Supplementary materials

Impact of the left ventricular mass index on the outcomes of severe aortic stenosis

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In line with the ASE recommendations[1], no LVH was defined as LVMI<115 in male, or <95 in female, mild LVH was 116≤LVMI<132 in male, or 96≤LVMI<109 in female, moderate LVH was 132≤LVMI≤148 in male, or 109≤LVMI≤121 in female, and severe was LVMI>148 in male, or >121 in female. These values were the consensus-based partition cutoffs which were derived from participants without hypertension, diabetes, dyslipidemia, chronic kidney disease, or marked obesity.[2-7]

We compared the 5-year clinical outcomes among 4 LVH classifications in the conservative management and initial AVR cohorts. Multivariable Cox proportional hazards models were used to estimate the risk of mild, moderate, and severe LVH relative to no LVH for the primary outcome.

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Supplementary Table 1. Numbers of patients with missing values for the calculation of LVMI

Variable	Numbers of patients with missing values
Body surface area	459
Left ventricular end-diastolic diameter	38
Interventricular septal wall thickness in diastole	85
Posterior wall thickness in diastole	75

LVMI=left ventricular mass index

Supplementary Table 2. Baseline characteristics of the patients available with LVMI data and those unavailable with LVMI data

Variable	Available LVMI data (N=3282)	Unavailable LVMI data (N=533)	P value
Clinical characteristics			
Age, years	77.0 (9.6)	82 (9.2)	<0.001
Age ≥80 years	1378 (42)	351 (66)	<0.001
Male	1275 (39)	168 (32)	0.0012
BMI ‖	22 (3.8)	21 (3.8)	0.29
BMI <22	1822 (56)	504 (95)	0.02
Hypertension	2326 (71)	341(64)	0.0013
Current smoking	180 (5)	16 (3)	0.016
History of smoking	758 (23)	72 (14)	<0.001
Dyslipidemia †	1226 (37)	101 (19)	<0.001
On statin therapy	903 (28)	67 (13)	<0.001
Diabetes mellitus	806 (25)	91 (17)	<0.001
On insulin therapy	177 (5)	1 (2)	0.0010
Coronary artery disease	1036 (32)	108 (20)	<0.001
Prior myocardial infarction	286 (9)	37 (7)	0.17
Prior PCI	459 (14)	43 (8)	<0.001
Prior open heart surgery	288 (9)	28 (5)	0.0062
Prior symptomatic stroke	428 (13)	75 (14)	0.51
Atrial fibrillation or flutter	698 (21)	130 (24)	0.10
Aortic/peripheral vascular disease	263 (8)	19(4)	<0.001
Serum creatinine, mg/dl	0.9 (0.7-1.3)	0.9 (0.7-1.3)	0.012
ESRD ‡	486 (15)	72 (14)	0.43
Anemia §	1784 (54)	333 (62)	<0.001
Liver cirrhosis (Child–Pugh B or C)	34 (1)	4 (1)	0.54
Malignancy	458 (14)	59 (11)	0.071
Malignancy currently under treatment	133 (4)	16 (3)	0.25
Chest wall irradiation	22 (1)	3 (1)	0.78
Immunosuppressive therapy	115 (4)	16 (3)	0.55
Chronic lung disease	365 (11)	35 (7)	0.0015
Chronic lung disease (moderate or severe)	97 (3)	15 (3)	0.86
Logistic EuroSCORE	9.5 (5.5-16.1)	12.1 (7.5-20.0)	<0.001
EuroSCORE II	2.8 (1.6-4.7)	3.6 (2.2-5.7)	<0.001
STS score (PROM)	3.8 (2.2-6.7)	3.4 (2.1-6.1)	0.052

Initial AVR group	1111 (34)	86 (16)	<0.001
Etiology of aortic stenosis			
Degenerative	2875 (88)	204 (95)	
Congenital (Unicuspid, Bicuspid, or Quadricuspid)	247 (8)	14 (3)	
Rheumatic	137 (4)	13 (2)	<0.001
Infective endocarditis	6 (0.2)	1 (0.2)	
Others	17 (0.5)	1 (0.1)	
Echocardiographic variables			
Vmax, m/s	4.1 (0.9)	4.2 (0.9)	0.69
Vmax ≥5m/s	609 (19)	89 (17)	0.30
Vmax ≥4m/s	1863 (57)	322 (60)	0.11
Peak aortic PG, mmHg	72 (32)	72 (29)	0.90
Mean aortic PG, mmHg	41 (20)	40 (18)	0.21
AVA (equation of continuity), cm^2	0.72 (0.18)	0.68 (0.19)	<0.001
LV end-systolic diameter, mm	30 (8)	30 (8)	0.11
LVEF, %	63 (13)	61 (14)	0.012
LVEF <40%	235 (7)	58 (11)	0.0028
LVEF <50%	497 (15)	96 (18)	0.090
LVEF <68%	1928 (59)	314 (59)	0.94
Any combined valvular disease (moderate or severe)	1310 (40)	248 (47)	0.0040
Moderate or severe AR	665 (20)	126 (24)	0.074
Moderate or severe MS	116 (4)	17 (3)	0.69
Moderate or severe MR	625 (19)	138 (26)	<0.001
Moderate or severe TR	527 (16)	101 (19)	0.095
TR pressure gradient ≥40mmHg	516 (16)	90 (17)	0.50

