ORIGINAL RESEARCH

Prognostic Impact of Aortic Valve Area in Conservatively Managed Patients With Asymptomatic Severe Aortic Stenosis With Preserved Ejection Fraction

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***Background*—**Data are scarce on the role of aortic valve area (AVA) to identify those patients with asymptomatic severe aortic stenosis (AS) who are at high risk of adverse events. We sought to explore the prognostic impact of AVA in asymptomatic patients with severe AS in a large observational database.

***Methods and Results*—**Among 3815 consecutive patients with severe AS enrolled in the CURRENT AS (Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis) registry, the present study included 1309 conservatively managed asymptomatic patients with left ventricular ejection fraction ≥50%. The study patients were subdivided into 3 groups based on AVA (group 1: AVA >0.80 cm^2, N=645; group 2: 0.8 cm^2 ≥AVA >0.6 cm^2, N=465; and group 3: AVA ≤0.6 cm^2, N=199). The prevalence of very severe AS patients (peak aortic jet velocity ≥5 m/s or mean aortic pressure gradient ≥60 mm Hg) was 2.0%, 5.8%, and 26.1% in groups 1, 2, and 3, respectively. The cumulative 5-year incidence of AVR was not different across the 3 groups (39.7%, 43.7%, and 39.9%; *P*=0.43). The cumulative 5-year incidence of the primary outcome measure (a composite of aortic valve–related death or heart failure hospitalization) was incrementally higher with decreasing AVA (24.1%, 29.1%, and 48.1%; *P*<0.001). After adjusting for confounders, the excess risk of group 3 and group 2 relative to group 1 for the primary outcome measure remained significant (hazard ratio, 2.21, 95% CI, 1.56–3.11, *P*<0.001; and hazard ratio, 1.34, 95% CI, 1.01–1.78, *P*=0.04, respectively).

***Conclusions*—**AVA ≤0.6 cm^2 would be a useful marker to identify those high-risk patients with asymptomatic severe AS, who might benefit from early AVR.

***Clinical Trial Registration*—**URL: www.umin.ac.jp. Unique identifier: UMIN000012140. **(*J Am Heart Assoc*. 2019;8:e010198. DOI: 10.1161/JAHA.118.010198.)**

Key Words: aortic valve area • aortic valve replacement • aortic valve stenosis • asymptomatic • echocardiography • prognosis

Current guidelines recommend aortic valve replacement (AVR) for severe aortic stenosis (AS) when the patients have symptoms and/or left ventricular (LV) systolic dysfunction.[1,2] However, we previously reported that the prognosis of asymptomatic patients with severe AS was dismal, and the initial AVR strategy in these patients was associated with better prognosis than the conservative strategy.[3] Risk stratification is important to identify the high-risk subsets of patients with asymptomatic severe AS, who might benefit from early AVR. Current guidelines recommend AVR in asymptomatic patients with very severe AS with peak aortic jet velocity (V_{max}) ≥5 m/s or mean aortic pressure gradient

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Accompanying Appendix S1, Tables S1 through S3, and Figures S1 through S12 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010198

*A complete list of the CURRENT AS registry Investigators can be found in the Supplemental Material.

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Clinical Perspective

What Is New?

- This is the first large-scale report exploring the ability of aortic valve area (AVA) to predict the prognosis of asymptomatic patients with severe aortic stenosis in a contemporary multicenter registry of consecutive patients with severe aortic stenosis.
- AVA ≤0.60 and 0.8 cm^2 ≥AVA >0.6 cm^2 as compared with AVA >0.80 cm^2 was associated with higher risk for the composite of aortic valve–related death or heart failure hospitalization.
- The excess risk of AVA ≤0.60 cm^2 relative to AVA >0.80 cm^2 remained significant even in patients without very severe AS defined by peak aortic jet velocity ≥5 m/s or mean aortic pressure gradient ≥60 mm Hg, who constituted 74% of those patients with AVA ≤0.6 cm^2.

What Are the Clinical Implications?

- AVA ≤0.6 cm^2 might be an additional objective echocardiographic parameter to identify the high-risk subsets of patients with asymptomatic severe aortic stenosis.
- Initial AVR strategy might be reasonable in patients with AVA ≤0.6 cm^2.

(MPG) ≥60 mm Hg, if the surgical risk is low.[1,2] However, there was no recommendation for AVR with respect to aortic valve area (AVA). Several studies reported that AVA was discordant with V_{max} in a significant proportion of patients.[4–6] There were a few single-center studies to investigate the ability of AVA obtained by Doppler echocardiography to identify a subgroup of patients with asymptomatic severe AS who are at high risk of events.[7–12] However, these previous studies were inconclusive about the role of AVA in predicting outcomes of patients with asymptomatic severe AS independent of V_{max} and/or MPG.

Therefore, we aimed to explore the ability of AVA to predict the prognosis of asymptomatic patients with severe AS in a large observational database in Japan.

Methods

We will not make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure.

Study Population

The study design, methodologies, and outcomes from the CURRENT AS (Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis) registry have been described previously.[3] Briefly, the CURRENT AS registry is a retrospective, multicenter registry that enrolled 3815 consecutive patients with severe AS among 27 centers in Japan between January 2003 and December 2011. We searched the hospital database of transthoracic echocardiography and enrolled consecutive patients who met the definition of severe AS (V_{max} >4.0 m/s, MPG >40 mm Hg, or AVA <1.0 cm^2) for the first time during the study period.[1,2] Angina, syncope, and heart failure (HF) symptoms including dyspnea were regarded as AS-related symptoms.

In the present analysis, we excluded 1197 patients in whom AVR was selected as the initial treatment strategy after the index echocardiography, 1100 patients who had AS-related symptom, 123 patients with left ventricular ejection fraction (LVEF) <50%, 1 patient whose symptomatic status was not available, 5 patients whose LVEF was unknown, and 80 patients whose AVA was unknown. Therefore, the current study population consisted of 1309 patients with asymptomatic severe AS and LVEF ≥50% who were managed conservatively after the index echocardiography (Figure 1). The number of patients excluded because of reduced LVEF was low because patients with severe AS with reduced LVEF were often symptomatic and/or received initial AVR. The reasons why the AVR was not performed in 123 patients with LVEF <50% at index echocardiography were decision making by the attending physicians in 80 patients (65%), high risk for AVR in 39 patients (32%), and patient's refusal in 4 patients (3%), although the decision regarding the ineligibility for AVR was not uniform in this retrospective study. The current study patients were subdivided into 3 groups based on the AVA: group 1 (AVA >0.80 cm^2, N=645), group 2 (0.8 cm^2 ≥AVA >0.6 cm^2, N=465), and group 3 (AVA ≤0.6 cm^2, N=199), based on a previous study of 2427 patients with AVA ≤2.0 cm^2 reporting that a V_{max} of 4.0 and >5.5 m/s corresponded to an AVA of 0.82 and 0.59 cm^2, respectively[4] (Figure 1). We compared the baseline characteristics and 5-year clinical outcomes among the 3 groups. Follow-up was commenced on the day of index echocardiography unless specified otherwise. All the institutional review boards approved the protocol. Written informed consent was waived because of the retrospective nature of this study, and no patients refused to participate in the study when contacted for follow-up.

Data Collection and Definitions of Outcome Measures

The collection of the baseline clinical information was conducted through review of hospital charts and database. All patients at each participating center underwent comprehensive 2-dimensional and Doppler echocardiographic evaluations. V_{max} and the MPG were calculated using the simplified

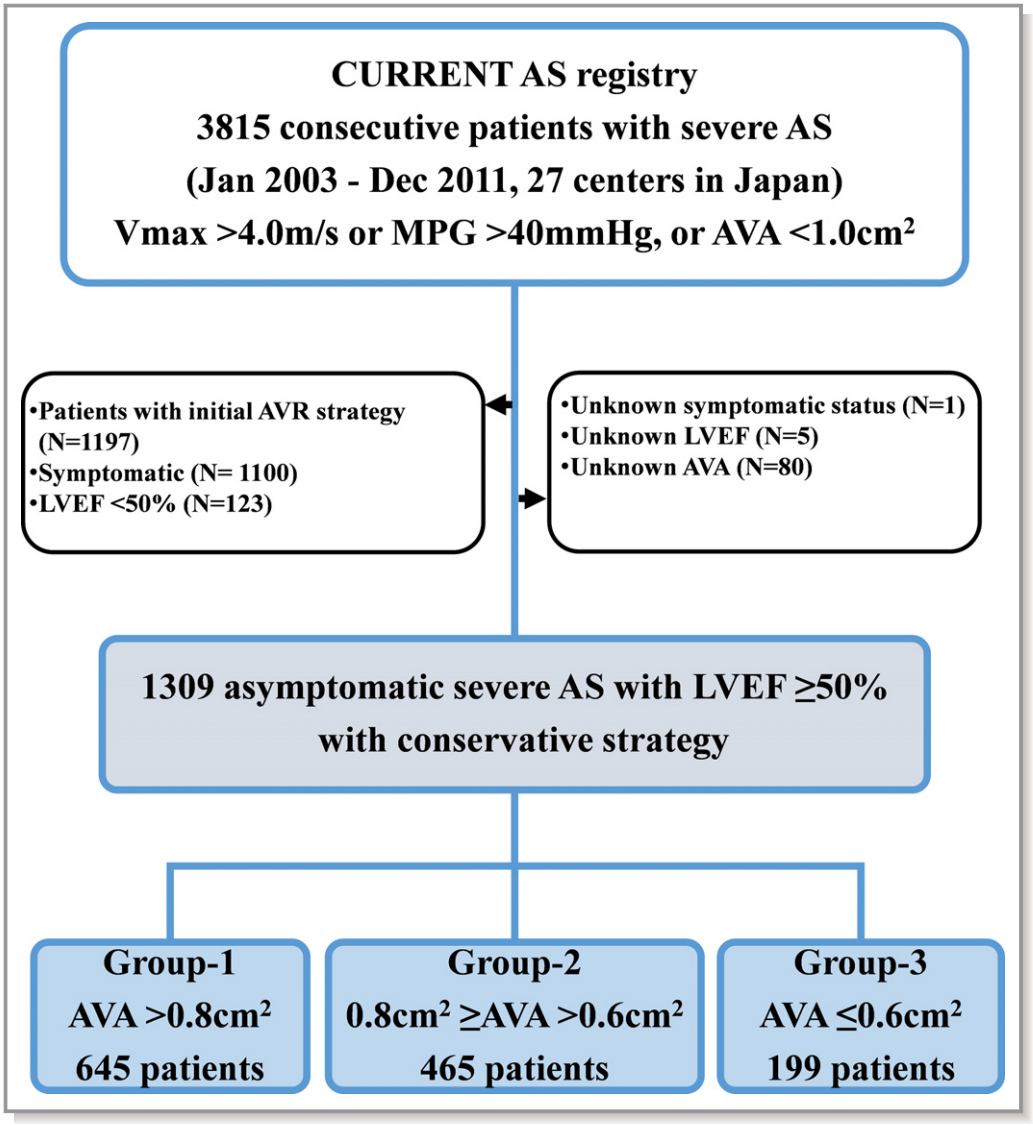


Figure 1. Study patient flow. AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; MPG, mean aortic pressure gradient; V_{max}, peak aortic jet velocity.

Bernoulli equation. AVA was calculated using the standard continuity equation.[13]

The primary outcome measure in the present analysis was a composite of aortic valve–related death or HF hospitalization. Other outcome measures included all-cause death, cardiovascular death, aortic valve–related death, aortic valve procedure death, sudden death, emerging symptoms related to AS, and HF hospitalization. The causes of death were classified according to the Valve Academic Research Consortium definitions, and were adjudicated by a clinical event committee.[14,15] Aortic valve–related deaths included aortic valve procedure death, sudden death, and death caused by HF possibly related to AS. HF hospitalization was defined as hospitalization because of worsening HF requiring intravenous drug therapy. Sudden death was defined as unexplained death in previously stable patients. Other definitions of clinical events have been described previously.[3]

Statistical Analysis

Continuous variables were expressed as the mean±standard deviation or median with the interquartile range. On the basis of their distributions, we compared continuous variables using 1-way ANOVA or the Kruskal–Wallis test. Categorical variables were presented as numbers and percentages and were compared using the chi-squared test. The cumulative incidences of events were estimated by the Kaplan–Meier method, and the differences were assessed with the log-rank test. We also had evaluated the Gray's test for secondary outcomes (AVR, emerging new symptoms–related AS, and HF

