Reasons for Choosing Conservative Management in Symptomatic Patients With Severe Aortic Stenosis
— Observations From the CURRENT AS Registry —

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Background: There has not been a previous report on the long-term outcomes of those patients who refuse aortic valve replacement (AVR) despite physicians' recommendations.

Methods and Results: Among 3,815 consecutive patients with severe aortic stenosis (AS) enrolled in the CURRENT AS registry, the study population comprised 2,005 symptomatic patients, who were subdivided into 3 groups by their treatment strategy and the reasons for conservative strategy (Initial AVR group: n=905; Patient rejection group: n=256; Physician judgment group, n=844). The primary outcome measure was a composite of aortic valve-related death and heart failure hospitalization. Patients in the patient rejection group as compared with those in the physician judgment group were younger, and had less comorbidities, and lower surgical risk scores. The cumulative 5-year incidence of the primary outcome measure in the patient rejection group was markedly higher than that in the initial AVR group, and was similar to that in the physician judgment group (60.7%, 19.0%, and 66.4%, respectively).

Conclusions: Patient rejection was the reason for non-referral to AVR in nearly one-quarter of the symptomatic patients with severe AS who were managed conservatively. The dismal outcome in patients who refused AVR was similar to that in patients who were not referred to AVR based on physician judgment despite less comorbidities and lower surgical risk scores in the former than in the latter.
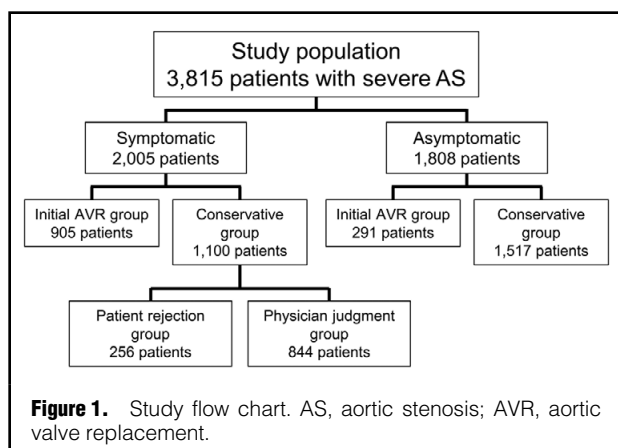
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A ortic stenosis (AS) is the most frequent valvular heart disease and its incidence is increasing with the aging of the population.[1] In symptomatic patients with severe AS, the current guidelines strongly recommend surgical aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI).[2–5] However, previous studies consistently report that a substantial proportion of symptomatic patients do not undergo AVR despite the fact that symptomatic patients with severe AS have an extremely unfavorable prognosis with impaired quality of life and high short-term mortality rate if not treated by AVR,[6–8] which can now be performed with relatively low mortality

Figure 1. Study flow chart. AS, aortic stenosis; AVR, aortic valve replacement.

Table 1. Reasons for Choosing Conservative Strategy Despite Symptomatic Severe Aortic Stenosis

Reasons	No. of patients
Patient rejection	256
Physician judgment	844
Too advanced age	443
Improved symptoms by medications	204
Prohibitive surgical risk	168
Dementia/Frailty	142
Symptoms related to CAD	54
Limited life expectancy	51
Other	13

The individual reasons for physician judgment were not mutually exclusive. Prohibitive surgical risk included cardiac dysfunction, renal dysfunction, liver cirrhosis, respiratory dysfunction, thoracic deformity and previous open cardiac surgery. Other includes referral to another hospital in 3 patients, cardiopulmonary arrest before further examination in 1 patient, need for non-cardiac surgery in 1 patient, and unknown in 8 patients. CAD, coronary artery disease.

rates even in elderly patients.[1,9,10] Previous studies have reported advanced age, frailty, the presence of multiple coexisting conditions, or patient rejection as the reasons for non-referral to AVR.[11–15] However, there is a scarcity of data on the relation between the reasons for non-referral to AVR and the long-term outcomes in these patients with severe AS who are managed conservatively despite symptoms.[16] More specifically, there has not been a previous report on the long-term outcomes of these patients who refuse AVR despite recommendations by physicians. Therefore, we aimed to investigate the baseline characteristics and long-term clinical outcome in symptomatic patients who denied AVR in comparison with those conservatively managed patients based on physician judgment in a large Japanese multicenter registry of consecutive patients with severe AS.

Methods

Study Population
The CURRENT AS (Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis) registry is a retrospective, multicenter registry enrolling consecutive patients with severe AS from among 27 centers (of which 20 had an on-site surgical facility) in Japan between January 2003 and December 2011. The design, patient enrollment, and outcomes of the registry were previously reported in detail.[17] In brief, we searched the hospitals' databases of transthoracic echocardiography, and enrolled consecutive patients who met the definition of severe AS (peak aortic jet velocity [V_{max}] >4.0 m/s, mean aortic pressure gradient [PG] >40 mmHg, or aortic valve area [AVA] <1.0 cm²) for the first time during the study period.[2] We excluded patients with a history of aortic valve surgery

or percutaneous aortic balloon valvuloplasty. The institutional review boards of all 27 participating centers approved the protocol. Written informed consent from each patient was waived in this retrospective study, because we used clinical information obtained during routine clinical practice, and no patients refused to participate in the study when contacted for follow-up.

Among 3,815 patients enrolled in the registry, there were 2,005 patients with and 1,808 patients without symptoms related to AS at the time of the index echocardiography, excluding 2 patients whose symptomatic status were not available. In the present analysis, 2,005 symptomatic patients with severe AS were divided into the initial AVR (n=905) and conservative (n=1,100) groups. Patients in the conservative group were further subdivided into 2 subgroups according to the main reasons for not choosing the initial AVR strategy after the index echocardiography, namely, patient rejection and physician judgment (**Figure 1**). We evaluated the baseline characteristics, AVR/TAVI during follow-up, and long-term clinical outcomes in the 2 subgroups of the conservative group with the initial AVR group used as the reference (**Figure 1**).

Data Collection and Definitions
Collection of baseline clinical information was conducted through review of the hospital charts or database. Angina, syncope, or congestive heart failure (HF) were regarded as symptoms related to AS. The presence of HF was determined as acute HF requiring hospitalization, or chronic exertional

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dyspnea. There was a specific data field for the reasons the patient was not referred to AVR despite the presence of symptoms. Site investigators entered the data field by searching the hospital chart for the notes regarding recommendation for AVR, the responses of the patient to the recommendation, and the reasons for no recommendation for AVR. All patients underwent comprehensive 2-D and Doppler echocardiographic evaluation in the participating centers. V_{max} and mean PG were obtained with the use of the simplified Bernoulli equation. AVA was calculated by standard continuity equation, and indexed to body surface area.[18] Follow-up information was mainly collected through review of the hospital charts and additional information was collected through contact with patients, relatives, and/or referring physicians by mailing a questionnaire regarding survival, symptoms and subsequent hospitalizations.

The primary outcome measure in the current analysis was a composite of aortic valve-related death and HF hospitalization. Secondary outcome measures included the individual components of the primary outcome measure: all-cause death, and non-cardiac death. The causes of death were classified according to the Valve Academic Research Consortium (VARC) definitions and were adjudicated by a clinical event committee.[19,20] Sudden death was defined as unexplained death in a previously stable patient. Aortic valve-related death included aortic procedure-related death, sudden death, and death attributed to HF that was possibly related to the aortic valve. HF hospitalization was defined as hospitalization attributed to worsening HF that required intravenous drug therapy.