Values are number (%), mean (SD), or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables.

|| Body mass index was calculated as weight in kilograms divided by height in meters squared.

† Dyslipidemia was defined as total cholesterol levels ≥240 mg/dL, high-density lipoprotein cholesterol levels <40 g/dL or the use of statin

§ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

‡ ESRD was defined as creatinine level >2mg/dl and/or hemodialysis.

AR=aortic regurgitation, AVA=aortic valve area, AVR=aortic valve replacement, BMI=body mass index,

ESRD=end-stage renal disease, IQR=interquartile range, LV=left ventricular, LVEF=left ventricular ejection

fraction, MR=mitral regurgitation, MS=mitral stenosis, PCI=percutaneous coronary intervention, PG=pressure gradient, PROM=predicted risk of mortality, SD=standard deviation, STS=Society of Thoracic Surgeons, TR=tricuspid regurgitation, and Vmax=peak aortic jet velocity

Other abbreviations are same as in supplementary table 1.

Supplementary Table 3. Baseline characteristics of all patients in whom LVMI data at the index echocardiography was available

Variable	All patients (N=3282)
Age, years	77.0 (9.6)
Age ≥80	1378 (42)
Female	2007 (61)
BMI <22	1822 (56)
LVEF <50%	497 (15)
TR pressure gradient ≥40 mmHg	516 (16)
Vmax ≥4m/s	1863 (57)
Moderate or severe AR	665 (20)
Moderate or severe MS	116 (4)
Moderate or severe MR	625 (19)
Moderate or severe TR	527 (16)
Degenerative etiology	2875 (88)
Prior PCI	459 (14)
Prior CABG	177 (5)
Prior myocardial infarction	286 (9)
Prior heart failure	541 (16)
Aortic/peripheral vascular disease	263 (8)
Hypertension	2326 (71)
Dyslipidemia	1226 (37)
On statin therapy	903 (28)
History of smoking	758 (23)
Diabetes mellitus on insulin therapy	177 (5)
Chronic lung disease (moderate or severe)	97 (3)
Anemia	1784 (54)
ESRD	486 (15)

Values are number (%), mean (SD).

CABG=coronary artery bypass grafting

Other abbreviations are same as in supplementary table 1 and 2.

Supplementary Table 4. Baseline clinical and echocardiographic characteristics in the conservative management and initial AVR cohort