Table 1. Baseline Characteristics and Echocardiographic Parameters

	Group 1: AVA >0.8 cm^2 (N=645)	Group 2: 0.8 cm^2 ≥AVA >0.6 cm^2 (N=465)	Group 3: AVA ≤0.6 cm^2 (N=199)	*P* Value
Clinical characteristics				
Age, y*	76±9	78±9	81±9	<0.001
Age ≥80 y	250 (38.8)	233 (50.1)	115 (57.8)	<0.001
Male*	296 (45.9)	151 (32.6)	56 (28.1)	<0.001
BMI, kg/m^2	22.5±3.7	21.8±4.0	21.2±3.3	<0.001
BMI <22 kg/m^2*	338 (52.4)	283 (60.9)	142 (71.4)	<0.001
BSA, m^2	1.50±0.18	1.44±0.17	1.40±0.17	<0.001
Hypertension*	463 (71.8)	333 (71.6)	125 (62.8)	0.04
Current smoking*	40 (6.2)	14 (3.0)	7 (3.5)	0.03
History of smoking	159 (24.7)	87 (18.7)	29 (14.6)	0.003
Dyslipidemia	250 (38.8)	148 (31.8)	62 (31.2)	0.03
On statin therapy	200 (31.0)	101 (21.7)	41 (20.6)	<0.001
Diabetes mellitus	162 (25.1)	113 (24.3)	38 (19.1)	0.21
On insulin therapy*	33 (5.1)	19 (4.1)	11 (5.5)	0.64
Prior myocardial infarction*	41 (6.4)	36 (7.7)	14 (7.0)	0.67
Prior PCI	112 (17.4)	75 (16.1)	23 (11.6)	0.15
Prior CABG	31 (4.8)	25 (5.4)	8 (4.0)	0.75
Prior open heart surgery	52 (8.1)	50 (10.8)	17 (8.5)	0.29
Prior symptomatic stroke*	102 (15.8)	65 (14.0)	26 (13.1)	0.54
Atrial fibrillation or flutter*	115 (17.8)	91 (19.6)	45 (22.6)	0.31
Aortic/peripheral vascular disease*	94 (14.6)	86 (18.5)	29 (14.6)	0.18
Serum creatinine, mg/dL*	0.9 (0.7–1.1)	0.8 (0.7–1.2)	0.8 (0.7–1.1)	0.69
Creatinine level >2 mg/dL	73 (11.3)	62 (13.3)	26 (13.1)	0.56
Hemodialysis*	56 (8.7)	52 (11.2)	23 (11.6)	0.29
Anemia*†	278 (43.1)	219 (47.1)	105 (52.8)	0.05
Liver cirrhosis (Child-Pugh B or C)*	4 (0.6)	4 (0.9)	1 (0.5)	0.84
Malignancy	95 (14.7)	75 (16.1)	26 (13.1)	0.58
Malignancy currently under treatment*	35 (5.4)	30 (6.5)	5 (2.5)	0.12
Chest wall irradiation	5 (0.8)	1 (0.2)	1 (0.5)	0.45
Immunosuppressive therapy	27 (4.2)	15 (3.2)	4 (2.0)	0.32
Chronic lung disease (moderate or severe)*	15 (2.3)	13 (2.8)	7 (3.5)	0.65
Coronary artery disease*	175 (27.1)	116 (24.9)	46 (23.1)	0.47
Logistic EuroSCORE, %	7.7 (4.8–11.5)	9.2 (5.8–15.5)	10.7 (6.6–15.2)	<0.001
EuroSCORE II, %	2.1 (1.3–3.3)	2.7 (1.7–3.8)	2.9 (2.0–4.1)	<0.001
STS score (PROM), %	3.0 (2.0–4.6)	3.7 (2.3–5.6)	4.1 (2.8–5.9)	<0.001
Etiology of aortic stenosis				0.18
Degenerative	573 (88.8)	414 (89.0)	181 (91.0)	
Congenital	43 (6.7)	26 (5.6)	9 (4.5)	
Rheumatic	24 (3.7)	23 (4.9)	5 (2.5)	
Infective endocarditis	0 (0.0)	0 (0.0)	1 (0.5)	
Other	5 (0.8)	2 (0.4)	3 (1.5)	

Continued

Table 1. Continued

	Group 1: AVA >0.8 cm^2 (N=645)	Group 2: 0.8 cm^2 ≥AVA >0.6 cm^2 (N=465)	Group 3: AVA ≤0.6 cm^2 (N=199)	*P* Value
Echocardiographic variables				
V_{max}, m/s	3.6±0.6	3.8±0.7	4.4±0.7	<0.001
V_{max} ≥5 m/s	12 (1.9)	23 (4.9)	47 (23.6)	<0.001
5.0 m/s >V_{max} ≥4.5 m/s	35 (5.5)	48 (10.3)	47 (23.6)	
4.5 m/s >V_{max} ≥4 m/s	128 (19.9)	121 (26.0)	53 (26.6)	
V_{max} <4 m/s	467 (72.7)	273 (58.7)	52 (26.1)	
Peak aortic PG, mm Hg	53±18	61±22	80±26	<0.001
MPG, mm Hg	29±11	35±13	47±17	<0.001
MPG ≥60 mm Hg	7 (1.3)	18 (4.5)	40 (23.4)	<0.001
60 mm Hg >MPG ≥40 mm Hg	82 (14.7)	107 (26.8)	74 (43.3)	
MPG <40 mm Hg	470 (84.1)	274 (68.7)	57 (33.3)	
Very severe AS (V_{max} ≥5 m/s or MPG ≥60 mm Hg)	13 (2.0)	27 (5.8)	52 (26.1)	<0.001
AVA (equation of continuity), cm^2	0.92±0.08	0.73±0.06	0.52±0.07	<0.001
AVA index, cm^2/m^2	0.62±0.08	0.52±0.07	0.38±0.06	<0.001
LV end-diastolic diameter, mm	45±6	44±5	43±5	<0.001
LV end-systolic diameter, mm	28±5	27±5	27±5	0.005
LVEF, %*	68±8	68±8	67±7	0.06
IVST in diastole, mm	10.8±2.1	11.0±2.0	11.5±2.3	<0.001
PWT in diastole, mm	10.4±1.8	10.6±1.8	11.2±2.1	<0.001
Any combined valvular disease (moderate or severe)*	218 (33.8)	128 (27.5)	62 (31.2)	0.08
Moderate or severe AR	127 (19.7)	56 (12.0)	23 (11.6)	0.001
Moderate or severe MS	21 (3.3)	11 (2.4)	5 (2.5)	0.65
Moderate or severe MR	76 (11.8)	43 (9.2)	26 (13.1)	0.26
Moderate or severe TR	82 (12.7)	58 (12.5)	32 (16.1)	0.41
TR pressure gradient ≥40 mm Hg*	56 (8.7)	52 (11.2)	24 (12.1)	0.24

Values are expressed as mean±SD, and number (%), or median (interquartile range). AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; IVST, interventricular septum thickness; LV, left ventricular; LVEF, left ventricular ejection fraction; MPG, mean aortic pressure gradient; MR, mitral regurgitation; MS, mitral stenosis; PCI, percutaneous coronary intervention; PG, pressure gradient; PROM, predicted risk of mortality; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation; V_{max}, peak aortic jet velocity.

*Risk-adjusting variables selected for the multivariable Cox proportional hazards models.

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

hospitalization), with death as competing risk because the secondary outcomes may be biased by death. The outcomes of group 2 and group 3 were compared with those of group 1 (reference) in the multivariable Cox proportional hazard models. Consistent with our previous report, we used the 20 clinically relevant risk-adjusting variables (age, sex, body mass index, hypertension, current smoking, diabetes mellitus on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, hemodialysis, anemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, LVEF ≥68%, and tricuspid regurgitation pressure gradient ≥40 mm Hg) to adjust for the differences in baseline characteristics (Table 1). The additive analysis for the prognostic impact of AVA over a multivariate model including very severe AS (V_{max} ≥5.0 m/s or MPG ≥60 mm Hg) were performed to show how much AVA add to the prognosis value of AS severity as compared with V_{max} or MPG. With the exception of age, continuous risk-adjusting variables were dichotomized using clinically meaningful reference values or median values. We treated age as a continuous variable in the Cox proportional hazards models. The center was incorporated as the stratification variable. The risk of group 2 and group 3 relative to group 1 for the clinical outcomes were expressed as hazard ratios (HRs) and their 95% CI. We also assessed the effects of AVA on long-term outcomes censored on the day of AVR. Subgroup analyses were also performed in

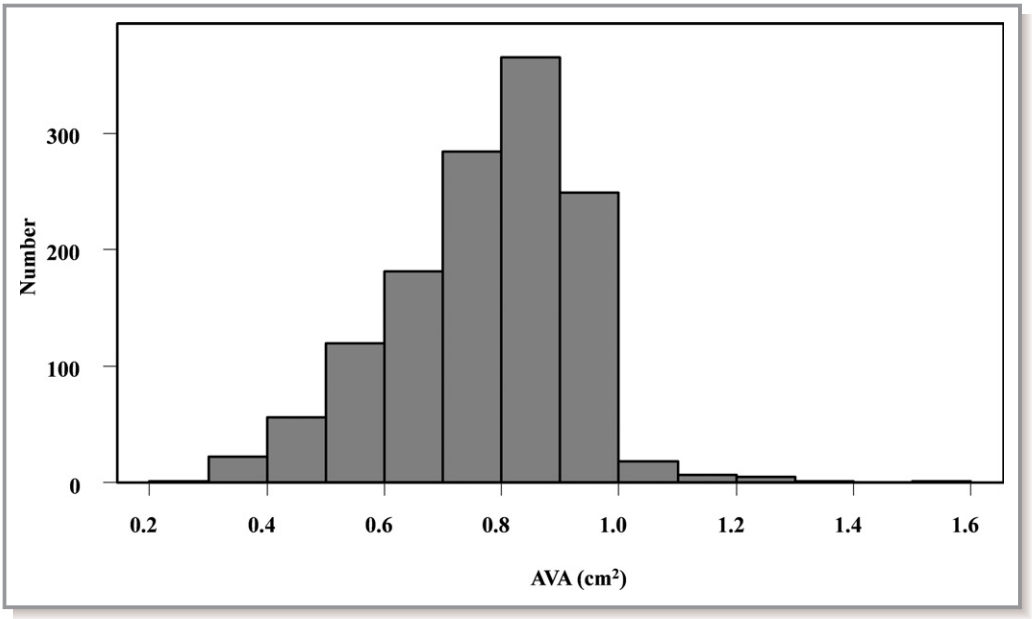


Figure 2. Distribution of AVA. AVA indicates aortic valve area.

patients with or without other valvular disease (moderate to severe aortic regurgitation, mitral regurgitation, and mitral stenosis), and high-gradient AS (V_{max} >4.0 m/s or MPG >40 mm Hg). Sensitivity analysis was performed in patient without very severe AS (V_{max} ≥5.0 m/s or MPG ≥60 mm Hg). All statistical analyses were performed with the statistical software R 3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria), SAS 9.4 (SAS Institute Inc, Cary, NC), or SPSS Statistics 19.0.0 (IBM Corp., Armonk, NY). All reported *P* values were 2-tailed, and $P<0.05$ was considered significant.

Results

Baseline Characteristics

Baseline clinical characteristics and echocardiographic parameters were substantially different across the 3 groups

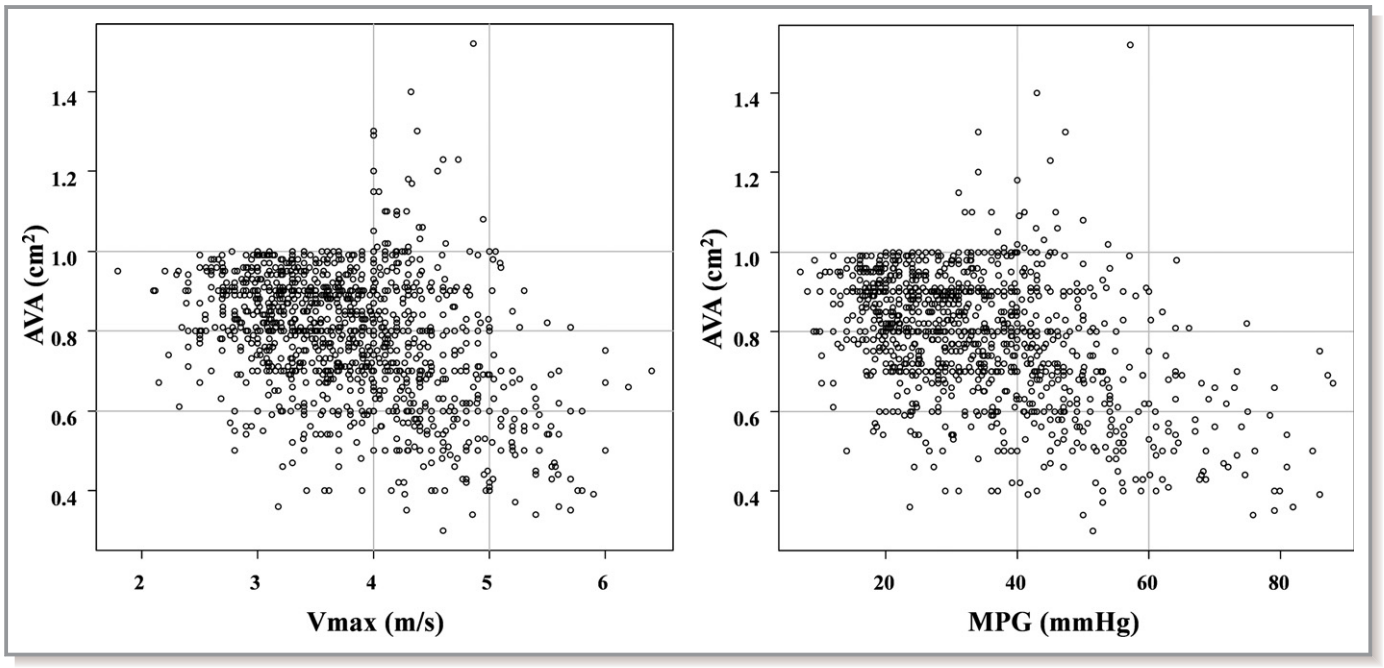


Figure 3. Scatterplot for V_{max} vs AVA, and for MPG vs AVA. AVA indicates aortic valve area; MPG, mean aortic pressure gradient; V_{max}, peak aortic jet velocity.

Table 2. Causes of Death

	Number of Patients (Proportion)		
	All (N=1309)	Patients With AVR (N=353)	Patients Without AVR (N=956)
All-cause death	414	34	380
Cardiovascular death	242 (58.5%)	22 (64.7%)	220 (57.9%)
Heart failure	68 (16.4%)	1 (2.9%)	67 (17.6%)
Sudden death	62 (15.0%)	2 (5.9%)	60 (15.8%)
Stroke	24 (5.8%)	1 (2.9%)	23 (6.1%)
Aortic valve procedure death	15 (3.6%)	15 (44.1%)	0 (0%)
Aortic/peripheral vascular disease	15 (3.6%)	0 (0%)	15 (3.9%)
Renal failure	10 (2.4%)	0 (0%)	10 (2.6%)
Myocardial infarction	6 (1.4%)	0 (0%)	6 (1.6%)
Other cardiac cause	6 (1.4%)	0 (0%)	6 (1.6%)
Unknown death	36 (8.7%)	3 (8.8%)	33 (8.7%)
Noncardiovascular death	172 (41.5%)	12 (35.3%)	160 (42.1%)
Infection	64 (15.5%)	6 (17.6%)	58 (15.3%)
Malignancy	57 (13.8%)	5 (14.7%)	52 (13.7%)
Respiratory failure	10 (2.4%)	0 (0%)	10 (2.6%)
Bleeding	4 (1.0%)	0 (0%)	4 (1.1%)
Liver failure	4 (1.0%)	0 (0%)	4 (1.1%)
Trauma	4 (1.0%)	0 (0%)	4 (1.1%)
Others	29 (7.0%)	1 (2.9%)	28 (7.4%)

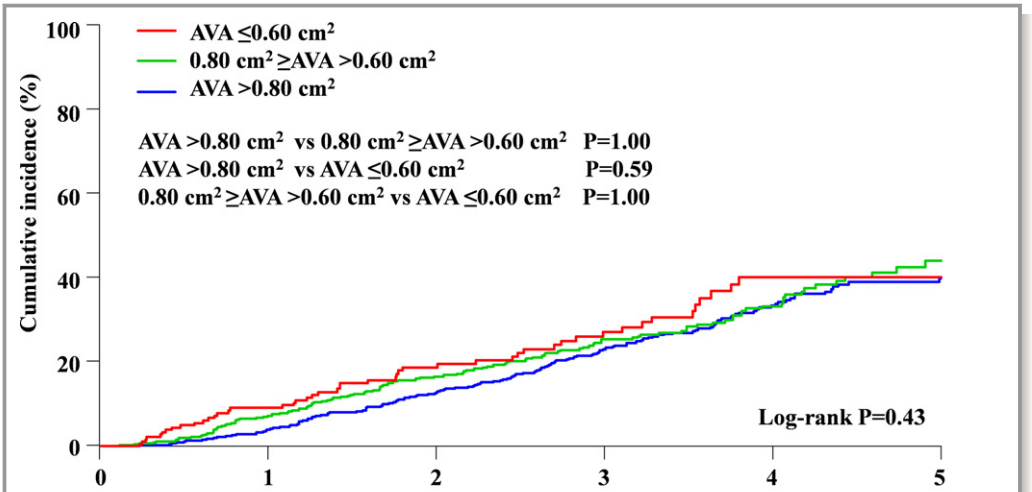
AVR indicates aortic valve replacement.