Table 2. Baseline Clinical and Echocardiographic Characteristics

	Initial AVR group (n=905)	Patient rejection group (n=256)	Physician judgment group (n=844)	P value 3-way comparison	P value Physician judgment vs. Patient rejection
Clinical characteristics					
Age, years	73.9±8.9	80.0±7.8	83.2±9.0	<0.0001	<0.0001
≥75 years, n (%)	478 (52.8)	201 (78.5)	711 (84.2)	<0.0001	0.04
Women, n (%)	524 (57.9)	178 (69.5)	590 (69.9)	<0.0001	0.91
BMI	22.4±3.6	21.4±3.9	20.7±3.8	<0.0001	0.02
<22, n (%)	476 (52.6)	171 (66.8)	621 (73.6)	<0.0001	0.04
BSA (m²)	1.49±0.18	1.42±0.18	1.39±0.19	<0.0001	0.07
Hypertension, n (%)	618 (68.3)	187 (73.1)	613 (72.6)	0.09	0.90
Current smoking, n (%)	240 (26.5)	50 (19.5)	138 (16.4)	<0.0001	0.24
Dyslipidemia, n (%)	360 (39.8)	78 (30.5)	241 (28.6)	<0.0001	0.56
On statin therapy, n (%)	267 (29.5)	60 (23.4)	179 (21.2)	0.0003	0.45
Diabetes mellitus, n (%)	217 (24.0)	55 (21.5)	191 (22.6)	0.65	0.70
On insulin therapy, n (%)	47 (5.2)	10 (3.9)	40 (4.7)	0.68	0.57
Prior MI, n (%)	46 (5.1)	22 (8.6)	104 (12.3)	<0.0001	0.09
Prior PCI, n (%)	82 (9.1)	22 (8.6)	112 (13.3)	0.009	0.04
Prior CABG, n (%)	28 (3.1)	16 (6.3)	60 (7.1)	0.0004	0.63
Prior open cardiac surgery, n (%)	38 (4.2)	22 (8.6)	94 (11.1)	<0.0001	0.22
Prior symptomatic stroke, n (%)	82 (9.1)	32 (12.5)	135 (16.0)	<0.0001	0.16
Atrial fibrillation, n (%)	168 (18.6)	65 (25.4)	257 (30.5)	<0.0001	0.12
Aortic/peripheral vascular disease, n (%)	125 (13.8)	25 (9.8)	130 (13.8)	0.06	0.02
Serum creatinine (mg/dL)	0.84 (0.70–1.16)	0.92 (0.70–1.38)	1.00 (0.73–1.59)	<0.0001	0.29
Creatinine level >2 mg/dL, n (%)	116 (12.8)	34 (13.3)	144 (17.1)	0.04	0.14
Hemodialysis, n (%)	103 (11.4)	19 (7.4)	76 (9.0)	0.09	0.42
Anemia, n (%)	499 (55.1)	149 (58.2)	606 (71.8)	<0.0001	<0.0001
Liver cirrhosis (Child-pugh B or C), n (%)	3 (0.3)	1 (0.4)	17 (2.0)	0.003	0.08
Malignancy, n (%)	97 (10.7)	24 (9.4)	119 (14.1)	0.04	0.04
Malignancy currently under treatment, n (%)	17 (1.9)	3 (1.2)	35 (4.2)	0.004	0.01
Chest wall irradiation, n (%)	6 (0.7)	2 (0.8)	5 (0.6)	0.95	0.75
Immunosuppressive therapy, n (%)	27 (3.0)	7 (2.7)	37 (4.4)	0.22	0.22
Chronic lung disease, n (%)	114 (12.6)	27 (10.6)	98 (11.6)	0.62	0.64
Chronic lung disease (moderate or severe), n (%)	17 (1.9)	9 (3.5)	43 (5.1)	0.0009	0.28
CAD, n (%)	330 (36.5)	64 (25.0)	252 (29.9)	0.0004	0.13
Logistic Euro Score, %	7.6 (4.8–12.6)	11.8 (7.9–19.3)	16.3 (10.5–27.1)	<0.0001	<0.0001
Euro Score, %	2.5 (1.5–4.1)	3.8 (2.6–6.1)	5.3 (3.3–8.5)	<0.0001	<0.0001
STS score (PROM), %	3.1 (1.9–5.2)	4.6 (2.8–7.9)	6.6 (10.8–3.9)	<0.0001	<0.0001

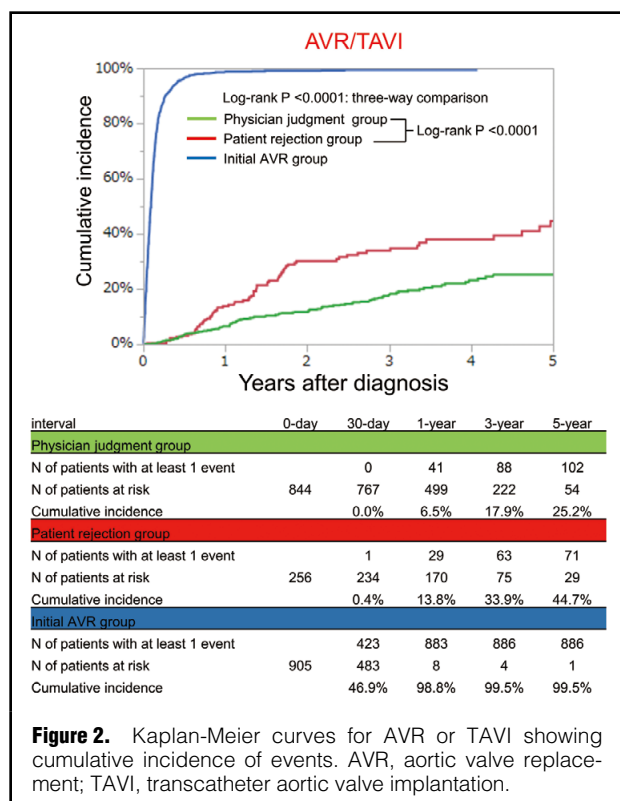(**Table 2** continued the next page.)

	Initial AVR group (n=905)	Patient rejection group (n=256)	Physician judgment group (n=844)	P value 3-way comparison	P value Physician judgment vs. Patient rejection
Symptoms					
Angina, n (%)	291 (32.2)	55 (21.5)	152 (18.0)	<0.0001	0.22
Syncope, n (%)	110 (12.2)	29 (11.3)	59 (7.0)	<0.0001	0.03
HF, n (%)	659 (72.8)	212 (82.8)	732 (86.7)	<0.0001	0.12
Acute HF requiring hospitalization, n (%)	270 (29.8)	93 (36.3)	427 (50.6)	<0.0001	0.0002
Etiology of aortic stenosis				<0.0001	0.87
Degenerative, n (%)	753 (83.2)	241 (94.1)	796 (94.3)		
Congenital, n (%)	100 (11.1)	4 (1.6)	14 (1.7)		
Rheumatic, n (%)	44 (4.9)	9 (3.5)	31 (3.7)		
Infective endocarditis, n (%)	3 (0.3)	0 (0.0)	0 (0)		
Other, n (%)	5 (0.6)	2 (0.8)	3 (0.4)		
Echocardiographic variables					
LV end-diastolic diameter (mm)	47.8±7.4	46.8±7.4	46.2±7.8	<0.0001	0.25
LV end-systolic diameter (mm)	32.1±9.0	31.6±8.8	31.8±8.7	0.76	0.75
LVEF (%)	61.4±14.9	60.5±14.8	58.1±14.8	<0.0001	0.03
LVEF <40%, n (%)	99 (10.9)	24 (9.4)	113 (13.4)	0.12	0.08
LVEF <50%, n (%)	186 (20.6)	53 (20.7)	212 (25.1)	0.057	0.14
IVST in diastole (mm)	11.9±2.4	11.8±2.4	11.1±2.3	<0.0001	<0.0001
PWT in diastole (mm)	11.6±2.1	11.3±1.9	10.7±2.0	<0.0001	0.0002
Peak aortic jet velocity (m/s)	4.7±0.8	4.5±0.9	3.9±0.9	<0.0001	<0.0001
Peak aortic jet velocity ≥4 m/s	748 (82.7)	195 (76.2)	377 (44.7)	<0.0001	<0.0001
Peak aortic jet velocity ≥5 m/s	314 (34.7)	71 (27.7)	105 (12.4)	<0.0001	<0.0001
Peak aortic pressure gradient (mmHg)	90.3±31.2	84.0±31.6	63.1±29.9	<0.0001	<0.0001
Mean aortic pressure gradient (mmHg)	53.4±19.2	48.5±21.1	35.6±18.8	<0.0001	<0.0001
AVA (equation of continuity) (cm²)	0.64±0.18	0.64±0.20	0.71±0.19	<0.0001	<0.0001
AVA index (cm²/m²)	0.43±0.12	0.46±0.13	0.52±0.14	<0.0001	<0.0001
Any combined valvular disease (moderate or severe)	397 (43.9)	144 (56.3)	456 (54.0)	<0.0001	0.53
Moderate or severe AR, n (%)	238 (26.3)	70 (27.3)	189 (22.4)	0.1	0.11
Moderate or severe MS, n (%)	44 (4.9)	8 (3.1)	32 (3.8)	0.35	0.61
Moderate or severe MR, n (%)	201 (22.2)	91 (35.6)	258 (30.6)	<0.0001	0.14
Moderate or severe TR, n (%)	125 (13.8)	54 (21.1)	233 (27.6)	<0.0001	0.03
TR pressure gradient ≥40 mmHg	159 (17.6)	73 (28.5)	201 (23.8)	0.0001	0.13

