	0.70	1.60 1.17-2.19	0.003	0.78 0.60-1.01	0.06	1.23 0.86-1.76	0.26
Body surface area, m ²	0.38 0.22-0.65	<0.001	0.44 0.20-0.96	0.04	0.28 0.15-0.54	<0.001	0.54 0.22-1.34	0.18
Hypertension	2.05 1.55-2.72	<0.001	1.18 0.88-1.60	0.27	2.78 1.94-3.98	<0.001	1.47 1.01-2.15	0.04
Diabetes	1.43 1.12-1.83	0.004	1.43 1.09-1.86	0.009	1.53 1.16-2.03	0.003	1.49 1.10-2.02	0.01
Coronary Artery Disease	1.71 1.34-2.18	<0.001	0.97 0.75-1.26	0.83	1.91 1.44-2.55	<0.001	1.12 0.82-1.52	0.47
COPD	2.28 1.78-2.92	<0.001	1.57 1.21-2.05	0.001	2.29 1.72-3.04	<0.001	1.54 1.13-2.08	0.006
Renal failure	2.70 2.09-3.49	<0.001	1.84 1.40-2.42	<0.001	2.92 2.19-3.90	<0.001	1.98 1.45-2.69	<0.001
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.28 1.19-1.37	<0.001	1.10 1.01-1.21	0.03	1.30 1.20-1.41	<0.001	1.08 0.97-1.20	0.14
Peak aortic jet velocity, m/s (per 1 m/s increase)	0.73 0.64-0.85	<0.001	–	–	0.72 0.61-0.85	<0.001	–	–
Mean Gradient, mmHg (per 10 mmHg increase)	0.85 0.79-0.92	<0.001	0.98 0.91-1.06	0.59	0.85 0.77-0.92	<0.001	0.99 0.91-1.08	0.86
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.10 1.04-1.17	0.001	–	–	1.15 1.07-1.23	<0.001	–	–

Aortic valve area index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.08 0.97-1.21	0.16	–	–	1.13 1.00-1.29	0.06	–	–
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.08 0.98-1.18	0.12	–	–	1.11 1.00-1.24	0.05	–	–
Dimensionless velocity index (per 0.1 decrease)	1.08 0.89-1.30	0.46	–	–	1.08 0.86-1.34	0.52	–	–
Mitral regurgitation	1.55 1.35-1.78	<0.001	1.03 0.88-1.20	0.74	1.59 1.35-1.87	<0.001	0.99 0.82-1.19	0.89
LVEF, % (per 5% decrease)	1.14 1.10-1.18	<0.001	1.07 1.02-1.13	0.006	1.15 1.10-1.20	<0.001	1.10 1.04-1.16	0.002
Valvulo-arterial impedance, mmHg/ml.m ²	1.32 1.19-1.46	<0.001	–	–	1.39 1.24-1.56	<0.001	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval

ONLINE TABLE 6: Predictors of All-Cause and Cardiovascular Mortality under Medical Treatment