(Table 1). With decreasing AVA from group 1 to group 3, the patients became older and more often were female and had a smaller body mass index or body surface area and higher surgical risk scores, while they less often had dyslipidemia or were smokers (Table 1). Regarding the echocardiographic variables, patients with lower AVA more often had higher V_{max} or MPG, smaller LV dimension, and LV hypertrophy. LVEF was comparable across the 3 groups (Table 1). The full distribution of AVA was provided in Figure 2, and the relationship between AVA and V_{max} or MPG was shown in Figure 3. Three quarters of patients with AVA <0.6 cm^2 were not included in the very severe AS defined by V_{max} or MPG criteria (Figure 3 and Table 1). Consequently, the prevalence of very severe AS defined by V_{max} or MPG was 2.0%, 5.8%, and 26.1%, in groups 1, 2, and 3, respectively (Table 1).

Clinical Outcomes

The median follow-up duration of the surviving patients was 1203 (interquartile range, 773–1575) days with 93% follow-up completed at 2 years. A total of 414 (32%) out of 1309 patients died, with HF (68 patients) and sudden death (62 patients) being the dominant cardiac causes (Table 2). During follow-up, 339 patients (25.9%) underwent surgical AVR and 14 patients (1.1%) underwent transcatheter aortic valve implantation. The cumulative 5-year incidence of AVR or transcatheter aortic valve implantation was not different across the 3 groups (Figure 4). Among 353 patients referred for AVR during follow-up, 311 (88%) patients had formal indications for AVR; emerging symptoms related to AS in 241 patients (61%), rapid hemodynamic progression in 77 patients (22%), very severe AS (V_{max} >5.0 m/s or mean aortic pressure gradient >60 mm Hg) in 11 patients (3%), candidates for other cardiac surgery in 8 patients (2%), and LV dysfunction (defined as LVEF <50%) in 1 patient (0.3%). A total of 380 (39%) of 965 patients without AVR died, with HF (67 patients) and sudden death (60 patients) being the dominant cardiac causes. On the other hand, 34 (9.6%) of 353 patients with AVR died, with aortic valve procedure death (15 patients) and infection (6 patients) being the dominant causes (Table 2).

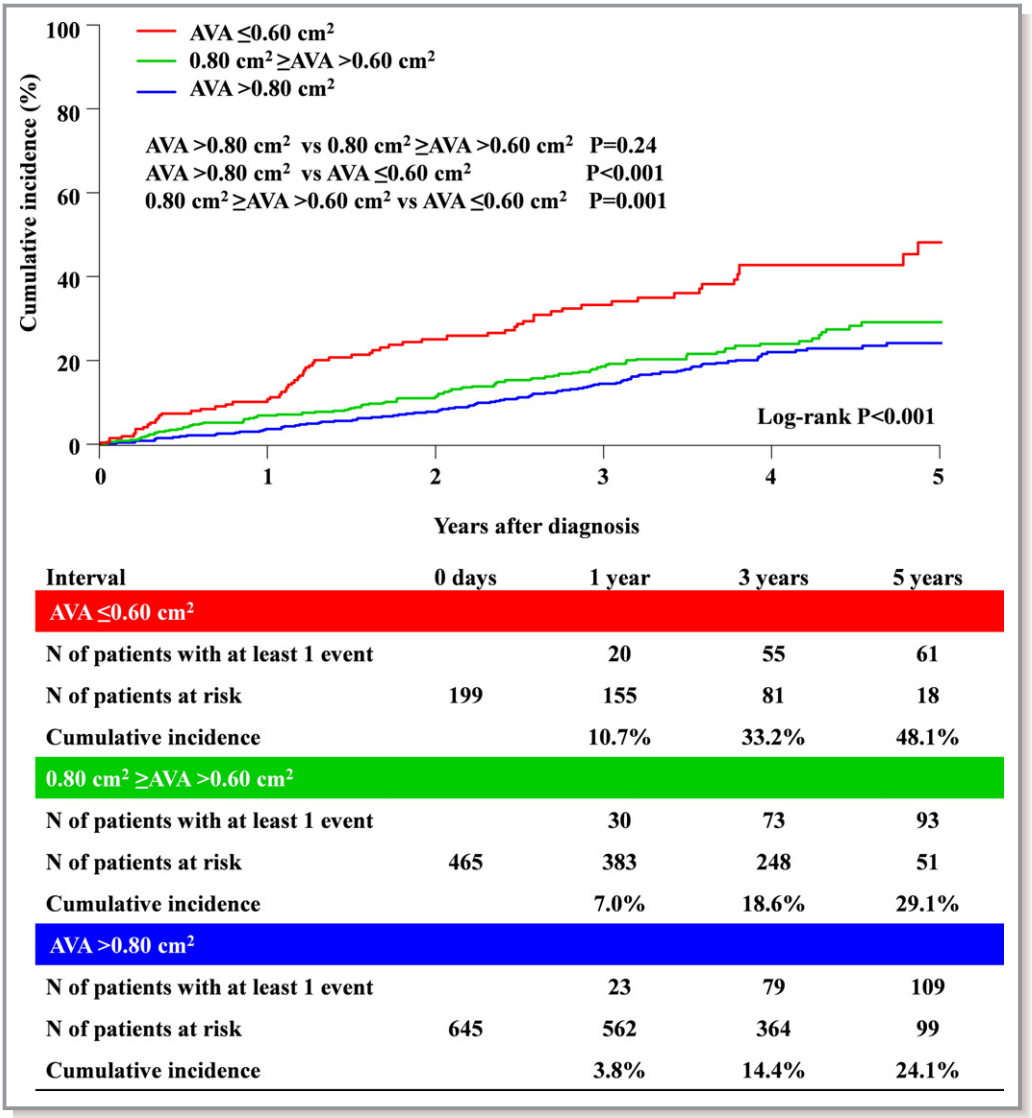
The cumulative 5-year incidence of the primary outcome measure (aortic valve–related death or HF hospitalization) was incrementally higher, with lower AVA from group 1 to group 3 (24.1%, 29.1%, and 48.1%; P<0.001) (Figure 5 and Table 3). After adjusting for confounders, the excess risk of group 3



Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with AVR		16	39	48
N of patients at risk	199	148	69	10
Cumulative incidence		9.0%	26.9%	39.9%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with AVR		30	92	120
N of patients at risk	465	367	202	37
Cumulative incidence		7.2%	25.2%	43.7%
AVA >0.80 cm²				
N of patients with AVR		23	122	165
N of patients at risk	645	553	308	71
Cumulative incidence		3.9%	23.3%	39.7%

Figure 4. Cumulative incidence of AVR. AVA indicates aortic valve area; AVR, aortic valve replacement.

and group 2 relative to group 1 for the primary outcome measure remained significant (HR, 2.21, 95% CI, 1.56–3.11, $P<0.001$; and HR, 1.34, 95% CI, 1.01–1.78, $P=0.04$, respectively) (Table 3). The excess risk of AVA as a continuous variable for the primary outcome measure remained significant (HR, 0.82/0.1 cm^2 AVA increment, 95% CI, 0.76–0.88; $P<0.001$). In addition to AVA, age, LVEF, any combined valvular disease, atrial fibrillation or flutter, chronic lung disease, chronic renal failure, and coronary artery disease were associated with higher risk for the primary outcome measure (Table S1). The result for the primary outcome measure was consistent even after censoring at AVR (Figure 6). The cumulative incidences of all-cause death and the other secondary outcome measures, including cardiovascular death, aortic valve–related death, aortic valve procedure death, emerging symptoms related to AS, and HF hospitalization, followed the same trend as that for the primary outcome measure (Figures S1–S6 and Table 3). On the other hand, the difference in the incidence of sudden death was not significant (Figure S7 and Table 3). After adjusting for confounders, the excess risks of group 3 relative to group 1 remained significant for all-cause death and the other individual secondary outcome measures, whereas the risks of group 2 relative to group 1 were significant for all-cause death and the other individual secondary outcome measures except for HF hospitalization (Table 3). The cumulative 5-year incidence of all-cause death starting the follow-up at the time of AVR in patients with AVR tended to be higher in group 3 than in groups 1 and 2 (12.3%, 12.9%, and 24.8%; $P=0.06$). Furthermore, after incorporating very severe AS (V_{max} ≥5.0 m/s or MPG ≥60 mm Hg) for the confounder, the excess risks of group 3 relative to group 1 remained significant for all individual outcome measures, whereas the risks of group 2 relative to group 1 were not significant for the



Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		20	55	61
N of patients at risk	199	155	81	18
Cumulative incidence		10.7%	33.2%	48.1%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		30	73	93
N of patients at risk	465	383	248	51
Cumulative incidence		7.0%	18.6%	29.1%
AVA >0.80 cm²				
N of patients with at least 1 event		23	79	109
N of patients at risk	645	562	364	99
Cumulative incidence		3.8%	14.4%	24.1%

Figure 5. Cumulative incidence of the primary outcome measure (aortic valve–related death or HF hospitalization). AVA indicates aortic valve area; HF, heart failure.

individual outcome measures except for all-cause death, cardiovascular death, and aortic valve–related death (Table S2). The additive analysis for secondary outcomes (AVR, emerging new symptoms–related AS and HF hospitalization) with death as competing risk were consistent with the initial analysis (Figures S8–S10 and Table S3). The AVR-free survival was incrementally lower, with lower AVA from group 1 to group 3 (71.2%, 53.8%, and 32.6%; $P<0.001$) (Figure S11). The symptom-free survival was incrementally lower, with lower AVA from group 1 to group 3 (77.2%, 71.8%, and 53.3%; $P=0.002$) (Figure S12).

In the subgroup analysis, the excess risk of group 3 relative to group 1 for the primary outcome measure was consistently seen without any interaction in the subgroups with or without other valvular disease, and high- or low-gradient AS. In patients with high-gradient AS, the excess risk of group 3 relative to group 1 was significant (HR, 1.75, 95% CI, 1.00–3.05; $P=0.048$). In the sensitivity analysis, even in patients without very severe AS defined by V_{max} or MPG criteria, the excess risk of group 3 relative to group 1 was highly significant (HR, 1.81, 95% CI, 1.21–2.71; $P<0.001$), whereas the excess risk of group 2 relative to group 1 was no longer significant (HR, 1.27, 95% CI, 0.95–1.70; $P=0.11$).

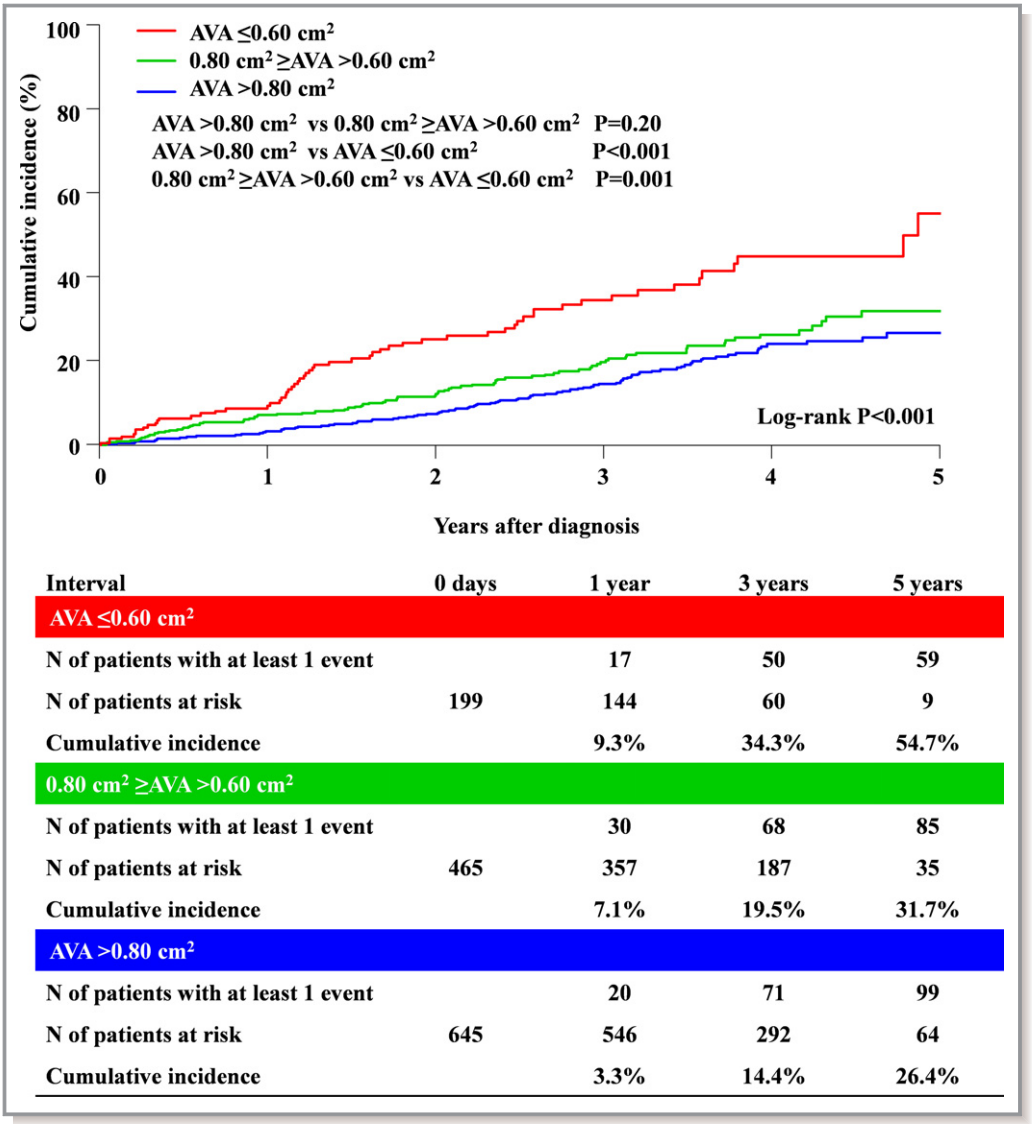
Discussion

The main findings of the present study evaluating the prognostic impact of AVA in asymptomatic patients with severe AS were as follows: (1) AVA ≤0.60 and 0.8 cm^2 ≥AVA >0.6 cm^2 as compared with AVA >0.80 cm^2 was associated