BMI was calculated as weight in kilograms divided by height in meters squared. Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men). AR, aortic regurgitation; AVA, aortic valve area; AVR, aortic valve replacement; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HF, heart failure; IVST, interventricular septum thickness; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; PCI, percutaneous coronary intervention; PROM, predicted risk of mortality; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation.

Statistical Analysis

We present continuous variables as the mean±standard deviation for normal distribution or median with interquartile range (IQR) for non-normal distribution and categorical variables as number and percentage. We compared continuous variables using ANOVA or the Kruskal-Wallis test according to their distributions. We analyzed categorical variables with the chi-squared test. We used the Kaplan-Meier method to estimate the cumulative incidences of clinical events and assessed intergroup differences with the log-rank test. The outcomes of the initial AVR group and physician judgment group were compared with those of the patient rejection group in the univariate and multivariable Cox proportional hazard models. Consistent with our previous report, we used the 21 clinically relevant risk-adjusting variables in the Cox proportional hazard models (age, male, body mass index (BMI) <22 kg/m², peak aortic jet velocity ≥4 m/s, coronary artery disease (CAD), creatinine level >0.83 mg/dL, malignancy current under treatment, anemia, ejection fraction (EF) <68%, chronic lung disease, hypertension, diabetes mellitus on insulin therapy, current smoking, prior myocardial infarction (MI), prior symptomatic stroke, atrial fibrillation or flutter, aortic/peripheral vascular disease, hemodialysis, liver cirrhosis, any combined valvular disease, and tricuspid regurgitation (TR) PG ≥40 mmHg) as indicated in **Table 2**. We assigned dummy variables for both the initial AVR and physician judgment groups compared with the patient rejection group and estimated hazard ratios (HR) and their 95% confidence intervals (CI). We also estimated the overall P values among the 3 groups. We performed a subgroup analysis based on age (<75 years or ≥75 years) for the primary outcome measure, because age is one of the most relevant factors for the choice of initial treatment strategy. The predictors of AVR/

Figure 2. Kaplan-Meier curves for AVR or TAVI showing cumulative incidence of events. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

TAVI during follow-up were estimated by univariate and multivariable logistic regression models. Based on the results of the univariate analyses, we incorporated 16 clinically relevant potential independent predictors in the logistic regression models (age, male, BMI <22 kg/m², peak aortic jet velocity ≥4 m/s, CAD, creatinine level >0.83 mg/dL, malignancy current under treatment, anemia, EF <68%, chronic lung disease, dyslipidemia, prior MI, prior symptomatic stroke, aortic/peripheral vascular disease, any combined valvular disease, and TRPG ≥40 mmHg) as indicated in **Supplementary Table 1**. We evaluated the effect of AVR/TAVI during follow-up on the primary outcome measure. We incorporated AVR/TAVI during follow-up as the time-updated covariate together with the same 21 risk-adjusting variables used in the main analysis into the multivariable Cox proportional hazard model and estimated the HR of AVR/TAVI during the follow-up for the primary outcome measure.

All statistical analyses were conducted by a physician using JMP 13.0.0 (SAS Institute Inc., Cary, NC, USA) or SPSS version 25.0.0.2 (IBM Corp.) in collaboration with a statistician. All reported P-values are 2-tailed, and P<0.05 was considered statistically significant.

Results

Reasons for Not Choosing the Initial AVR Strategy
In symptomatic patients with severe AS, the 2 main reasons for not choosing the initial AVR strategy were patient rejection despite physician recommendation for AVR (patient rejection group: n=256) and physician judgment considering the risk-benefit balance of the AVR procedure (physician judgment: n=844). In the physician judgment group,

the dominant reasons included very advanced age, improvement of symptoms by medications, prohibitive surgical risk, and dementia/frailty (**Table 1**). Dementia/frailty accounted for 16.8% of the physician judgment group. Prohibitive surgical risk included cardiac dysfunction, renal dysfunction, liver cirrhosis, respiratory dysfunction, thoracic deformity and previous open cardiac surgery.

Baseline Characteristics
The baseline characteristics of the 2 conservative subgroups were much different from those of the initial AVR group, with advanced age, preponderance of women, lower BMI, more comorbidities, higher prevalence of HF symptoms, and higher surgical risk scores (**Table 2**). Patients in the patient rejection group were younger, and had less comorbidities, less acute HF, and lower surgical risk scores than those in the physician judgment group (**Table 2**). The severity of AS evaluated by V_{max} was greater in the initial AVR than in the patient rejection group and was greater in the patient rejection than in the physician judgment group (**Table 2**).

Clinical Outcomes
Median follow-up interval of the surviving patients was 1,294 (IQR: 973–1,710) days. During follow-up, patients in the patient rejection group more often underwent AVR or TAVI than those in the physician judgment group (cumulative 5-year incidence: 44.7% and 25.2%, respectively), while the vast majority of patients in the initial AVR group actually underwent AVR within 6 months of the index echocardiography (**Figure 2**). In the logistic regression analyses for the predictors of AVR/TAVI during follow-up in the entire cohort, the independent predictors included patients with advanced age, low BMI, peak aortic jet velocity ≥4 m/s, CAD, anemia, and EF <68% (**Supplementary Table 1**). The cumulative 5-year incidence of the primary outcome measure (aortic valve-related death or HF hospitalization) in the patient rejection group was markedly higher than that in the initial AVR group, and was similar to that in the physician judgment group (60.7%, 19.0%, and 66.4%, respectively) (**Figure 3**). After adjusting for potential confounders, the excess risk of the patient rejection group relative to the initial AVR group for the primary outcome measure remained significant, while the risk of the patient rejection group for the primary outcome measure was comparable to that of the physician judgment group (**Table 3**). The cumulative 5-year incidences of all-cause death and non-cardiac death in the patient rejection group trended to be lower than those in the physician judgment group (**Figure 3**). In the patient rejection group, almost 80% of patients who underwent AVR/TAVI did so within 2 years of the index echocardiography, and the mortality rate was much higher in patients without AVR/TAVI than in patients with AVR/TAVI (**Supplementary Figures 1,2**). The cumulative incidence of death after AVR/TAVI was similar across the 3 groups (patient rejection/physician judgment/initial AVR) (**Supplementary Figure 3**).

Subgroup Analysis Based on Age
In the subgroup analysis stratified by age, the proportion of 'patient rejection' among those managed conservatively was numerically higher in patients <75 years of age (29%) than in patients ≥75 years of age (22%) (**Table 4**).