Baseline variables	All-cause Mortality n=348 deaths (33%)				CV Mortality n=252 CV deaths (24%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	2.08 1.85-2.33	<0.001	1.98 1.72-2.28	<0.001	2.55 2.19-2.97	<0.001	2.35 1.96-2.82	<0.001
Male gender	0.99 0.80-1.22	0.92	1.53 1.15-2.05	0.004	0.83 0.65-1.06	0.14	1.45 1.02-2.04	0.04
Body surface area, m ²	0.51 0.31-0.84	0.008	0.87 0.43-1.76	0.70	0.31 0.17-0.57	<0.001	0.78 0.33-1.84	0.57
Hypertension	2.00 1.53-2.60	<0.001	1.39 1.06-1.84	0.02	2.22 1.61-3.05	<0.001	1.45 1.03-2.03	0.03
Diabetes	1.50 1.20-1.89	<0.001	1.30 1.02-1.65	0.03	1.74 1.34-2.26	<0.001	1.50 1.13-1.98	0.004
Coronary Artery Disease	1.74 1.40-2.16	<0.001	0.95 0.75-1.21	0.69	1.98 1.53-2.57	<0.001	1.08 0.81-1.44	0.59
COPD	2.36 1.88-2.96	<0.001	1.52 1.19-1.92	0.001	2.39 1.84-3.12	<0.001	1.36 1.03-1.81	0.03
Renal failure	3.27 2.58-4.16	<0.001	1.70 1.31-2.20	<0.001	4.39 3.36-5.74	<0.001	2.13 1.59-2.86	<0.001
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.22 1.14-1.30	<0.001	1.06 0.98-1.14	0.13	1.29 1.19-1.39	<0.001	1.10 1.01-1.20	0.045
Peak aortic jet velocity, m/s (per 1 m/s increase)	1.10 0.94-1.28	0.22	—	—	1.20 1.00-1.43	0.05	—	—
Mean Gradient, mmHg (per 10 mmHg increase)	1.55 1.36-1.76	<0.001	1.17 1.08-1.27	<0.001	1.12 1.02-1.24	0.02	1.25 1.14-1.37	<0.001
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.10 1.06-1.14	<0.001	—	—	1.17 1.12-1.23	<0.001	—	—
Aortic valve area index, cm ² /m ²	1.15	<0.001	—	—	1.26 1.16-1.37	<0.001	—	—

(per 0.1 cm ² /m ² decrease)	1.07-1.23							
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.11 1.05-1.17	<0.001	–	–	1.18 1.11-1.26	<0.001	–	–
Dimensionless velocity index (per 0.1 decrease)	1.24 1.10-1.40	0.001	–	–	1.39 1.20-1.61	<0.001	–	–
Mitral regurgitation	1.55 1.36-1.76	<0.001	1.15 1.00-1.32	0.06	1.71 1.47-1.99	<0.001	1.16 0.98-1.37	0.08
LVEF, % (per 5% decrease)	1.15 1.11-1.19	<0.001	1.07 1.02-1.12	0.008	1.17 1.13-1.22	<0.001	1.06 1.01-1.12	0.04
Valvulo-arterial impedance, mmHg/ml.m ²	1.41 1.06-1.87	0.02	–	–	1.45 1.04-2.02	0.03	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval

ONLINE TABLE 7: Predictors of All-Cause and Cardiovascular Mortality in the 919 Patients with Evaluation of Symptomatic Status

Baseline variables	All-cause Mortality n=482 deaths (52%)				CV Mortality n=357 CV deaths (39%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	2.04 1.84-2.27	<0.001	1.97 1.74-2.23	<0.001	2.34 2.06-2.66	<0.001	2.22 1.90-2.59	<0.001
Male gender	0.95 0.79-1.13	0.56	1.26 0.99-1.62	0.07	0.84 0.68-1.02	0.09	1.16 0.87-1.55	0.31
Body surface area, m ²	0.53 0.34-0.81	0.004	0.92 0.51-1.67	0.79	0.38 0.23-0.64	<0.001	0.87 0.44-1.75	0.71
Symptoms (NYHA _≥ 2)	2.01 1.59-2.56	<0.001	1.28 0.99-1.66	0.06	2.14 1.61-2.83	<0.001	1.23 0.91-1.68	0.18
Hypertension	2.09 1.66-2.64	<0.001	1.27 0.98-1.61	0.07	2.59 1.94-3.46	<0.001	1.45 1.07-1.96	0.02
Diabetes	1.49 1.24-1.81	<0.001	1.39 1.13-1.70	0.001	1.61 1.30-2.01	<0.001	1.54 1.22-1.94	<0.001
Coronary Artery Disease	1.71 1.41-2.06	<0.001	0.95 0.77-1.17	0.61	1.93 1.54-2.42	<0.001	1.07 0.84-1.38	0.58
COPD	2.29 1.88-2.77	<0.001	1.52 1.24-1.86	<0.001	2.25 1.79-2.82	<0.001	1.49 1.17-1.89	<0.001
Renal failure	2.77 2.27-3.38	<0.001	1.63 1.32-2.02	<0.001	3.18 2.54-3.98	<0.001	1.78 1.40-2.26	<0.001
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.25 1.18-1.32	<0.001	1.07 1.01-1.14	0.03	1.29 1.21-1.38	<0.001	1.09 1.01-1.17	0.03
Peak aortic jet velocity, m/s (per 1 m/s increase)	0.84 0.76-0.94	0.003	—	—	0.85 0.75-0.96	0.01	—	—
Mean Gradient, mmHg (per 10 mmHg increase)	0.91 0.86-0.97	0.004	1.00 0.94-1.06	0.93	0.92 0.85-0.99	0.02	1.01 0.95-1.09	0.72

Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.05 1.01-1.08	0.005	—	—	1.08 1.04-1.12	<0.001	—	—
Aortic valve area index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.05 0.99-1.11	0.10	—	—	1.09 1.02-1.17	0.008	—	—
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.03 0.99-1.07	0.19	—	—	1.06 1.01-1.12	0.02	—	—
Dimensionless velocity index (per 0.1 decrease)	1.05 0.94-1.16	0.43	—	—	1.10 0.97-1.24	0.13	—	—
Mitral regurgitation	1.50 1.34-1.68	<0.001	1.09 0.97-1.23	0.16	1.62 1.42-1.85	<0.001	1.12 0.98-1.29	0.11
LVEF, % (per 5% decrease)	1.16 1.13-1.20	<0.001	1.08 1.04-1.12	<0.001	1.17 1.13-1.22	<0.001	1.08 1.03-1.13	0.002
Valvulo-arterial impedance, mmHg/ml.m ²	1.31 1.20-1.43	<0.001	—	—	1.38 1.25-1.52	<0.001	—	—

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval

ONLINE TABLE 8: Predictors of the Composite of AVR or Death and AVR alone in the subset of 212 Asymptomatic Patients (patients with NYHA class I; median follow-up: 7.4 [4.2-9.2])

Baseline variables	AVR or Death n=175 AVR or death (83%)				AVR n=119 AVR (56%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	1.17 1.06-1.29	0.002	1.18 1.05-1.32	0.004	0.96 0.87-1.06	0.41	–	–
Male gender	1.36 1.00-1.85	0.05	1.19 0.85-1.67	0.31	1.59 1.08-2.34	0.02	1.16 0.70-1.94	0.56
Body surface area, m ²	1.53 0.79-2.95	0.21	–	–	2.65 1.20-5.86	0.02	0.99 0.34-2.89	0.98
Hypertension	1.33 0.97-1.82	0.08	1.62 1.14-2.31	0.007	0.96 0.67-1.40	0.85	–	–
Diabetes	1.15 0.79-1.68	0.47	–	–	1.14 0.72-1.21	0.58	–	–
Coronary Artery Disease	1.33 0.97-1.80	0.07	1.07 0.76-1.52	0.70	1.15 0.78-1.68	0.48	–	–
COPD	1.95 1.14-3.31	0.01	2.73 1.53-4.86	0.001	0.74 0.27-1.99	0.55	–	–
Renal failure	1.67 1.03-2.70	0.04	1.23 0.72-2.10	0.45	0.62 0.25-1.51	0.29	–	–
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.03 0.94-1.13	0.52	–	–	0.92 0.82-1.02	0.11	1.04 0.93-1.18	0.43
Peak aortic jet velocity, m/s (per 1 m/s increase)	2.19 1.80-2.67	<0.001	–	–	3.03 2.40-3.81	<0.001	–	–
Mean Gradient, mmHg (per 10 mmHg increase)	1.49 1.35-1.66	<0.001	1.66 1.48-1.85	<0.001	1.73 1.54-1.95	<0.001	1.74 1.53-1.97	<0.001
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.25 1.18-1.33	<0.001	–	–	1.29 1.19-1.39	<0.001	–	–