Table 3. Clinical Outcomes

	No. of Patients With Events (Cumulative 5-Year Incidence)	Log-Rank *P* Value	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Primary outcome measure						
Composite of aortic valve–related death or hospitalization due to HF		<0.001				
Group 1 (AVA >0.8 cm^2)	124 (24.1%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	106 (29.1%)		1.26 (0.98–1.64)	0.08	1.34 (1.01–1.78)	0.04
Group 3 (AVA ≤0.6 cm^2)	67 (48.1%)		2.22 (1.65–2.98)	<0.001	2.21 (1.56–3.11)	<0.001
Secondary outcome measures						
All-cause death		<0.001				
Group 1 (AVA >0.8 cm^2)	160 (27.4%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	160 (40.0%)		1.47 (1.18–1.83)	<0.001	1.49 (1.17–1.89)	0.001
Group 3 (AVA ≤0.6 cm^2)	94 (59.5%)		2.28 (1.77–2.94)	<0.001	2.61 (1.96–3.47)	<0.001
Cardiovascular death		<0.001				
Group 1 (AVA >0.8 cm^2)	91 (16.9%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	85 (24.2%)		1.38 (1.02–1.85)	0.03	1.48 (1.07–2.05)	0.02
Group 3 (AVA ≤0.6 cm^2)	66 (47.9%)		2.83 (2.06–3.88)	<0.001	3.36 (2.34–4.83)	<0.001
Aortic valve–related death		<0.001				
Group 1 (AVA >0.8 cm^2)	46 (10.0%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	56 (16.3%)		1.80 (1.22–2.66)	0.003	2.01 (1.31–3.08)	0.001
Group 3 (AVA ≤0.6 cm^2)	42 (34.1%)		3.60 (2.37–5.47)	<0.001	4.53 (2.79–7.34)	<0.001
Aortic valve procedure death		0.01				
Group 1 (AVA >0.8 cm^2)	6 (1.3%)		Reference			
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	3 (1.1%)		0.73 (0.18–2.91)	0.65	N/A	
Group 3 (AVA ≤0.6 cm^2)	6 (4.7%)		3.72 (1.20–11.5)	0.02	N/A	
Sudden death		0.08				
Group 1 (AVA >0.8 cm^2)	26 (5.8%)		Reference			
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	22 (5.2%)		1.23 (0.70–2.17)	0.47	N/A	
Group 3 (AVA ≤0.6 cm^2)	14 (14.8%)		2.12 (1.11–4.07)	0.02	N/A	
Emerging symptoms related to AS		<0.001				
Group 1 (AVA >0.8 cm^2)	186 (18.5%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	151 (44.1%)		1.20 (0.97–1.49)	0.09	1.27 (1.01–1.56)	0.045
Group 3 (AVA ≤0.6 cm^2)	77 (63.0%)		1.77 (1.36–2.31)	<0.001	1.82 (1.35–2.45)	<0.001
HF hospitalization		<0.001				
Group 1 (AVA >0.8 cm^2)	97 (19.3%)		Reference		Reference	
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	83 (23.9%)		1.27 (0.95–1.70)	0.11	1.33 (0.96–1.83)	0.08
Group 3 (AVA ≤0.6 cm^2)	50 (37.7%)		2.14 (1.52–3.01)	<0.001	1.95 (1.31–2.92)	0.001
AVR		0.43				
Group 1 (AVA >0.8 cm^2)	178 (39.7%)		Reference			
Group 2 (0.8 cm^2 ≥AVA >0.6 cm^2)	125 (43.7%)		1.08 (0.86–1.35)	0.53	N/A	
Group 3 (AVA ≤0.6 cm^2)	50 (39.9%)		1.23 (0.90–1.68)	0.20	N/A	

The number of patients with at least 1 event was counted through the entire follow-up period, while cumulative incidence was estimated at 5 years. Aortic valve–related death included aortic procedure–related death, sudden death, and death due to HF. HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy. Risk-adjusting variables: age, sex, body mass index, hypertension, current smoking, diabetes mellitus on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, hemodialysis, anemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, LVEF ≥68% and TR pressure gradient ≥40 mm Hg. AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N/A, not assessed; TR, tricuspid regurgitation.



Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		17	50	59
N of patients at risk	199	144	60	9
Cumulative incidence		9.3%	34.3%	54.7%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		30	68	85
N of patients at risk	465	357	187	35
Cumulative incidence		7.1%	19.5%	31.7%
AVA >0.80 cm²				
N of patients with at least 1 event		20	71	99
N of patients at risk	645	546	292	64
Cumulative incidence		3.3%	14.4%	26.4%

Figure 6. Cumulative incidence of the primary outcome measure (aortic valve–related death or HF hospitalization) with censoring at AVR. AVA indicates aortic valve area; AVR, aortic valve replacement; HF, heart failure.

with higher risk for the composite of aortic valve–related death or HF hospitalization; (2) the excess risk of AVA ≤0.60 cm^2 relative to AVA >0.80 cm^2 remained significant even in patients without very severe AS defined by V_{max} or MPG, who constituted 74% of those patients with AVA ≤0.6 cm^2.

Current guidelines recommend AVR for the asymptomatic severe AS patients, if they have LVEF <50%, very severe AS with low surgical risk, and decreased exercise tolerance or fall in systemic blood pressure during exercise.[1,2] Very severe AS was defined using V_{max} and MPG, while there is no description with regard to AVA.[1,2] These guidelines were based on the previous single-center studies suggesting that a peak aortic velocity, but not AVA, was associated with a high risk of events in asymptomatic severe AS patients.[7,8] Nevertheless, AVA decreases with increasing severity of AS, and therefore AVA might theoretically be used to define very severe AS. Our present study clearly demonstrated that patients with AVA ≤0.6 cm^2 had a poorer prognosis compared with AVA >0.8 cm^2. The cumulative 5-year incidence of a composite outcome measure of aortic valve–related death or HF hospitalization, sudden death, and AVR were high in patients with AVA ≤0.6 cm^2 (48.1%, 14.8%, and 39.9%, respectively).

Previous studies were inconclusive about the role of AVA in predicting outcomes of patients with asymptomatic severe AS independent of V_{max} and/or MPG. Rosenhek et al[7] prospectively followed 116 consecutive asymptomatic patients with very severe isolated AS defined by V_{max} >5.0 m/s and reported that the outcome of patients with AVA <0.6 cm^2 was not significantly different from the outcome of those with AVA

≥0.6 cm^2. Pellikka et al[8] reported that in 622 isolated asymptomatic AS with V_{max} >4 m/s who did not undergo surgery at the initial evaluation, the relative risk of developing symptom or sustaining a cardiac event per 0.2 cm^2 decrease in AVA was 1.26 and 1.20, respectively. Lancellotti et al[9] examined the prognosis of 69 patients with severe asymptomatic AS (AVA <1 cm^2) and reported that AVA <0.75 cm^2 was one of the main predictors of outcome. More recently, Maréchaux et al[12] reported that among 199 asymptomatic severe AS patients, the event rate including AVR and mortality was >80% in 39 patients with AVA ≤0.60 cm^2 during 2 years of follow-up. On the other hand, there was no difference in terms of mortality between patients with an AVA between 0.6 and 0.8 cm^2 and those with an AVA between 0.8 and 1.0 cm^2.[12] The present study evaluating a much larger number of patients with asymptomatic severe AS unequivocally demonstrated the poor prognosis of those patients with AVA ≤0.6 cm^2. In addition, our results showed that the mortality of the patients with an AVA between 0.6 and 0.8 cm^2 was higher than those with an AVA >0.8 cm^2 significantly. Therefore, patients with an AVA between 0.6 and 0.8 cm^2 also might be a high-risk group of events. The cumulative 5-year incidence of the primary outcome measure in patients with AVA ≤0.60 cm^2 in the present study (48.1%) was comparable to that in patients with V_{max} ≥5.0 m/s (47.7%) in our previous report.[16] Recently, Bohbot et al[17] reported that 559 asymptomatic or minimal symptomatic patients with severe AS and preserved LVEF with MPG ≥60 mm Hg (median AVA of 0.65 cm^2, interquartile range, 0.55–0.75 cm^2) at the time of diagnosis represented a high-risk group with >70% increase in all-cause mortality during 4 years of follow-up. The surgical risk score in our patients with AVA ≤0.6 cm^2 was moderate (Society of Thoracic Surgeons score, 4.1%), while the annual incidences of the primary outcome measure and sudden death were unacceptably high (9% and 3%, respectively). AVR during follow-up would be the critical determinant on the prognosis of patients with severe AS who were initially managed with the conservative strategy. Previous reports suggested AVR during follow-up increased with decreasing AVA.[12] In the present study, however, the proportion of patients who underwent AVR during follow-up was not influenced by baseline AVA. With decreasing AVA from group 1 to group 3, the patients became older and had higher surgical risk scores, suggesting that the proportion of patients at high risk for surgical AVR also increased with decreasing AVA. The increase in patients at high risk for surgical AVR might have offset the potentially higher likelihood of AVR during follow-up with decreasing AVA. Thus, the initial AVR strategy might be reasonable in patients with AVA ≤0.6 cm^2. In the present study, only 26% of patients among the 199 patients (15%) with AVA ≤0.6 cm^2 were classified as very severe AS defined by V_{max} or MPG criteria. Inconsistencies between V_{max} and AVA have been reported in previous studies.[4–6] V_{max} and MPG are strongly influenced by volume flow rate. Therefore, even with the same valve area, these parameters increase with anemia, decreasing peripheral vascular resistance and hyperthyroidism, and decrease with mitral regurgitation, LV dysfunction, and low stroke volume.[13] Furthermore, V_{max} and MPG values might be underestimated due to a measurement error, although accurate data recording mandates multiple acoustic windows in order to obtain the highest velocity.[13] Actually, the average V_{max} and MPG values were 4.4±0.7 m/s and 47±17 mm Hg in our patients with AVA ≤0.6 cm^2, suggesting underestimation of the severity of AS in a substantial proportion of patients. However, the impact of AVA ≤0.6 cm^2 in terms of composite criteria was found only in patients with high-gradient severe AS, although no interaction was found. Hence, whether AVA truly adds prognostic information over V_{max} or MPG is not clear in patients with low-gradient severe AS, although the relationship between AVA and outcome was found in patients without very severe AS. On the other hand, data of stroke volume, which are a component of the calculation of AVA with the continuity equation, are not available in this registry. Previous reports suggested that patients with an AVA ≤0.6 cm^2 are often in a low-flow state, which may explain their low-gradient AS.[12] Therefore, data of stroke volume might have refined the predictive value of AVA.[11,18,19] Consequently, severity of AS would be better determined using a multiparametric approach incorporating data derived from less flow-dependent parameter such as AVA in addition to transaortic velocities.

Although the severe AS was dominant pathology in the majority of patients, 408 of 1309 (31%) patients had other valvular disease. However, the prevalence of combined valvular disease was not different across the 3 groups except for the significantly higher prevalence of AR in group 1 (Table 1). In the real clinical practice, we have to make a decision for AVR based on the echocardiographic parameters such as V_{max} or AVA in the presence of other valvular disease. Therefore, we prefer to stick to analysis in the whole study population as the main analysis, conducting a subgroup analysis based on the presence or absence of concomitant valvular disease.

In real clinical practice, some patients with severe AS may not complain recognizable symptoms, if daily living activity is decreased. Furthermore, many patients are unable to perform an exercise test for noncardiac reasons (eg, orthopedic, vascular, respiratory, and obese). Thus, physicians may underestimate the presence of symptoms in patients with severe AS.[20] Therefore, the availability of objective echocardiographic parameters may be useful for identifying subjects at a higher risk of adverse events among asymptomatic patients with severe AS. We should further pursue implementation of early AVR in selected asymptomatic patients with severe AS.

Limitations

Our study has several limitations. First, echocardiographic data were site reported, and we had no echocardiographic core laboratory. The quality of echocardiographic examination might be variable across centers. Therefore, we could not deny the possibility for measurement error in some patients. However, the echocardiographic measurement was performed according to the guidelines by the experienced cardiologists and/or ultrasonographers in each participating center. Second, the calculation of the AVA by the continuity equation is prone to errors because of the difficulty in measuring LV outflow tract cross-sectional area owing to noncircular geometry of LV outflow tract.[21] Third, data of stroke volume, which are a component of the calculation of AVA with the continuity equation, are not available in this registry. Fourth, we did not assess the changes of AVA during follow-up. Fifth, we could not exclude the possibility of ascertainment bias for symptoms related to AS at baseline, although we thoroughly reviewed all patient charts and referred to the hospital database to evaluate symptomatic status. An exercise test was rarely performed to ensure that patients were truly asymptomatic. Finally, most of this study period was in the era before transcatheter aortic valve implantation introduction in Japan. Therefore, transcatheter aortic valve implantation could not be performed in a majority of high-risk patients.

Conclusions

AVA $\leq$0.60 cm^2 would be a useful marker to identify those high-risk patients with asymptomatic severe AS, who might be benefit from early AVR.