Cumulative 5-year incidence of the primary outcome measure for patient rejection was markedly higher than in the
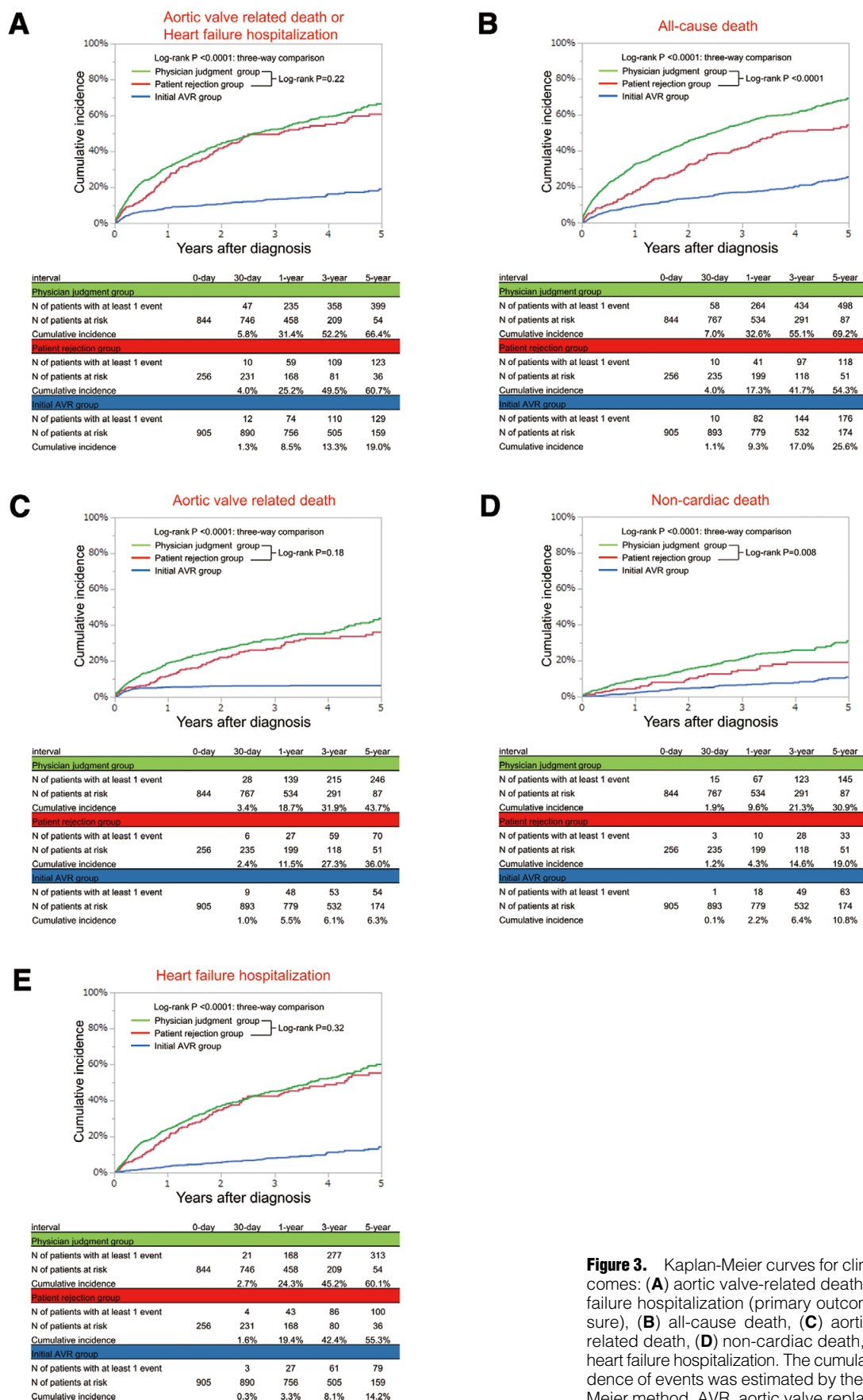
A Aortic valve related death or Heart failure hospitalization

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		47	235	358	399
N of patients at risk	844	746	458	209	54
Cumulative incidence		5.8%	31.4%	52.2%	66.4%
Patient rejection group					
N of patients with at least 1 event		10	59	109	123
N of patients at risk	256	231	168	81	36
Cumulative incidence		4.0%	25.2%	49.5%	60.7%
Initial AVR group					
N of patients with at least 1 event		12	74	110	129
N of patients at risk	905	890	756	505	159
Cumulative incidence		1.3%	8.5%	13.3%	19.0%

B All-cause death

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		58	264	434	498
N of patients at risk	844	767	534	291	87
Cumulative incidence		7.0%	32.6%	55.1%	69.2%
Patient rejection group					
N of patients with at least 1 event		10	41	97	118
N of patients at risk	256	235	199	118	51
Cumulative incidence		4.0%	17.3%	41.7%	54.3%
Initial AVR group					
N of patients with at least 1 event		10	82	144	176
N of patients at risk	905	893	779	532	174
Cumulative incidence		1.1%	9.3%	17.0%	25.6%

C Aortic valve related death

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		28	139	215	246
N of patients at risk	844	767	534	291	87
Cumulative incidence		3.4%	18.7%	31.9%	43.7%
Patient rejection group					
N of patients with at least 1 event		6	27	59	70
N of patients at risk	256	235	199	118	51
Cumulative incidence		2.4%	11.5%	27.3%	36.0%
Initial AVR group					
N of patients with at least 1 event		9	48	53	54
N of patients at risk	905	893	779	532	174
Cumulative incidence		1.0%	5.5%	6.1%	6.3%

D Non-cardiac death

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		15	67	123	145
N of patients at risk	844	767	534	291	87
Cumulative incidence		1.9%	9.6%	21.3%	30.9%
Patient rejection group					
N of patients with at least 1 event		3	10	28	33
N of patients at risk	256	235	199	118	51
Cumulative incidence		1.2%	4.3%	14.6%	19.0%
Initial AVR group					
N of patients with at least 1 event		1	18	49	63
N of patients at risk	905	893	779	532	174
Cumulative incidence		0.1%	2.2%	6.4%	10.8%

E Heart failure hospitalization

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		21	168	277	313
N of patients at risk	844	746	458	209	54
Cumulative incidence		2.7%	24.3%	45.2%	60.1%
Patient rejection group					
N of patients with at least 1 event		4	43	86	100
N of patients at risk	256	231	168	80	36
Cumulative incidence		1.6%	19.4%	42.4%	55.3%
Initial AVR group					
N of patients with at least 1 event		3	27	61	79
N of patients at risk	905	890	756	505	159
Cumulative incidence		0.3%	3.3%	8.1%	14.2%

Figure 3. Kaplan-Meier curves for clinical outcomes: (**A**) aortic valve-related death or heart failure hospitalization (primary outcome measure), (**B**) all-cause death, (**C**) aortic valve-related death, (**D**) non-cardiac death, and (**E**) heart failure hospitalization. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

Table 3. Risk of the Patient Rejection and Physician Judgment Groups Relative to the Initial AVR Group for the Primary and Secondary Outcome Measures

Variables	No. of patients with event (Cumulative 5-year incidence, %)	Unadjusted				Adjusted			
		HR	95% CI	P value	Overall P value	HR	95% CI	P value	Overall P value
Composite of aortic valve-related death or HF hospitalization									
Initial AVR group	142 (19.0)	0.23	0.18–0.30	<0.0001		0.28	0.22–0.36	<0.0001	
Patient rejection group	132 (60.7)	1 (Ref.)			<0.0001	1 (Ref.)			<0.0001
Physician judgment group	407 (66.4)	1.14	0.94–1.39	0.19		0.93	0.76–1.15	0.52	
All-cause death									
Initial AVR group	196 (25.6)	0.36	0.29–0.44	<0.0001		0.44	0.35–0.56	<0.0001	
Patient rejection group	138 (54.3)	1 (Ref.)			<0.0001	1 (Ref.)			<0.0001
Physician judgment group	532 (69.2)	1.48	1.23–1.80	<0.0001		1.07	0.88–1.31	0.49	
Aortic valve-related death									
Initial AVR group	55 (6.3)	0.17	0.12–0.23	<0.0001		0.21	0.15–0.30	<0.0001	
Patient rejection group	84 (36.0)	1 (Ref.)			<0.0001	1 (Ref.)			<0.0001
Physician judgment group	260 (43.7)	1.16	0.91–1.49	0.25		0.90	0.69–1.18	0.46	
Non-cardiac death									
Initial AVR group	70 (10.8)	0.47	0.32–0.71	0.0004		0.58	0.38–0.88	0.01	
Patient rejection group	37 (19.0)	1 (Ref.)			<0.0001	1 (Ref.)			0.001
Physician judgment group	155 (30.9)	1.65	1.17–2.40	0.004		1.08	0.73–1.58	0.71	
HF hospitalization									
Initial AVR group	92 (14.2)	0.18	0.14–0.24	<0.0001		0.22	0.16–0.29	<0.0001	
Patient rejection group	106 (55.3)	1 (Ref.)			<0.0001	1 (Ref.)			<0.0001
Physician judgment group	320 (60.1)	1.14	0.92–1.43	0.23		0.94	0.74–1.19	0.63	