Aortic valve area index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.50 1.34-1.68	<0.001	–	–	1.68 1.46-1.94	<0.001	–	–
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.37 1.25-1.50	<0.001	–	–	1.50 1.34-1.67	<0.001	–	–
Dimensionless velocity index (per 0.1 decrease)	1.86 1.52-2.29	<0.001	–	–	2.48 1.90-3.24	<0.001	–	–
Mitral regurgitation	1.09 0.89-1.33	0.42	–	–	0.97 0.76-1.25	0.82	–	–
LVEF, % (per 5% decrease)	1.03 0.94-1.12	0.51	–	–	0.93 0.83-1.05	0.24	–	–
Valvulo-arterial impedance, mmHg/ml.m ²	1.41 1.16-1.70	<0.001	–	–	1.32 1.05-1.66	0.02	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval.

ONLINE TABLE 9: Predictors of All-Cause and Cardiovascular Mortality in the subset of 212 Asymptomatic Patients (patients with NYHA class I; median follow-up: 7.4 [4.2-9.2])

Baseline variables	All-cause Mortality n=81 deaths (38%)				CV Mortality n=57 CV deaths (27%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	3.01 2.26-3.99	<0.001	2.79 2.00-3.90	<0.001	3.66 2.56-5.29	<0.001	3.54 2.24-5.61	<0.001
Male gender	0.79 0.50-1.24	0.31	–	–	0.93 0.54-1.60	0.09	1.24 0.58-2.65	0.58
Body surface area, m ²	0.36 0.13-1.04	0.06	0.68 0.19-2.38	0.54	0.25 0.07-0.88	0.03	0.47 0.07-3.00	0.42
Hypertension	2.72 1.64-4.53	<0.001	1.45 0.83-2.54	0.19	3.08 1.65-5.74	<0.001	1.55 0.80-3.07	0.21
Diabetes	1.47 0.88-2.47	0.14	–	–	1.29 0.68-2.45	0.43	–	–
Coronary Artery Disease	2.25 1.45-3.48	<0.001	1.26 0.79-1.99	0.33	2.90 1.71-4.91	<0.001	1.48 0.77-2.84	0.24
COPD	4.63 2.59-8.28	<0.001	4.24 1.15-8.38	<0.001	4.78 2.39-9.53	<0.001	4.83 2.07-11.31	<0.001
Renal failure	4.36 2.56-7.41	<0.001	1.49 0.77-2.85	0.23	4.16 2.18-7.95	<0.001	1.25 0.55-2.82	0.60
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.28 1.11-1.48	0.001	1.27 1.08-1.50	0.004	1.31 1.11-1.56	0.002	1.34 1.09-1.64	0.006
Peak aortic jet velocity, m/s (per 1 m/s increase)	0.74 0.54-1.01	0.06	–	–	0.73 0.50-1.05	0.09	–	–
Mean Gradient, mmHg (per 10 mmHg increase)	0.84 0.70-1.01	0.07	1.16 0.97-1.39	0.10	0.84 0.68-1.04	0.11	1.19 0.96-1.46	0.11
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.07 0.98-1.16	0.14	–	–	1.08 0.98-1.21	0.10	–	–

Aortic valve area index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.03 0.89-1.19	0.72	–	–	1.04 0.88-1.24	0.64	–	–
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.02 0.92-1.14	0.67	–	–	1.03 0.90-1.17	0.64	–	–
Dimensionless velocity index (per 0.1 decrease)	0.90 0.70-1.15	0.40	–	–	0.92 0.68-1.24	0.59	–	–
Mitral regurgitation	1.30 0.97-1.75	0.08	0.93 0.70-1.25	0.64	1.38 0.97-1.96	0.07	0.96 0.68-1.38	0.86
LVEF, % (per 5% decrease)	1.17 1.05-1.31	0.005	1.04 0.92-1.18	0.56	1.18 1.03-1.34	0.02	1.02 0.87-1.19	0.81
Valvulo-arterial impedance, mmHg/ml.m ²	1.41 1.06-1.87	0.02	–	–	1.45 1.04-2.02	0.03	–	–