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Disclosures

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SUPPLEMENTAL MATERIAL

Appendix

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A clinical event committee

Hirotoshi Watanabe, MD (Kyoto University Graduate School of Medicine); Kenji Nakatsuma, MD (Kyoto University Graduate School of Medicine), Tomoki Sasa, MD (Kishiwada City Hospital).

Table S1. Clinical factors associated with composite of aortic valve-related death or hospitalization due to HF in the multivariable analyses.

Variables	Adjusted HR (95% CI)	P value
Age	1.05 (1.03-1.06)	<0.001
Sex	1.16 (0.90-1.55)	0.23
BMI <22 kg/m²	1.31 (1.00-1.72)	0.05
LVEF ≥68%	1.34 (1.03-1.75)	0.03
TR pressure gradient ≥40mmHg	0.78 (0.51-1.20)	0.26
Any valvular disease	1.60 (1.20-2.14)	0.0014
Prior myocardial infarction	1.18 (0.75-1.86)	0.48
Prior symptomatic stroke	1.23 (0.89-1.69)	0.21
Atrial fibrillation or flutter	1.42 (1.04-1.93)	0.03
Chronic lung disease	1.93 (1.09-3.40)	0.02
Malignancy currently under treatment	0.94 (0.50- 1.77)	0.84
Aorta/peripheral artery disease	1.15 (0.76-1.76)	0.50
Liver cirrhosis	1.37 (0.17-10.84)	0.76
Hemodialysis	1.37 (0.9q-2.08)	0.13
Hypertension	1.23 (0.91-1.68)	0.18
Current smoking	0.64 (0.33-1.23)	0.18
Diabetes on insulin	1.46 (0.87-2.43)	0.15

Coronary artery disease	1.46 (1.06-2.02)	0.02
Anemia	1.29 (0.99-1.67)	0.06
Serum creatinine	1.67 (1.27 2.19)	0.0002
AVA, per 0.1 cm^2 increment	0.82 (0.76-0.88)	<0.001

Aortic valve-related death included aortic procedure-related death, sudden death, and death due to HF. HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy.

AS=aortic stenosis; AVA=aortic valve area; AVR=aortic valve replacement; BMI=body mass index; CI=confidence interval; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; TR=tricuspid regurgitation.

Table S2. Clinical outcomes incorporating very severe AS (peak aortic jet velocity ≥5 m/s or mean aortic pressure gradient ≥60 mmHg) for confounder.

	N of patients with events (Cumulative 5-year incidence)	Log-rank P value	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Primary Outcome Measure		<0.001				
Composite of aortic valve-related death or hospitalization due to HF						
Group-1 (AVA >0.8 cm^2)	124 (24.1%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	106 (29.1%)		1.26 (0.98-1.64)	0.08	1.29 (0.97-1.72)	0.08
Group-3 (AVA ≤0.6 cm^2)	67 (48.1%)		2.22 (1.65-2.98)	<0.001	1.83 (1.27-2.63)	0.001
Secondary Outcome Measures						
All-cause death		<0.001				
Group-1 (AVA >0.8 cm^2)	160 (27.4%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	160 (40.0%)		1.47 (1.18-1.83)	<0.001	1.47 (1.16-1.88)	0.002

Group-3 (AVA ≤0.6 cm^2)	94 (59.5%)		2.28 (1.77-2.94)	<0.001	2.50 (1.83-3.40)	<0.001
Cardiovascular death		<0.001				
Group-1 (AVA >0.8 cm^2)	91 (16.9%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	85 (24.2%)		1.38 (1.02-1.85)	0.03	1.45 (1.05-2.01)	0.03
Group-3 (AVA ≤0.6 cm^2)	66 (47.9%)		2.83 (2.06-3.88)	<0.001	3.01 (2.03-4.47)	<0.001
Aortic valve-related death		<0.001				
Group-1 (AVA >0.8 cm^2)	46 (10.0%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	56 (16.3%)		1.80 (1.22-2.66)	0.003	1.95 (1.27-2.99)	0.002
Group-3 (AVA ≤0.6 cm^2)	42 (34.1%)		3.60 (2.37-5.47)	<0.001	3.72 (2.20-6.28)	<0.001
Emerging symptoms related to AS		<0.001				
Group-1 (AVA >0.8 cm^2)	186 (18.5%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	151 (44.1%)		1.20 (0.97-1.49)	0.09	1.24 (0.98-1.57)	0.07
Group-3 (AVA ≤0.6 cm^2)	77 (63.0%)		1.77 (1.36-2.31)	<0.001	1.57 (1.14-2.17)	0.005
HF hospitalization		<0.001				

Group-1 (AVA >0.8 cm^2)	97 (19.3%)	Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	83 (23.9%)	1.27 (0.95-1.70)	0.11	1.28 (0.92-1.77)	0.14
Group-3 (AVA ≤0.6 cm^2)	50 (37.7%)	2.14 (1.52-3.01)	<0.001	1.61 (1.06-2.46)	0.03

The number of patients with at least 1 event was counted through the entire follow-up period, while cumulative incidence was estimated at 5-year.

Aortic valve-related death included aortic procedure-related death, sudden death, and death due to HF. HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy.

Risk-adjusting variables: age, sex, body mass index, hypertension, current smoking, diabetes on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, hemodialysis, anemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, TR pressure gradient ≥40mmHg and very severe AS (peak aortic jet velocity ≥5 m/s or mean aortic pressure gradient ≥60 mmHg).

AS=aortic stenosis; AVA=aortic valve area; CI=confidence interval; HF=heart failure; HR=hazard ratio; TR=tricuspid regurgitation.

Table S3. Secondary outcomes with death as competing risk.

	N of patients with events (Cumulative 5-year incidence)	Gray's test P value	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Emerging symptoms related to AS		0.008				
Group-1 (AVA >0.8 cm^2)	186 (33.1%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	151 (37.1%)		1.18 (0.95-1.45)	0.14	1.26 (1.01-1.58)	0.04
Group-3 (AVA ≤0.6 cm^2)	77 (47.7%)		1.53 (1.17-1.99)	0.002	1.54 (1.15-2.05)	0.004
HF hospitalization		0.003				
Group-1 (AVA >0.8 cm^2)	97 (16.5%)		Reference		Reference	
Group-2 (0.8 cm^2 ≥AVA >0.6 cm^2)	83 (19.6%)		1.22 (0.91-1.61)	0.19	1.31 (0.96-1.78)	0.09
Group-3 (AVA ≤0.6 cm^2)	50 (29.6%)		1.85 (1.30-2.62)	<0.001	1.64 (1.11-2.43)	0.01

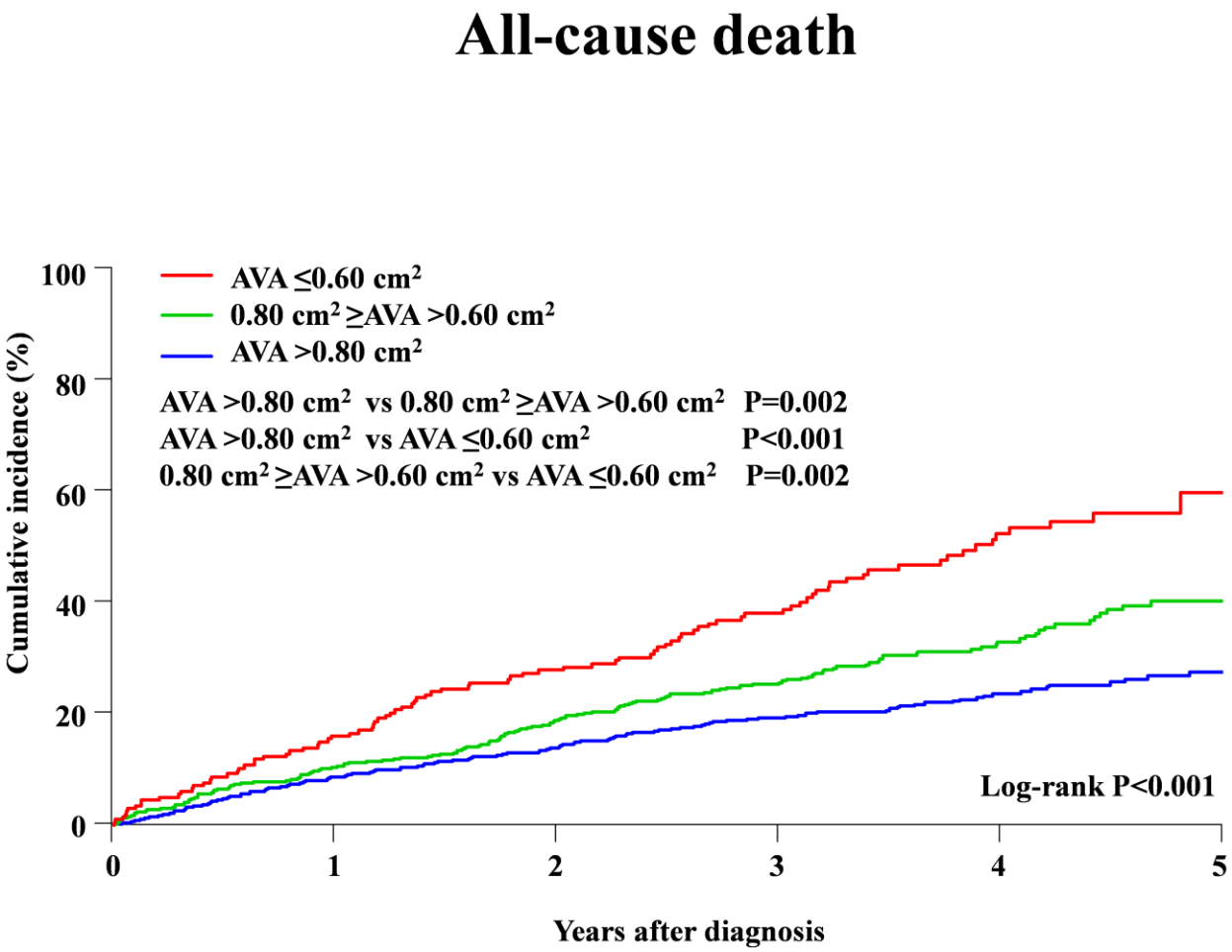
The number of patients with at least 1 event was counted through the entire follow-up period, while cumulative incidence was estimated at 5-year.

HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy.

Risk-adjusting variables: age, sex, body mass index, hypertension, current smoking, diabetes on insulin, coronary artery disease, prior myocardial infarction, prior symptomatic stroke, atrial fibrillation or flutter, aorta/peripheral artery disease, serum creatinine, hemodialysis, anemia, liver cirrhosis, malignancy currently under treatment, chronic lung disease, any valvular disease, LVEF ≥68% and TR pressure gradient ≥40mmHg.

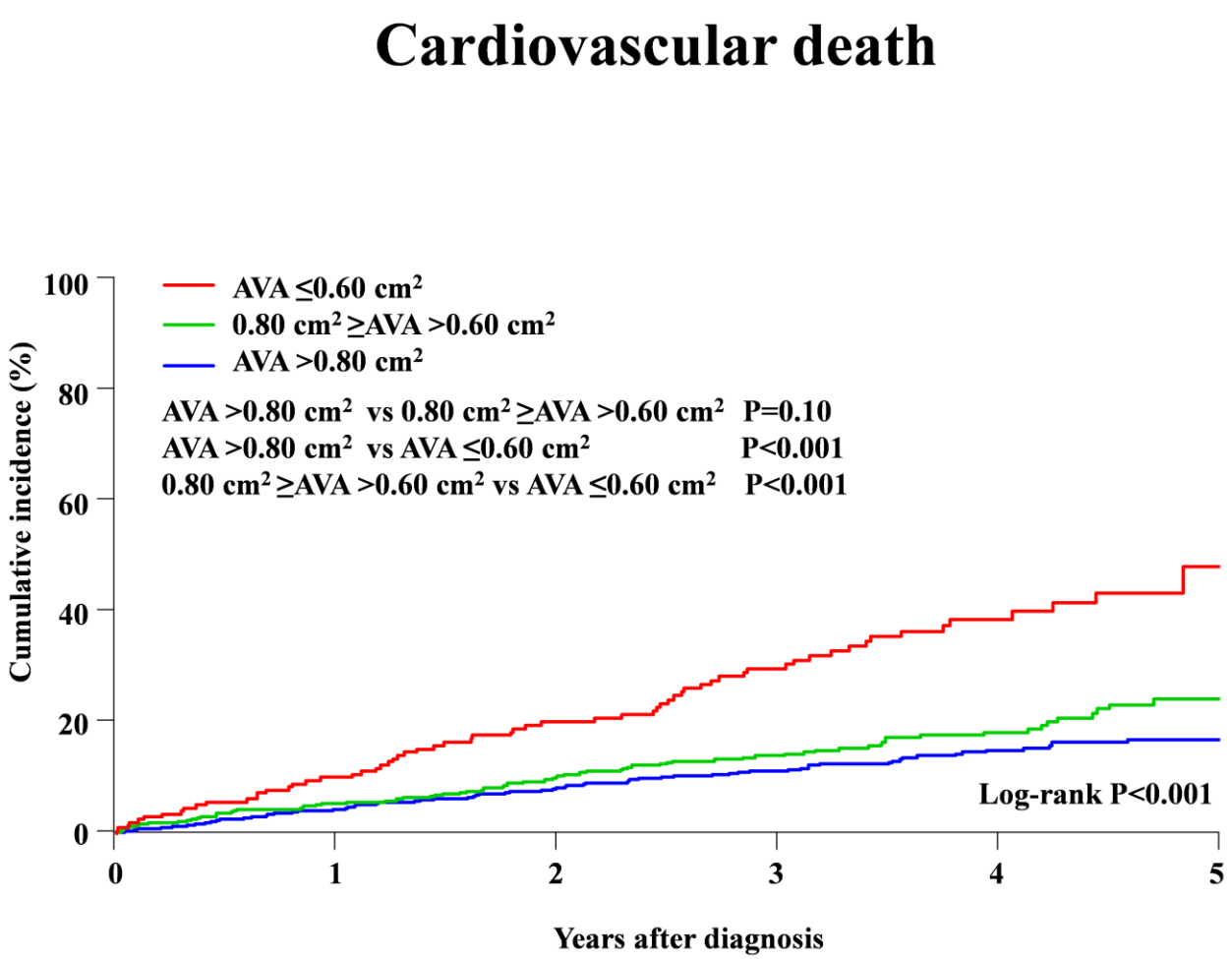
AS=aortic stenosis; AVA=aortic valve area; CI=confidence interval; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; TR=tricuspid regurgitation.