Aortic valve-related death included aortic procedure-related death, sudden death, and death from HF. HF hospitalization was defined as hospitalization for worsening HF requiring intravenous drug therapy. AVR, aortic valve replacement; CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 4. Risk of the Patient Rejection and Physician Judgment Groups Relative to the Initial AVR Group on the Primary Outcome Measure Stratified by Age

Variables	No. of events (Cumulative 5-year incidence, %)	Unadjusted					Adjusted				
		HR	95% CI	P value	Overall P value	Interaction P value	HR	95% CI	P value	Overall P value	Interaction P value
						0.32					0.39
Age <75 years											
Initial AVR group (n=427)	54 (13.0)	0.33	0.20–0.55	<0.0001			0.29	0.17–0.49	<0.0001		
Patient rejection group (n=55)	22 (40.7)	1 (Ref.)			<0.0001		1 (Ref.)			0.0006	
Physician judgment group (n=133)	45 (41.7)	1.03	0.62–1.75	0.92			0.52	0.30–0.93	0.03		
Age ≥75 years											
Initial AVR group (n=478)	88 (25.9)	0.24	0.18–0.32	<0.0001			0.26	0.20–0.36	<0.0001		
Patient rejection group (n=201)	110 (67.2)	1 (Ref.)			<0.0001		1 (Ref.)			<0.0001	
Physician judgment group (n=711)	362 (72.4)	1.09	0.89–1.36	0.41			1.07	0.85–1.35	0.55		

Aortic valve-related death included aortic procedure-related death, sudden death, and death from HF. HF hospitalization was defined as hospitalization for worsening HF requiring intravenous drug therapy. Abbreviations as in Table 3.
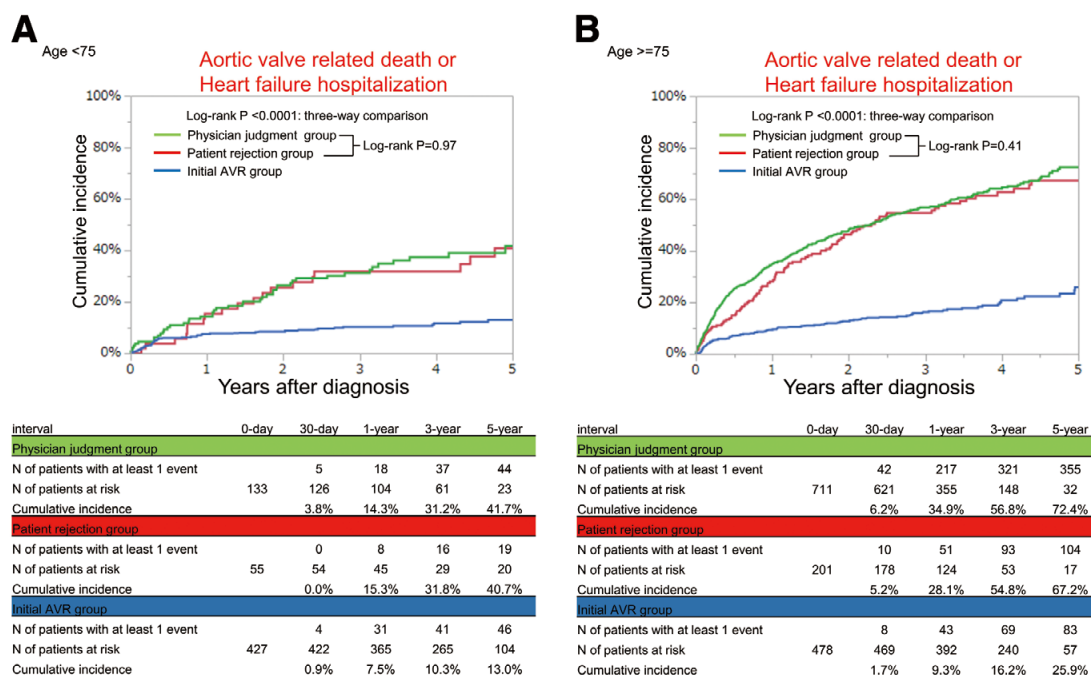
Figure 4. Kaplan-Meier curves for the primary outcome measure according to age: (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

initial AVR group and was similar to that in the physician judgment group regardless of the age category (age < or ≥75 years) (**Figure 4**, **Table 4**, **Supplementary Figures 4–8**). After adjusting for potential confounders, the excess risk of the patient rejection group relative to the initial AVR group for the primary outcome measure remained significant regardless of the age category (**Table 4**). There was no significant interaction between the age category and the risk of the initial AVR group relative to the patient rejection group for the primary outcome measure (**Table 4**). The adjusted risk of the patient rejection group for the primary outcome measure was significantly higher than that of the physician judgment group in the <75 years age category and was similar to that of the physician judgment group in the ≥75 years age category (**Table 4**).

Effect of AVR/TAVI During Follow-up on Clinical Outcomes

In the Cox hazard model incorporating AVR/TAVI during follow-up as a time-dependent covariate, AVR/TAVI during the follow-up group was associated with a significantly lower risk for the primary outcome measure compared with the never AVR/TAVI group (HR 0.27, 95% CI 0.16–0.44, P<0.001; **Supplementary Table 2**).

Discussion

The main findings in the present study were: (1) patient rejection was the reason for non-referral to AVR in nearly one-quarter of the symptomatic patients with severe AS who were managed conservatively; and (2) the dismal outcome in patients who refused AVR was similar to that in patients who were not referred to AVR based on physician judgment despite less comorbidities and lower surgical risk

scores in the former than in the latter.

In the present study, a conservative management strategy was chosen for more than half of the symptomatic patients with severe AS, which is consistent with previous reports.[2–4] Obviously, symptomatic patients with severe AS who are managed conservatively have markedly worse adjusted aortic valve-related clinical outcomes than those who are managed with an initial AVR strategy. The dominant reason for non-referral to AVR was physician judgment based on factors such as very advanced age, improvement of symptoms by medication, prohibitive surgical risk, dementia/frailty, symptoms considered to be related to CAD, and limited life expectancy, etc. Frailty is reported to be associated with a higher rate of poor outcome after both AVR and TAVR.[21,22] However, consistent with previous reports,[16] patient rejection was the reason for non-referral to AVR in nearly one-quarter of the symptomatic patients with severe AS who were managed conservatively in the present study. It was somewhat surprising that the proportion of 'patient rejection' among those managed conservatively was numerically higher in patients aged <75 years than in patients aged ≥75 years. The dismal outcome in patients who refused AVR was similar to that in patients who were not referred to AVR based on physician judgment, despite less comorbidities and lower surgical risk scores in the former than in the latter. We might reasonably speculate that the proportion of patients who were truly contraindicated for AVR was smaller in the patient rejection group than in the physician judgment group. Indeed, the proportion of patients who underwent AVR later during follow-up was higher in the patient rejection group than in the physician judgment group (45% and 25%, respectively). Delaying AVR in symptomatic patients with severe AS might have a detrimental

effect on prognosis.[17,23] However, in the patient rejection group of this study, almost 80% of patients who underwent AVR/TAVI did so within 2 years after the index echocardiography. Death after AVR/TAVI in the patient rejection group was similar to that in the initial AVR group. Therefore, the high mortality of patients in the patient rejection group was largely driven by the very high mortality of those patients who ultimately did not undergo AVR/TAVI. It is also be important to note that the dismal outcome of patients who refused AVR was consistently seen regardless of the age category (age < or ≥75 years).