Variable	All patients	Conservative management cohort			Initial AVR cohort		
		Normal LVMI (N=691)	High LVMI (N=1480)	P value	Normal LVMI (N=217)	High LVMI (N=894)	P value
Clinical characteristics							
History of smoking	758 (23)	186 (27)	280 (19)	<0.001	68 (31)	224 (25)	0.059
Dyslipidemia	1226 (37)	282 (41)	490 (33)	<0.001	109 (50)	345 (39)	0.0018
On statin therapy	903 (28)	223 (32)	357 (24)	<0.001	76 (35)	247 (28)	0.031
Prior myocardial infarction	286 (9)	88 (13)	152 (10)	0.088	11 (5)	35 (4)	0.44
Prior PCI	459 (14)	129 (19)	236 (16)	0.11	26 (12)	68 (8)	0.038
Prior CABG	177 (5)	56 (8)	90 (6)	0.080	8 (4)	23 (3)	0.37
Prior open heart surgery	288 (9)	90 (13)	152 (10)	0.058	11 (5)	35 (4)	0.44
Aortic/peripheral vascular disease	263 (8)	79 (11)	117 (8)	0.0076	14 (6)	53 (6)	0.77
Chest wall irradiation	22 (1)	6 (1)	9 (1)	0.58	3 (1.4)	4 (0.5)	0.14
Immunosuppressive therapy	115 (4)	23 (3)	65 (4)	0.24	3 (1)	24 (3)	0.26
Chronic lung disease	365 (11)	77 (11)	155 (10)	0.64	25 (12)	108 (12)	0.82
Malignancy	458 (14)	137 (20)	199 (13)	<0.001	23 (11)	99 (11)	0.84
Logistic EuroSCORE, %	9.5 (5.5-16.1)	9.0 (5.5-16.1)	11.4 (7.0-20.0)	<0.001	5.4 (2.1-8.4)	7.5 (4.8-12.4)	<0.001
EuroSCORE II, %	2.8 (1.6-4.7)	2.7 (1.6-4.5)	3.4 (2.1-5.5)	<0.001	1.6 (1.1-2.6)	2.3 (1.4-3.7)	<0.001
Etiology of aortic stenosis							
Degenerative	2875 (88)	622 (90)	1355 (92)		154 (71)	744 (83)	
Congenital (Unicuspid, Bicuspid, or Quadricuspid)	247 (8)	40 (6)	57 (4)	0.11	49 (23)	98 (11)	<0.001
Rheumatic	137 (4)	24 (3)	62 (4)		13 (6)	38 (4)	
Infective endocarditis	6 (0.2)	1 (0.1)	0 (0)		0 (0)	5 (0.6)	
Others	17 (0.5)	4 (0.6)	6 (0.4)		1 (0.5)	9 (1)	
Echocardiographic variables							
IVST in diastole, mm	11.3 (2.3)	9.7 (1.5)	11.7 (2.1)	<0.001	10.0 (1.6)	12.4 (2.3)	<0.001
PWT in diastole, mm	10.9 (2.0)	9.4 (1.4)	11.2 (1.8)	<0.001	9.8 (1.5)	12.0 (2.0)	<0.001
Moderate or severe AR	665 (20)	82 (12)	309 (21)	<0.001	26 (12)	248 (28)	<0.001
Moderate or severe MS	116 (4)	21 (3)	46 (3)	0.93	12 (6)	37 (4)	0.37
Moderate or severe MR	625 (19)	75 (11)	340 (23)	<0.001	20 (9)	190 (21)	<0.001
Moderate or severe TR	527 (16)	116 (17)	274 (19)	0.33	29 (13)	108 (12)	0.61

Values are number (%), mean (SD), or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables.

IVST=interventricular septal wall thickness, and PWT=posterior wall thickness

Other abbreviations are same as in supplementary table 1, 2 and 3.

Supplementary Table 5. Baseline clinical and echocardiographic characteristics in the conservative management and initial AVR cohorts: no LVH, mild LVH, moderate LVH, and severe LVH groups.

Variable	Conservative management cohort (N=2171)					Initial AVR cohort (N=1111)				
	Severity partition of LVMI †					Severity partition of LVMI †				
	No LVH (N=691)	Mild LVH (N=353)	Moderate LVH (N=319)	Severe LVH (N=808)	P value	No LVH (N=217)	Mild LVH (N=160)	Moderate LVH (N=143)	Severe LVH (N=591)	P value
Clinical characteristics										
Age, years #	77.8 (9.6)	78.9 (9.0)	79.1 (8.9)	79.9 (9.3)	<0.001	71.6 (9.4)	73.3 (8.6)	73.3 (9.0)	73.7 (8.8)	0.040
Age ≥80 years	321 (46)	170 (48)	164 (51)	453 (56)	0.0017	40 (18)	32 (20)	43 (30)	155 (26)	0.024
Atrial fibrillation or flutter #	157 (23)	79 (22)	79 (25)	193 (24)	0.84	43 (20)	29 (18)	31 (22)	87 (15)	0.13
Malignancy currently under treatment #	53 (8)	10 (3)	9 (3)	38 (5)	<0.001	2 (1)	4 (3)	4 (3)	13 (2)	0.53
Admission for heart failure at index echocardiography #	66 (10)	49 (14)	44 (14)	225 (28)	<0.001	21 (10)	22 (14)	20 (14)	174 (29)	<0.001
Echocardiographic variables										
Vmax, m/s	3.6 (0.7)	3.8 (0.8)	3.9 (0.8)	4.1 (0.9)	<0.001	4.4 (0.7)	4.6 (0.7)	4.6 (0.8)	4.9 (0.9)	<0.001
Vmax >4m/s #	204 (30)	142 (40)	143 (45)	455 (56)	<0.001	165 (76)	131 (82)	116 (81)	507 (86)	0.012
LVEF, %	65 (11)	64 (12)	64 (13)	60 (15)	<0.001	69 (9)	66 (12)	63 (13)	60 (15)	<0.001
LVEF <68% #	393 (57)	205 (58)	177 (55)	537 (66)	<0.001	92 (42)	80 (50)	81 (57)	363 (61)	<0.001
LVMI, g/m^2	89 (79-99)	106 (101-122)	118 (113-143)	154 (137-176)	<0.001	91 (82-100)	109 (104-122)	132 (116-139)	164 (144-189)	<0.001
Any combined valvular disease (moderate or severe) #	199 (29)	118 (33)	130 (41)	414 (51)	<0.001	60 (28)	56 (35)	54 (38)	279 (47)	<0.001

Values are number (%), mean (SD), or median (interquartile range).