Figure S1. Cumulative incidence of all-cause death.
AVA=aortic valve area.



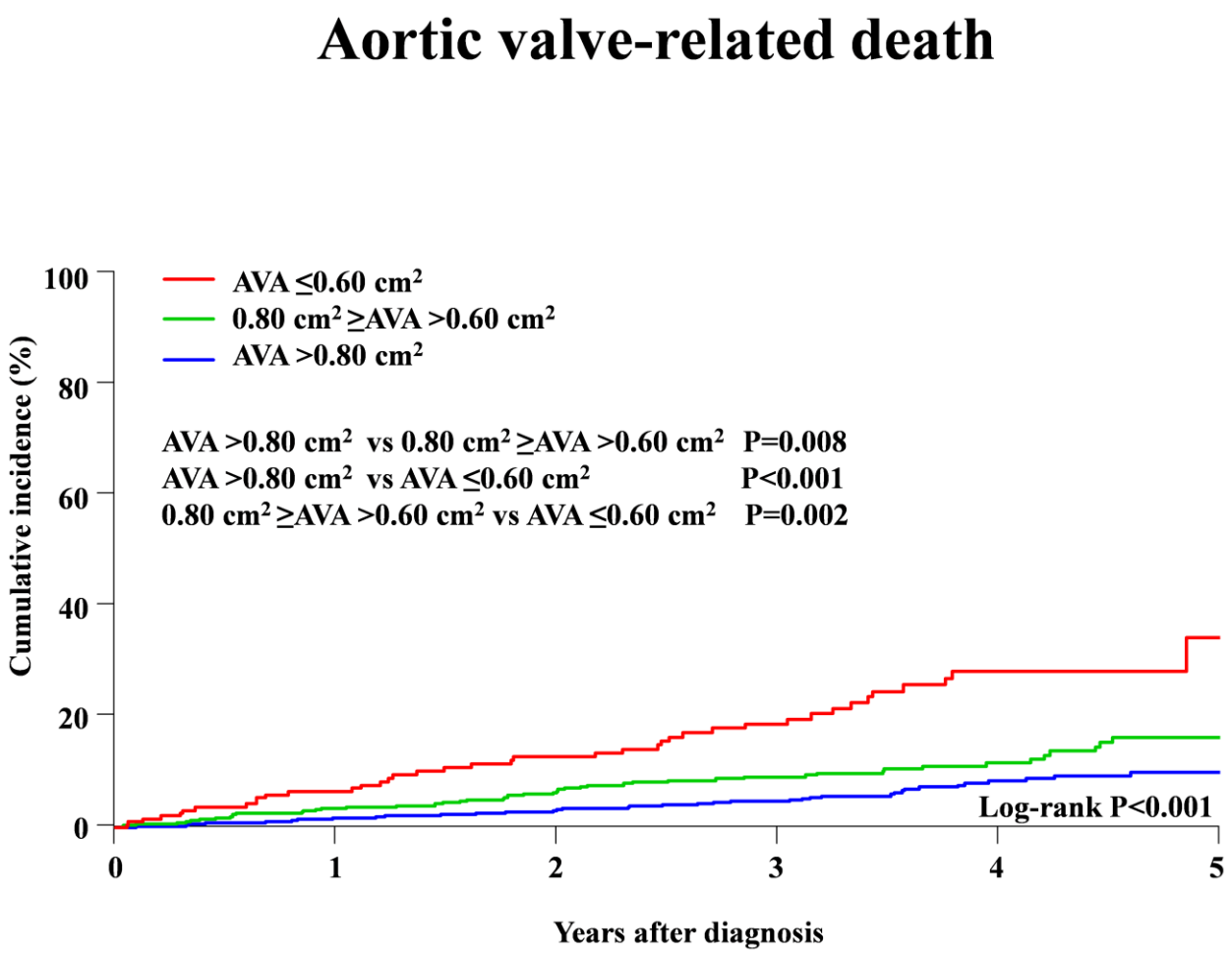
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		31	70	93
N of patients at risk	199	161	94	21
Cumulative incidence		15.9%	38.0%	59.5%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		47	110	145
N of patients at risk	465	397	272	58
Cumulative incidence		10.5%	25.2%	40.0%
AVA >0.80 cm²				
N of patients with at least 1 event		54	118	142
N of patients at risk	645	572	394	112
Cumulative incidence		8.5%	19.2%	27.4%

Figure S2. Cumulative incidence of cardiovascular death.
AVA=aortic valve area.



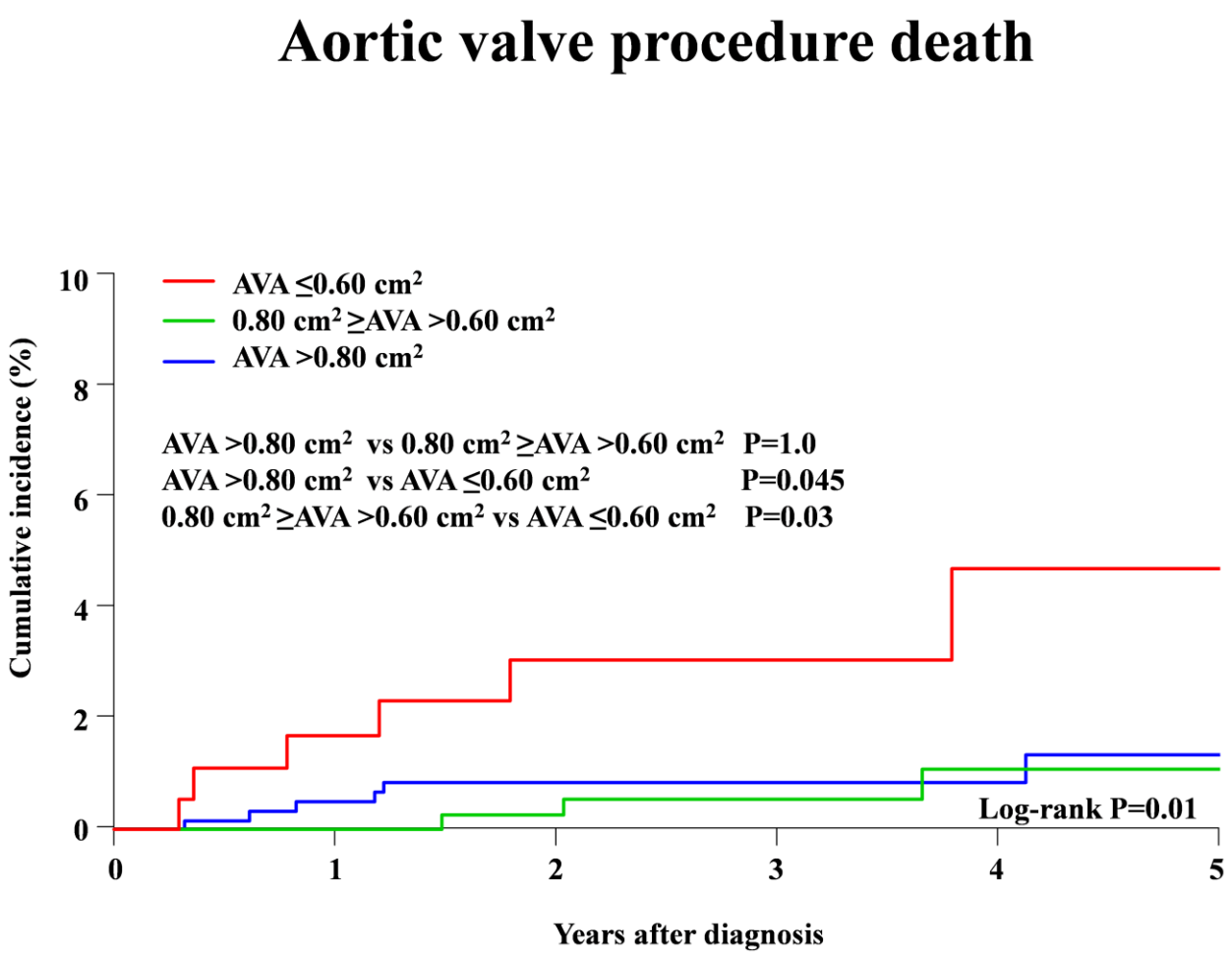
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		19	50	65
N of patients at risk	199	161	94	21
Cumulative incidence		10.0%	29.6%	47.9%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		24	57	76
N of patients at risk	465	397	272	58
Cumulative incidence		5.4%	13.9%	24.2%
AVA >0.80 cm²				
N of patients with at least 1 event		27	66	83
N of patients at risk	645	572	394	112
Cumulative incidence		4.4%	11.3%	16.9%

Figure S3. Cumulative incidence of aortic valve-related death.
AVA=aortic valve area.



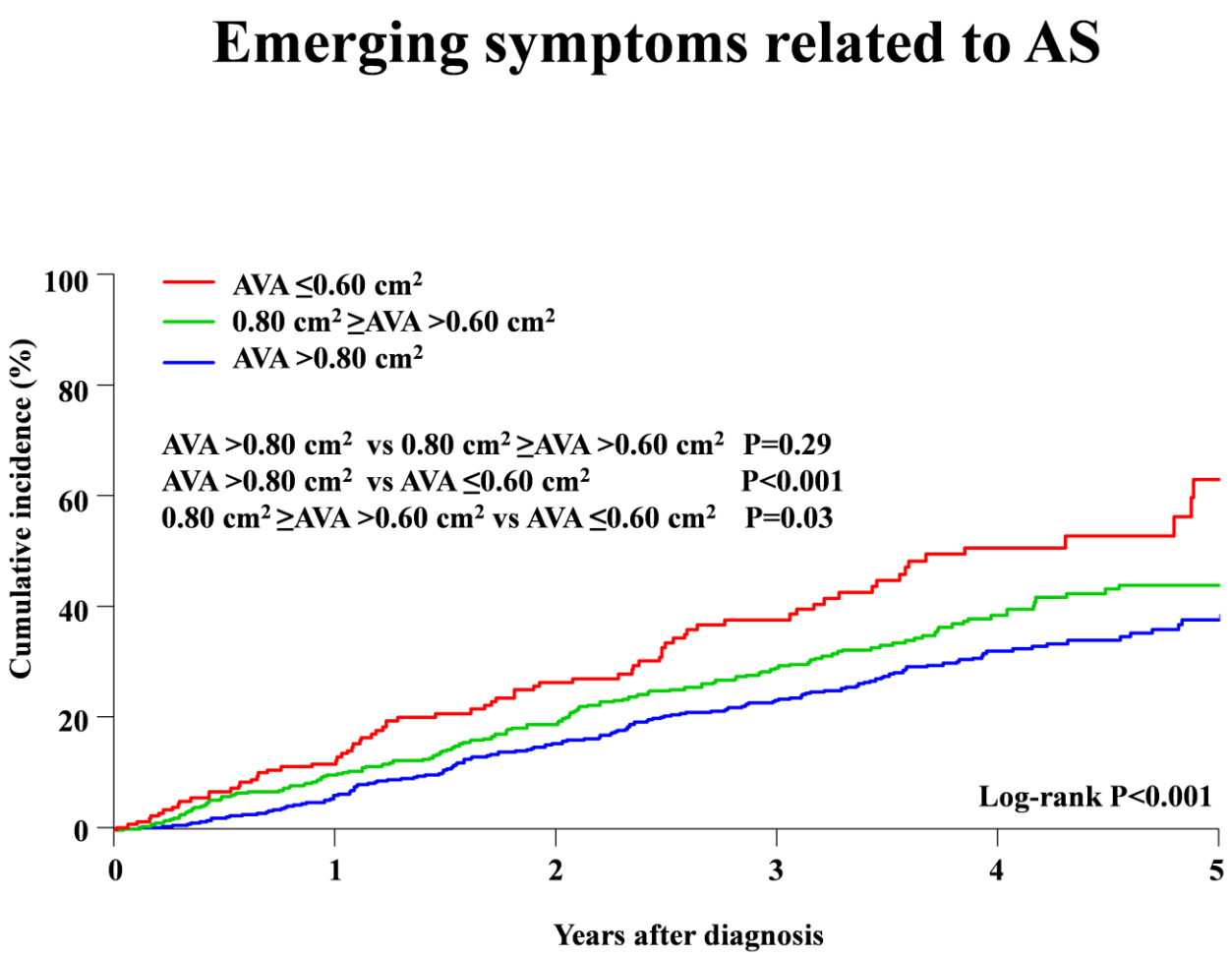
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		12	30	41
N of patients at risk	199	161	94	21
Cumulative incidence		6.5%	18.6%	34.1%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		15	36	48
N of patients at risk	465	397	272	58
Cumulative incidence		3.5%	9.1%	16.3%
AVA >0.80 cm²				
N of patients with at least 1 event		10	26	41
N of patients at risk	645	572	394	112
Cumulative incidence		1.7%	4.7%	10.0%

Figure S4. Cumulative incidence of aortic valve procedure death.
AVA=aortic valve area.