Patients refuse AVR for many reasons, which might differ according to age, and social environment. The introduction of TAVI might have already substantially changed patients' decisions.[24] Patients in the patient refusal group were heterogeneous in terms of their risk for AVR. TAVI has already become the firstline treatment in patients with high surgical risk who have refused surgical AVR (SAVR). Recently, 2 randomized trials that enrolled low surgical risk patients clearly demonstrated non-inferiority or even superiority of TAVI relative to SAVR in terms of the hard clinical endpoints.[25,26] Considering its less invasive nature, TAVI would also be the preferred option in patients with low surgical risk who refuse SAVR. Nevertheless, the present study results are important because they highlight the profound risk of patient rejection for AVR as well as the risk of delaying AVR, which should be adequately informed to the patients and the family members.

Study Limitations

This study has several important limitations. First, the present analysis was a post-hoc substudy from the retrospective CURRENT AS registry. We did not collect information on the severity of symptoms, frailty, frailty scores such as Clinical Frailty Scale,[27] or activities in daily living, all of which would be important in the decision making for the treatment strategy. Second, in this retrospective registry it might sometimes have been very difficult to make a clear distinction between patients who refused AVR and those whom the physician did not recommend AVR. Furthermore, those patients who rejected AVR may have recognized their own morbidities not captured in the database that would make AVR high risk. Third, we do not know the specific reasons for patient rejection, or how strongly the physician recommended AVR. Fourth, we should be cautious in extrapolating the present study results to current clinical practice after the introduction of TAVI.

Conclusions

Patient rejection was the reason for non-referral to AVR in nearly one-quarter of the symptomatic patients with severe AS who were managed conservatively in this retrospective registry. The dismal outcome in patients who refused AVR was similar to that in patients who were not referred to AVR based on physician judgment, despite less comorbidities and lower surgical risk scores in the former than in the latter.

Disclosures

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Supplementary Files

Please find supplementary file(s);
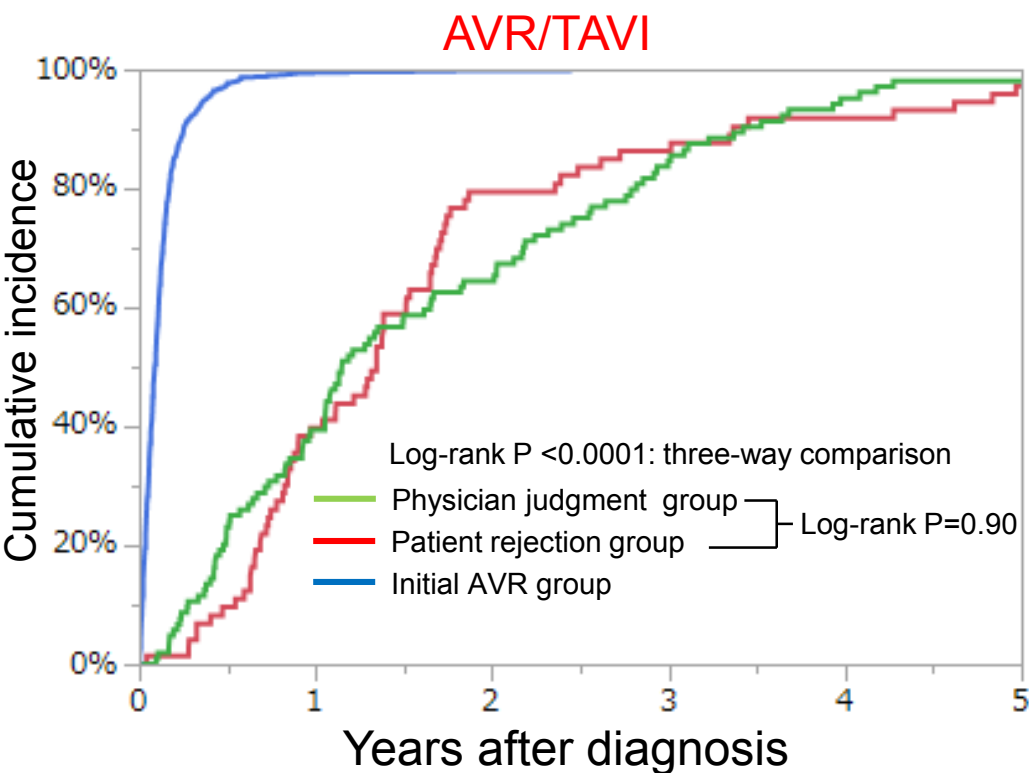http://dx.doi.org/10.1253/circj.CJ-19-0247

Reasons for Choosing Conservative Management in Symptomatic Patients With Severe Aortic Stenosis

— Observations From the CURRENT AS Registry —

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Supplementary Figure 1

AVR/TAVI

Log-rank P <0.0001: three-way comparison

Physician judgment group ┐
Patient rejection group ─┤─ Log-rank P=0.90
Initial AVR group ┘

interval	Median period to procedure	0-day	30-day	1-year	3-year	5-year
Physician judgment group	419.5 days					
N of patients with event			0	41	88	102
N of patients at risk		104	104	63	16	2
Cumulative incidence			0.0%	39.4%	84.6%	98.1%
Patient rejection group	491 days					
N of patients with event			1	29	63	71
N of patients at risk		73	72	44	10	2
Cumulative incidence			1.4%	39.7%	86.3%	97.3%
Initial AVR group	33 days					
N of patients with event			418	883	886	886
N of patients at risk		886	468	3	0	0
Cumulative incidence			47.7%	99.7%	100.0%	100.0%

Supplementary Figure 2

All-cause death
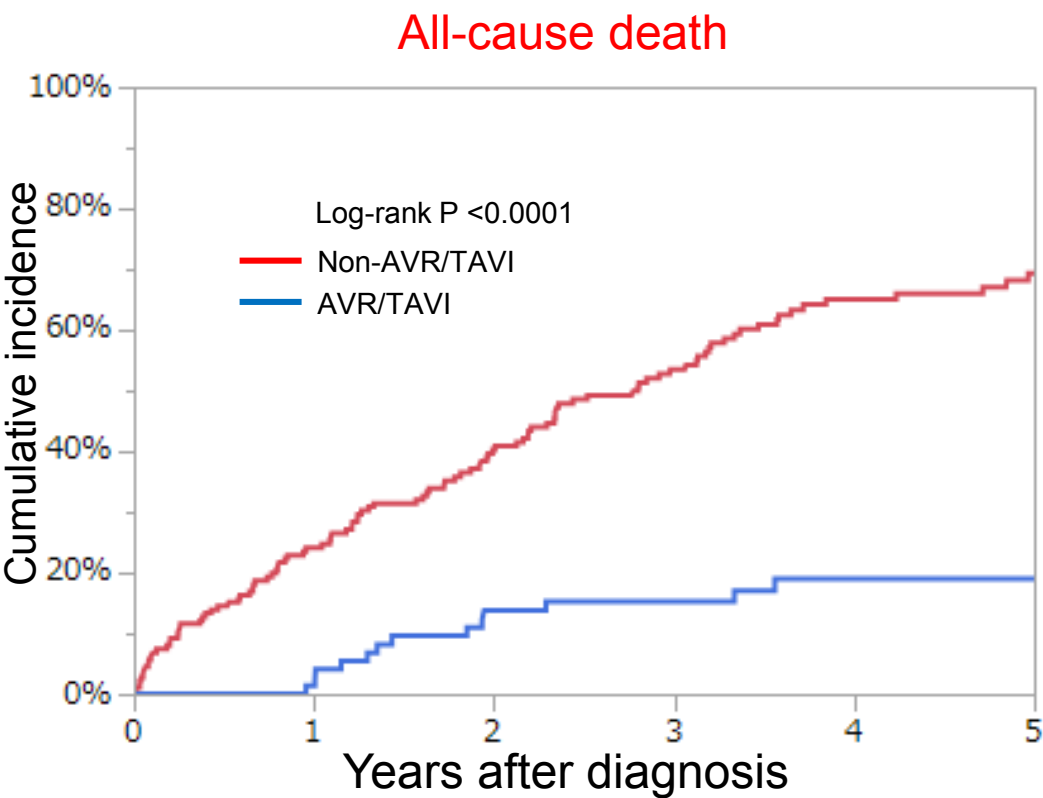
interval	0-day	30-day	1-year	3-year	5-year
Non-AVR/TAVI					
N of patients with at least 1 event		10	50	87	106
N of patients at risk	183	162	126	65	27
Cumulative incidence		5.7%	24.1%	53.5%	69.3%
AVR/TAVI					
N of patients with at least 1 event		0	1	11	13
N of patients at risk	73	73	73	54	25
Cumulative incidence		0.0%	1.4%	15.3%	19.1%