P values were calculated from a chi-square test or Fisher's exact test for categorical variables, and the one-way analysis of variance or Krusukal-Wallis test for continuous variables.

† No LVH was defined as LVMI<115 in male, or <95 in female, mild LVH was 116≤LVMI<132 in male, or 96≤LVMI<109 in female, moderate LVH was 132≤LVMI≤148 in male, or 109≤LVMI≤121 in female, and severe LVH was LVMI>148 in male, or >121 in female.

Potential risk-adjusting variables selected for parsimonious Cox proportional hazard models.

LVH=left ventricular hypertrophy

Other abbreviations are same as in supplementary table 1, and 2.

Supplementary Table 6. Clinical outcomes of patients in the conservative management and initial AVR cohorts: no LVH, mild LVH, moderate LVH, and severe LVH groups.

Variables	No. of patients with event (Cumulative 5-Year Incidence)	Adjusted		P value for interaction
		Hazard Ratio (95% CI)	P value	
Conservative management cohort				
No LVH	164/691 (33%)	1 (Reference)		
Mild LVH	109/353 (37%)	1.36 (1.07-1.75)	0.014	
Moderate LVH	103/319 (39%)	1.45 (1.12-1.86)	0.0044	
Severe LVH	370/808 (59%)	1.87 (1.52-2.29)	<0.001	
Initial AVR cohort				0.034
No LVH	26/217 (14%)	1 (Reference)		
Mild LVH	15/160 (9.8%)	0.71 (0.37-1.36)	0.30	
Moderate LVH	15/143 (14%)	0.71 (0.36-1.40)	0.33	
Severe LVH	93/591 (19%)	1.26 (0.78-2.04)	0.35	

CI=confidence interval, HR=hazard ratio

Abbreviations are same as in Supplementary table 1, 2, and 5.

Supplementary Table 7. Subgroup analysis for the primary outcome measure in the conservative management and initial AVR cohort

		Normal LVMI	High LVMI	Unadjusted		Adjusted		
		N of patients with event/N of patients at risk (Cumulative 5-year incidence [%])	N of patients with event/N of patients at risk (Cumulative 5-year incidence [%])	HR (95% CI)	P value	HR (95% CI)	P value	P value for interaction
Conservative stratum	Vmax <4 m/s	120/487 (35)	267/740 (47)	1.74 (1.41-2.17)	<0.001	1.41 (1.11-1.80)	0.0051	0.38
	Vmax ≥4 m/s	44/204 (28)	315/740 (51)	2.34 (1.72-3.24)	<0.001	1.77 (1.25-2.50)	0.0013	
Initial AVR stratum	Vmax <4 m/s	7/52 (16)	31/140 (34)	1.47 (0.68-3.65)	0.34	0.78 (0.29-2.09)	0.63	0.82
	Vmax ≥4 m/s	19/165 (13)	92/754 (14)	1.03 (0.65-1.75)	0.90	1.04 (0.61-1.78)	0.88	
Conservative stratum	LVEF ≥50%	139/630 (30)	443/1229 (45)	1.89 (1.56-2.29)	<0.001	1.47 (1.19-1.83)	<0.001	0.20
	LVEF <50%	25/61 (66)	139/251 (74)	1.33 (0.88-2.08)	0.18	1.42 (0.86-2.36)	0.17	
Initial AVR stratum	LVEF ≥50%	24/209 (14)	94/717 (16)	1.12 (0.73-1.79)	0.62	1.00 (0.61-1.62)	0.99	0.60
	LVEF <50%	2/8 (13)	29/177 (19)	0.66 (0.20-4.12)	0.60	0.96 (0.20-4.69)	0.96	
Conservative stratum	Without AHF	123/625 (28)	393/1162 (42)	1.97 (1.61-2.42)	<0.001	1.73 (1.39-2.17)	<0.001	<0.001

	With AHF	41/66 (84)	189/318 (75)	0.86 (0.62-1.22)	0.39	1.01 (0.67-1.53)	0.96	
Initial AVR stratum	Without AHF	19/196 (11)	79/678 (13)	1.19 (0.74-2.03)	0.48	1.28 (0.74-2.23)	0.38	0.057
	With AHF	7/21 (55)	44/216 (27)	0.42 (0.20-1.04)	0.060	0.38 (0.14-1.00)	0.050	

The primary outcome measure was defined as a composite of aortic valve-related death or hospitalization due to heart failure.