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval

ONLINE TABLE 10: Predictors of All-Cause and Cardiovascular Mortality under Medical Treatment

Baseline variables	All-cause Mortality n=348 deaths (33%)				CV Mortality n=252 CV deaths (24%)			
	Individual		Multivariable		Individual		Multivariable	
	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value	HR 95% CI	p value
Age, years (per 10 yrs increase)	2.08 1.85-2.33	<0.001	1.98 1.72-2.28	<0.001	2.55 2.19-2.97	<0.001	2.35 1.96-2.82	<0.001
Male gender	0.99 0.80-1.22	0.92	1.53 1.15-2.05	0.004	0.83 0.65-1.06	0.14	1.45 1.02-2.04	0.04
Body surface area, m ²	0.51 0.31-0.84	0.008	0.87 0.43-1.76	0.70	0.31 0.17-0.57	<0.001	0.78 0.33-1.84	0.57
Hypertension	2.00 1.53-2.60	<0.001	1.39 1.06-1.84	0.02	2.22 1.61-3.05	<0.001	1.45 1.03-2.03	0.03
Diabetes	1.50 1.20-1.89	<0.001	1.30 1.02-1.65	0.03	1.74 1.34-2.26	<0.001	1.50 1.13-1.98	0.004
Coronary Artery Disease	1.74 1.40-2.16	<0.001	0.95 0.75-1.21	0.69	1.98 1.53-2.57	<0.001	1.08 0.81-1.44	0.59
COPD	2.36 1.88-2.96	<0.001	1.52 1.19-1.92	0.001	2.39 1.84-3.12	<0.001	1.36 1.03-1.81	0.03
Renal failure	3.27 2.58-4.16	<0.001	1.70 1.31-2.20	<0.001	4.39 3.36-5.74	<0.001	2.13 1.59-2.86	<0.001
Stroke Volume index, ml/m ² (per 5 ml/m ² decrease)	1.22 1.14-1.30	<0.001	1.06 0.98-1.14	0.13	1.29 1.19-1.39	<0.001	1.10 1.01-1.20	0.045
Peak aortic jet velocity, m/s (per 1 m/s increase)	1.10 0.94-1.28	0.22	—	—	1.20 1.00-1.43	0.05	—	—
Mean Gradient, mmHg (per 10 mmHg increase)	1.55 1.36-1.76	<0.001	1.17 1.08-1.27	<0.001	1.12 1.02-1.24	0.02	1.25 1.14-1.37	<0.001
Aortic valve area, cm ² (per 0.1 cm ² decrease)	1.10 1.06-1.14	<0.001	—	—	1.17 1.12-1.23	<0.001	—	—
Aortic valve area index, cm ² /m ²	1.15	<0.001	—	—	1.26 1.16-1.37	<0.001	—	—

(per 0.1 cm ² /m ² decrease)	1.07-1.23							
Energy loss index, cm ² /m ² (per 0.1 cm ² /m ² decrease)	1.11	<0.001	–	–	1.18	<0.001	–	–
	1.05-1.17				1.11-1.26			
Dimensionless velocity index (per 0.1 decrease)	1.24	0.001	–	–	1.39	<0.001	–	–
	1.10-1.40				1.20-1.61			
Mitral regurgitation	1.55	<0.001	1.15	0.06	1.71	<0.001	1.16	0.08
	1.36-1.76		1.00-1.32		1.47-1.99		0.98-1.37	
LVEF, % (per 5% decrease)	1.15	<0.001	1.07	0.008	1.17	<0.001	1.06	0.04
	1.11-1.19		1.02-1.12		1.13-1.22		1.01-1.12	
Valvulo-arterial impedance, mmHg/ml.m ²	1.41	0.02	–	–	1.45	0.03	–	–
	1.06-1.87				1.04-2.02			

Legend: AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Z_{va}: valvulo-arterial impedance; HR: hazard ratio; CI: confidence interval

ONLINE FIGURE