All-cause death
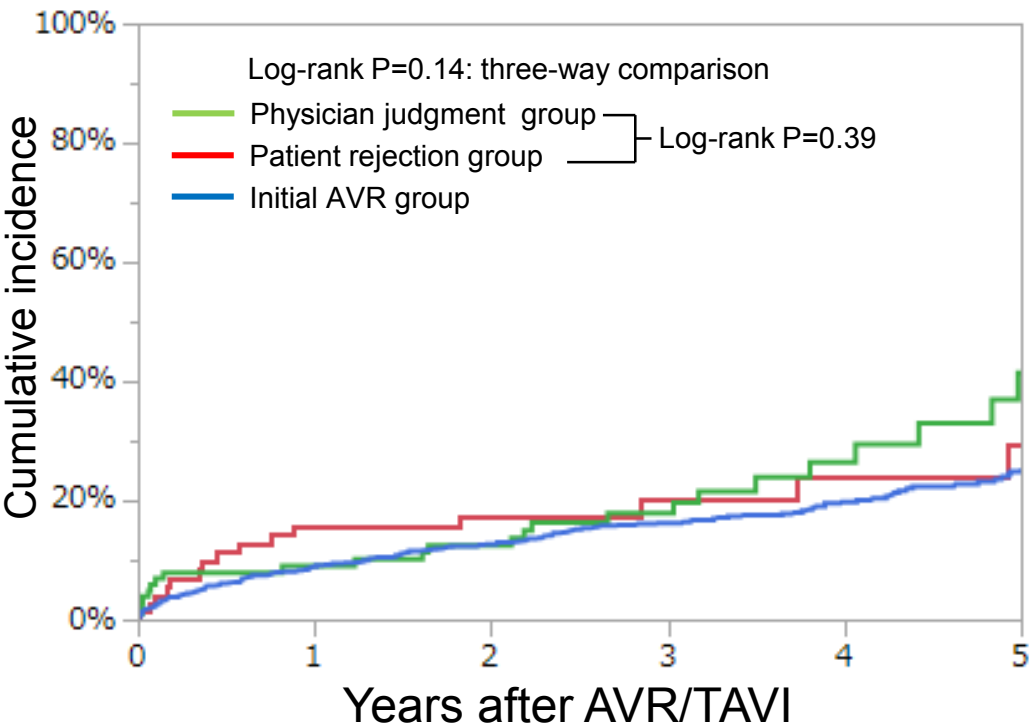
Interval after procedure	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		6	9	16	24
N of patients at risk	104	95	83	49	14
Cumulative incidence		5.9%	9.0%	17.8%	41.4%
Patient rejection group					
N of patients with at least 1 event		2	11	13	15
N of patients at risk	73	71	58	29	14
Cumulative incidence		2.8%	15.7%	20.1%	29.5%
Initial AVR group					
N of patients with at least 1 event		19	77	134	165
N of patients at risk	886	852	762	495	165
Cumulative incidence		2.2%	9.0%	16.2%	25.4%

Supplementary Figure 4

A. Age <75
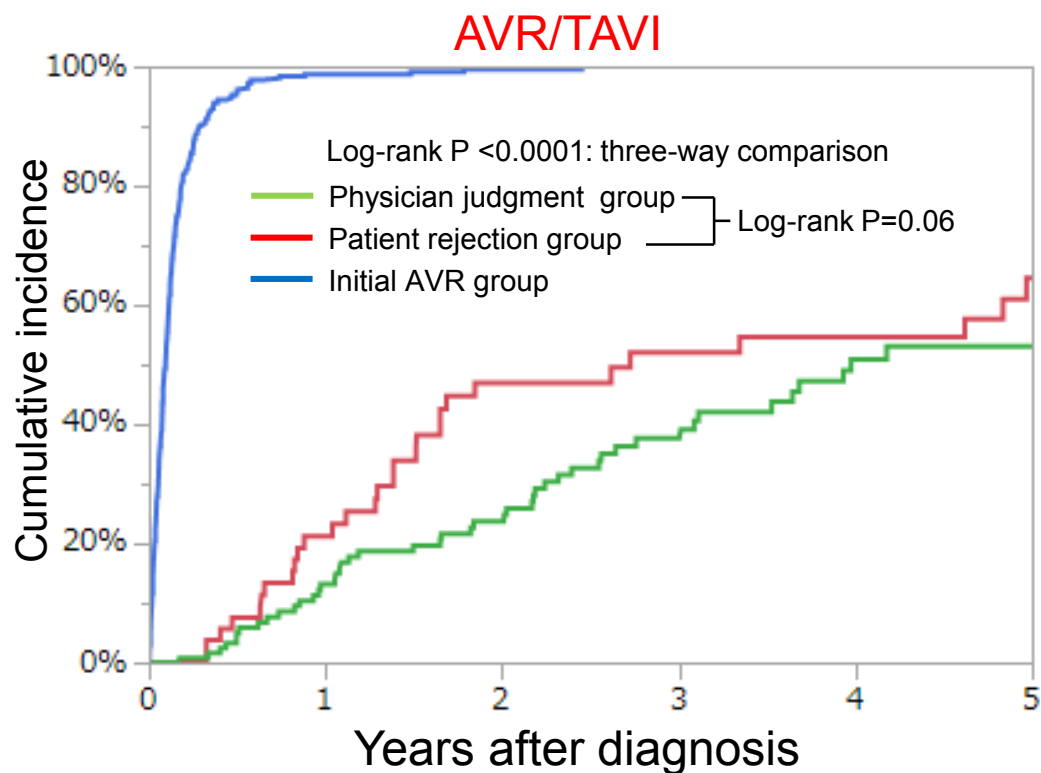
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		0	15	38	47
N of patients at risk	133	128	96	45	15
Cumulative incidence		0.0%	13.1%	37.7%	53.0%
Patient rejection group					
N of patients with at least 1 event		0	11	25	29
N of patients at risk	55	54	40	19	11
Cumulative incidence		0.0%	21.2%	52.0%	64.5%
Initial AVR group					
N of patients with at least 1 event		199	414	417	417
N of patients at risk	427	229	4	0	0
Cumulative incidence		46.9%	98.7%	100.0%	100.0%