AHF=acute heart failure

Other abbreviations are same as in supplementary table 1, 2, 5 and 6.

Supplementary figure legend

Supplementary Figure 1. Cumulative incidence of the primary outcome measure (a

composite of aortic valve-related death or hospitalization due to heart failure): no LVH, mild

LVH, moderate LVH, and severe LVH groups

A) Conservative management cohort and B) Initial AVR cohort

AVR=aortic valve replacement, and LVH=left ventricular hypertrophy
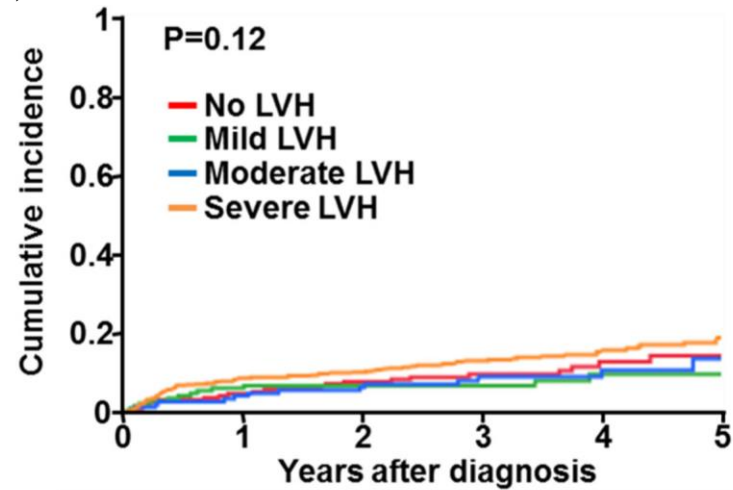
Supplementary Figure 1.

A)
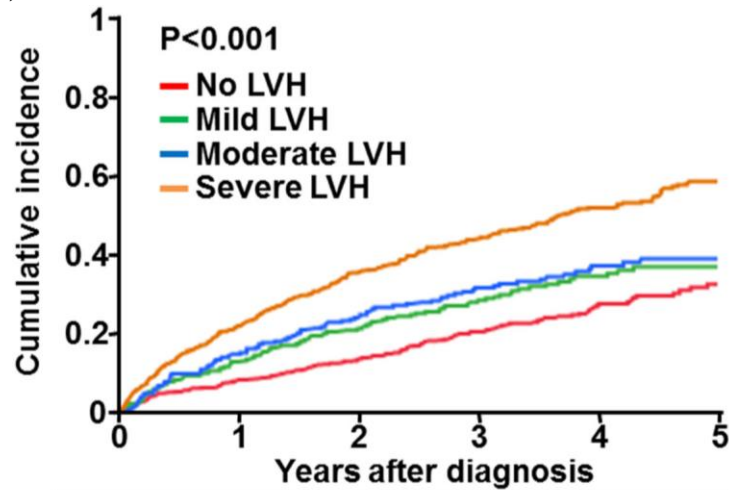
Interval	0 day	1 year	3 years	5 years
No LVH				
N of patients with at least 1 event		54	121	153
N of patients at risk	691	561	349	81
Cumulative incidence (%)		8.3	21	33
Mild LVH				
N of patients with at least 1 event		43	86	100
N of patients at risk	353	269	157	45
Cumulative incidence (%)		13	28	37
Moderate LVH				
N of patients with at least 1 event		44	87	98
N of patients at risk	319	239	139	36
Cumulative incidence (%)		15	32	39
Severe LVH				
N of patients with at least 1 event		164	302	353
N of patients at risk	808	546	273	84
Cumulative incidence (%)		22	44	59

B)

Interval	0 day	1 year	3 years	5 years
No LVH				
N of patients with at least 1 event		10	19	23
N of patients at risk	217	190	123	32
Cumulative incidence (%)		4.8	10	14
Mild LVH				
N of patients with at least 1 event		10	11	13
N of patients at risk	160	145	99	30
Cumulative incidence (%)		6.3	6.9	9.8
Moderate LVH				
N of patients with at least 1 event		6	12	14
N of patients at risk	143	131	89	28
Cumulative incidence (%)		4.3	9.2	14
Severe LVH				
N of patients with at least 1 event		50	71	85
N of patients at risk	591	488	336	129
Cumulative incidence (%)		8.8	13	19

References of supplementary materials

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