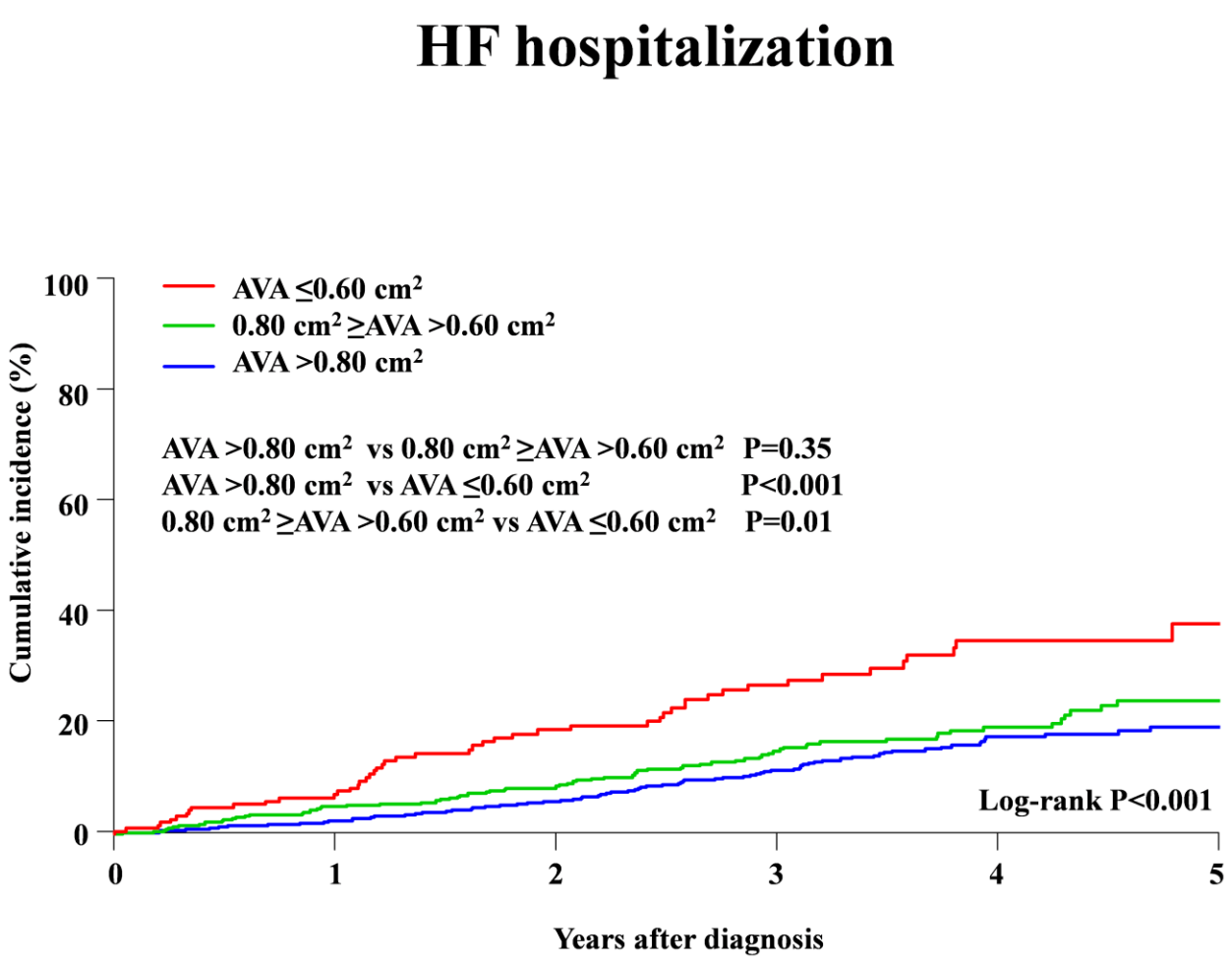
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		3	5	6
N of patients at risk	199	161	94	21
Cumulative incidence		1.7%	3.0%	4.7%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		0	2	3
N of patients at risk	465	397	272	58
Cumulative incidence		0%	0.5%	1.1%
AVA >0.80 cm²				
N of patients with at least 1 event		3	5	6
N of patients at risk	645	572	394	112
Cumulative incidence		0.5%	0.9%	1.3%

Figure S5. Cumulative incidence of emerging symptoms related to AS.
AS= aortic stenosis; AVA=aortic valve area.



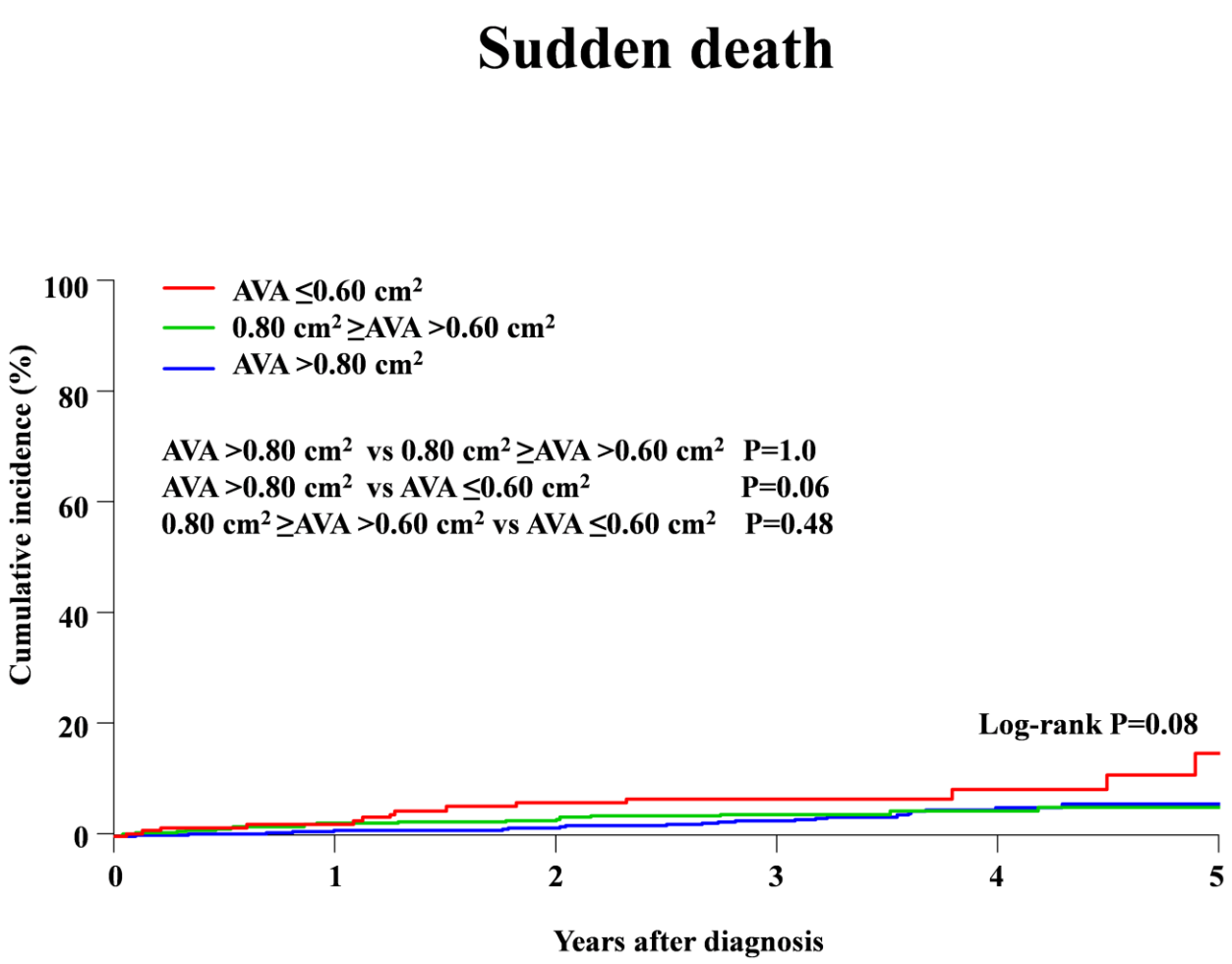
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		24	59	75
N of patients at risk	199	148	67	10
Cumulative incidence		13.1%	37.8%	63.0%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		43	113	142
N of patients at risk	465	362	206	44
Cumulative incidence		10.1%	29.5%	44.1%
AVA >0.80 cm²				
N of patients with at least 1 event		38	129	167
N of patients at risk	645	540	314	71
Cumulative incidence		6.4%	23.6%	38.5%

Figure S6. Cumulative incidence of HF hospitalization.
AVA=aortic valve area; HF=heart failure.



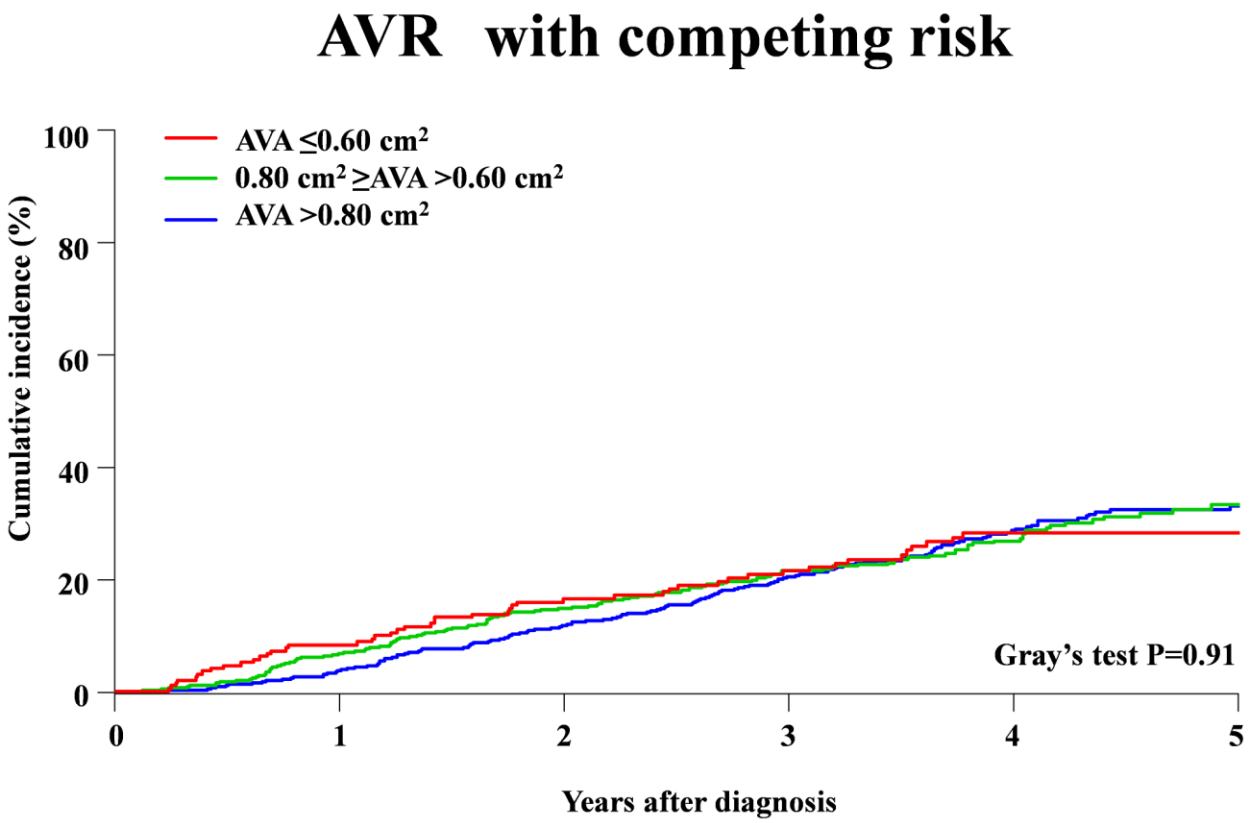
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		13	41	49
N of patients at risk	199	155	81	18
Cumulative incidence		7.1%	26.8%	37.7%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		21	56	72
N of patients at risk	465	383	248	51
Cumulative incidence		5.0%	14.9%	23.9%
AVA >0.80 cm²				
N of patients with at least 1 event		15	61	84
N of patients at risk	645	562	364	99
Cumulative incidence		2.5%	11.4%	19.3%

Figure S7. Cumulative incidence of sudden death.
AVA=aortic valve area.



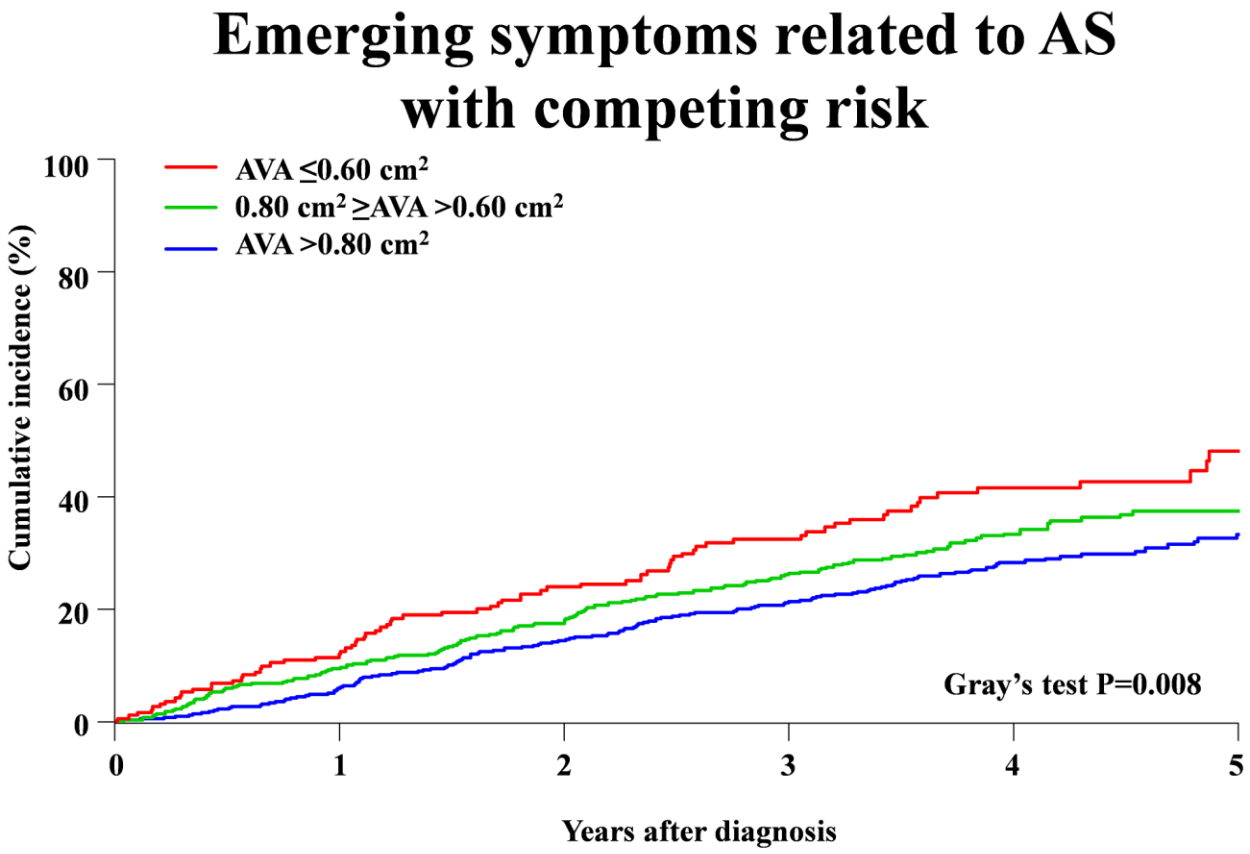
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		4	11	14
N of patients at risk	199	161	94	21
Cumulative incidence		2.1%	6.8%	14.8%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		10	16	18
N of patients at risk	465	397	272	58
Cumulative incidence		2.3%	4.0%	5.2%
AVA >0.80 cm²				
N of patients with at least 1 event		6	15	24
N of patients at risk	645	572	394	112
Cumulative incidence		1.0%	2.8%	5.8%

Figure S8. Cumulative incidence of AVR with competing risk.
AVA=aortic valve area; AVR=aortic valve replacement.



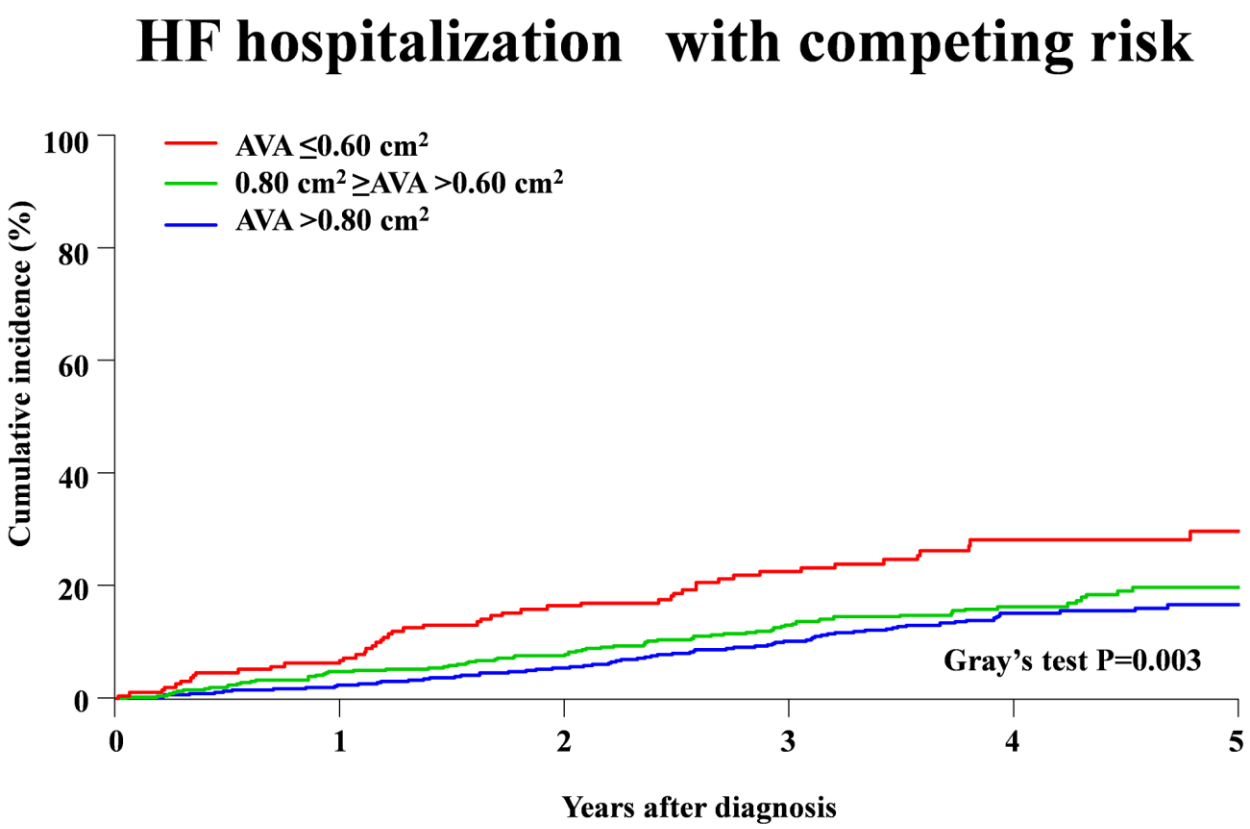
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with AVR		16	39	48
N of patients at risk	199	148	69	10
Cumulative incidence		8.3%	21.4%	28.1%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with AVR		30	92	120
N of patients at risk	465	367	202	37
Cumulative incidence		6.7%	21.3%	33.0%
AVA >0.80 cm²				
N of patients with AVR		23	122	165
N of patients at risk	645	553	308	71
Cumulative incidence		3.7%	20.4%	32.8%

Figure S9. Cumulative incidence of emerging symptoms related AS with competing risk. AS=aortic stenosis; AVA=aortic valve area.



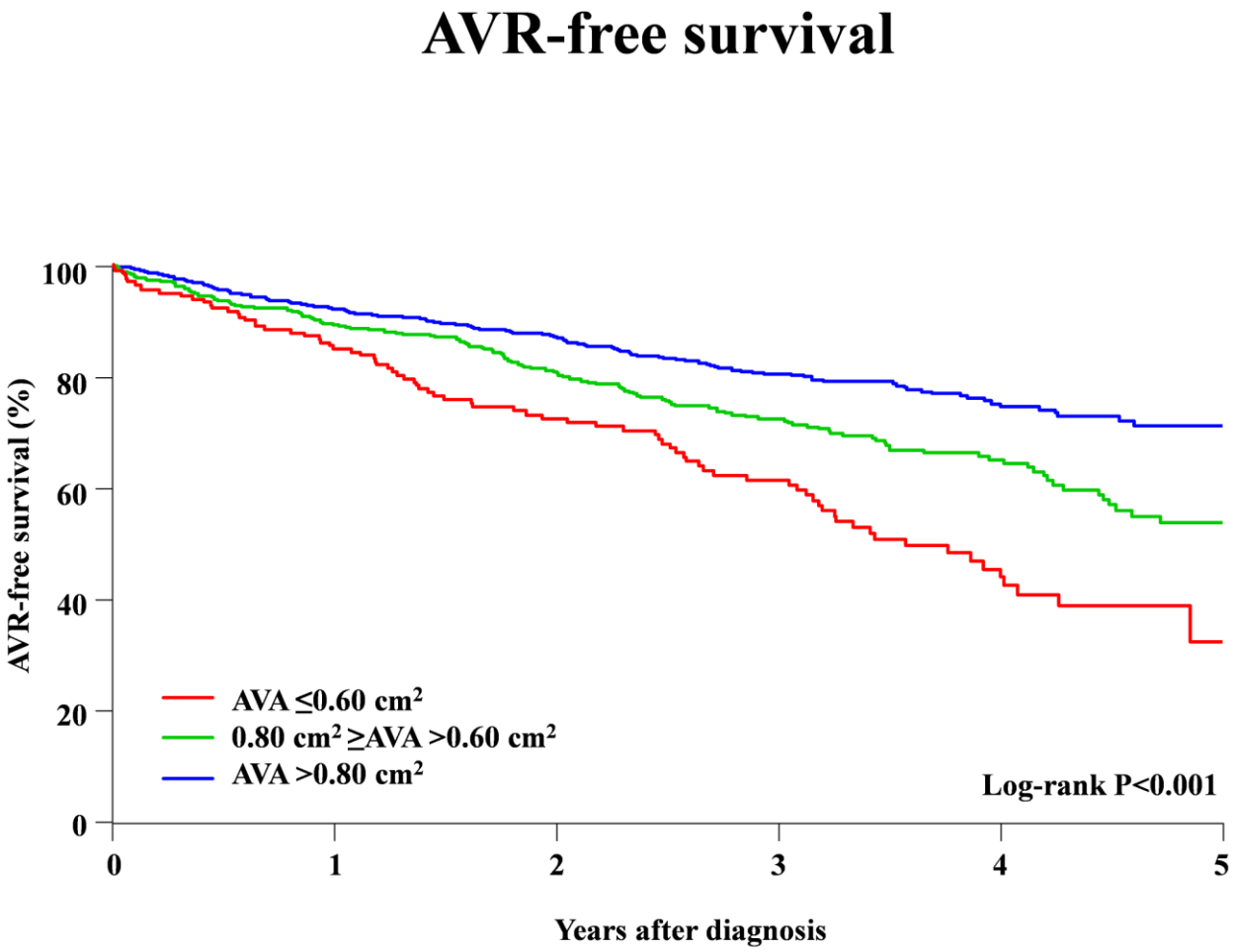
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		24	59	75
N of patients at risk	199	148	67	10
Cumulative incidence		12.4%	32.2%	47.7%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		43	113	142
N of patients at risk	465	362	206	44
Cumulative incidence		9.6%	26.1%	37.1%
AVA >0.80 cm²				
N of patients with at least 1 event		38	129	167
N of patients at risk	645	540	314	71
Cumulative incidence		6.0%	21.2%	33.1%

Figure S10. Cumulative incidence of HF hospitalization with competing risk.
AVA=aortic valve area; HF=heart failure



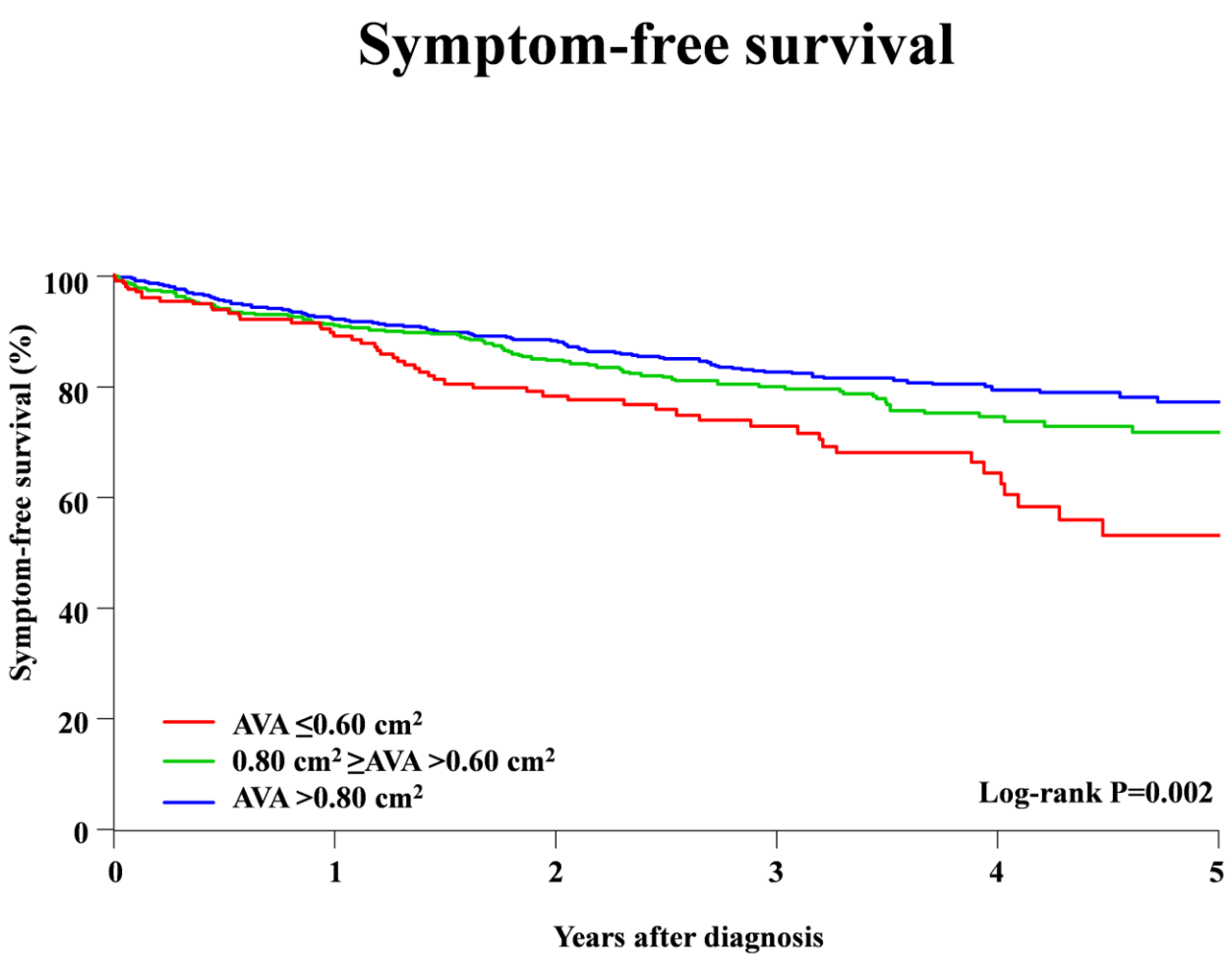
Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		13	41	49
N of patients at risk	199	155	81	18
Cumulative incidence		6.7%	22.4%	29.6%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		21	56	72
N of patients at risk	465	383	248	51
Cumulative incidence		4.7%	13.0%	19.6%
AVA >0.80 cm²				
N of patients with at least 1 event		16	61	84
N of patients at risk	645	562	364	99
Cumulative incidence		2.4%	10.1%	16.5%

Figure S11. AVR-free survival.
AVA=aortic valve area;
AVR=aortic valve replacement.



Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		28	62	83
N of patients at risk	199	148	69	10
AVR-free survival		85.0%	61.5%	32.6%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		47	107	137
N of patients at risk	465	367	202	37
AVR-free survival		89.3%	72.5%	53.8%
AVA >0.80 cm²				
N of patients with at least 1 event		50	110	131
N of patients at risk	645	553	308	71
AVR-free survival		92.0%	80.4%	71.2%

Figure S12. Symptom-free survival.
AVA=aortic valve area.



Interval	0 days	1 year	3 years	5 years
AVA ≤0.60 cm²				
N of patients with at least 1 event		20	42	53
N of patients at risk	199	148	67	10
Symptom-free survival		89.1%	72.8%	53.3%
0.80 cm² ≥AVA >0.60 cm²				
N of patients with at least 1 event		39	77	91
N of patients at risk	465	362	206	44
Symptom-free survival		91.0%	80.0%	71.8%
AVA >0.80 cm²				
N of patients with at least 1 event		49	97	109
N of patients at risk	645	540	314	71
Symptom-free survival		92.1%	82.5%	77.2%