Supplementary Figure 4

B. Age >=75
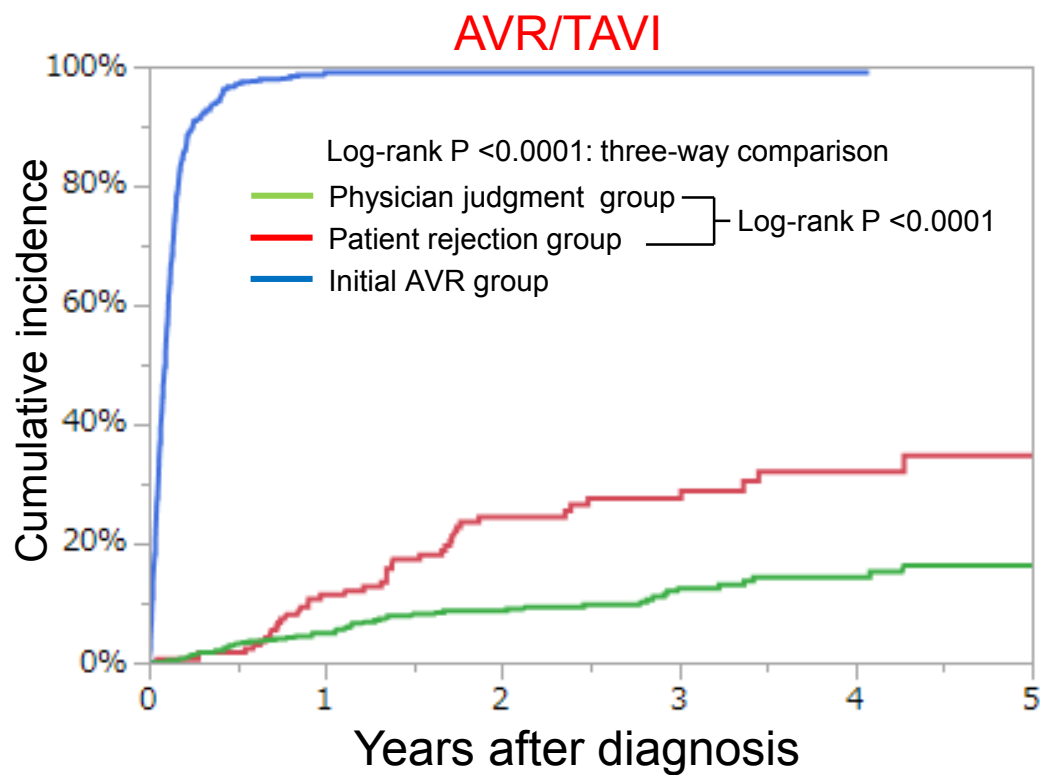
AVR/TAVI

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		0	26	50	55
N of patients at risk	711	640	404	178	40
Cumulative incidence		0.0%	4.9%	12.5%	16.3%
Patient rejection group					
N of patients with at least 1 event		0	18	38	42
N of patients at risk	201	181	131	57	19
Cumulative incidence		0.5%	11.4%	27.6%	34.7%
Initial AVR group					
N of patients with at least 1 event		224	468	469	469
N of patients at risk	478	254	5	4	1
Cumulative incidence		47.0%	99.1%	99.1%	99.1%

A. Age <75

All-cause death
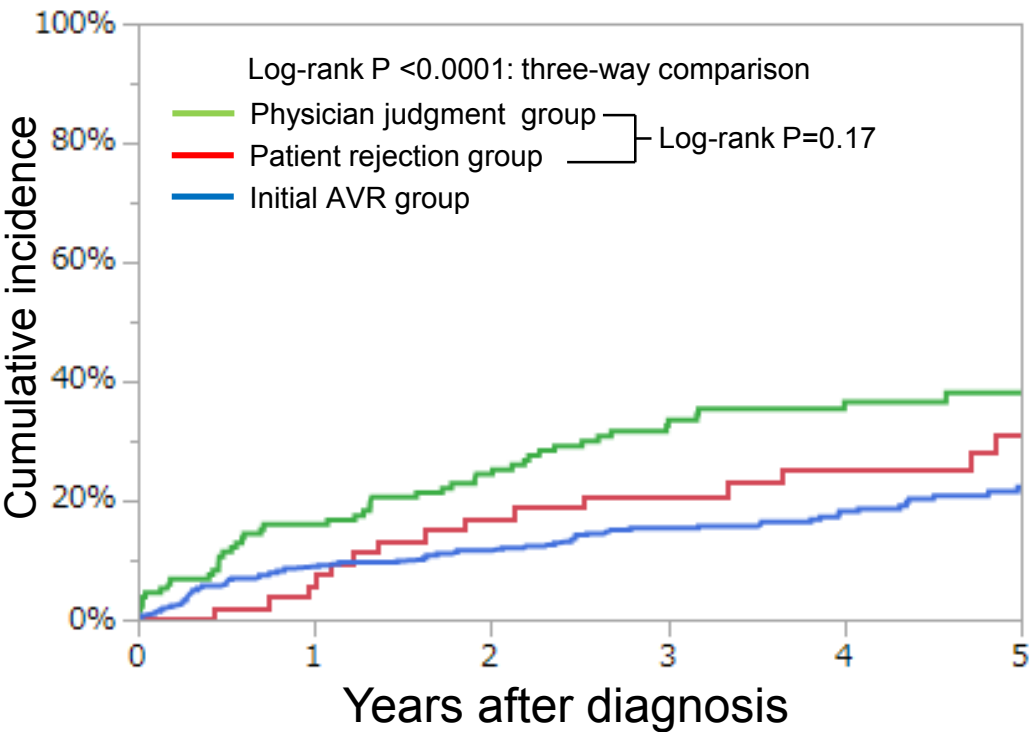
Log-rank P <0.0001: three-way comparison
— Physician judgment group ⌉
— Patient rejection group ⌐ Log-rank P=0.17
— Initial AVR group   ⌋

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		6	21	42	47
N of patients at risk	133	128	111	75	34
Cumulative incidence		4.5%	16.0%	32.6%	38.1%
Patient rejection group					
N of patients with at least 1 event		0	3	11	15
N of patients at risk	55	54	51	38	25
Cumulative incidence		0.0%	7.6%	20.8%	31.0%
Initial AVR group					
N of patients with at least 1 event		4	37	62	76
N of patients at risk	427	423	374	274	111
Cumulative incidence		0.9%	8.9%	15.3%	22.2%

Supplementary Figure 5

B. Age >=75

All-cause death
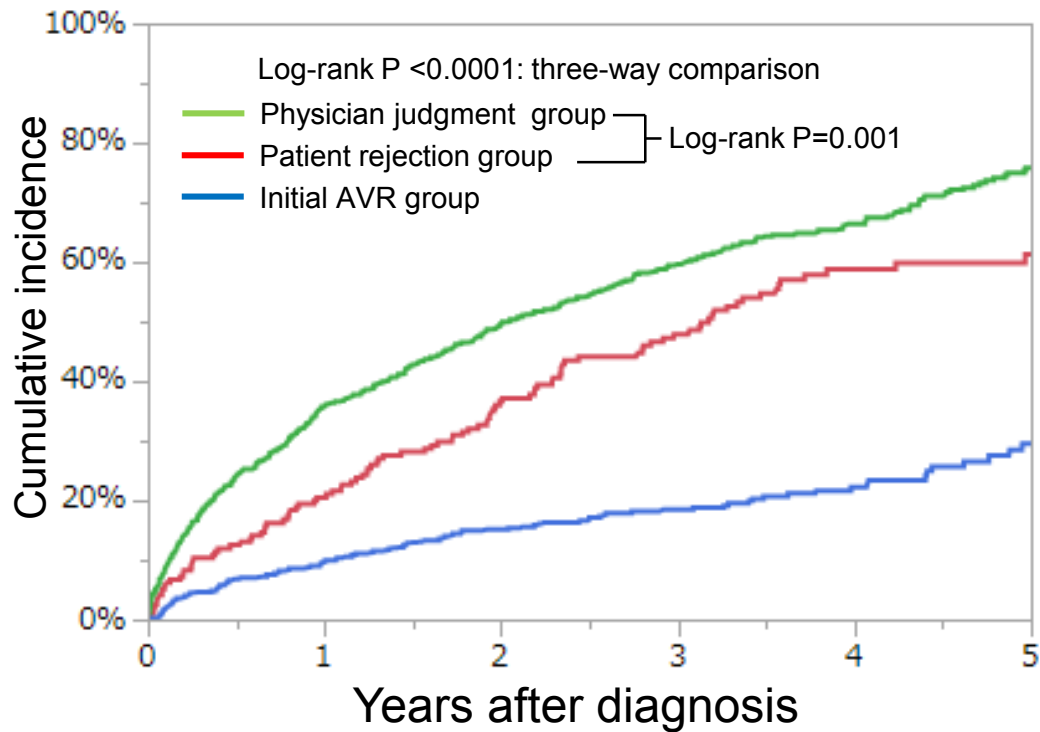
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		52	243	392	451
N of patients at risk	711	640	424	216	54
Cumulative incidence		7.5%	35.8%	59.6%	75.8%
Patient rejection group					
N of patients with at least 1 event		10	39	87	104
N of patients at risk	201	182	148	81	27
Cumulative incidence		5.7%	20.5%	47.9%	61.3%
Initial AVR group					
N of patients with at least 1 event		6	45	82	100
N of patients at risk	478	471	406	258	65
Cumulative incidence		1.3%	9.7%	18.5%	29.6%

Supplementary Figure 6

A. Age <75

Aortic valve related death
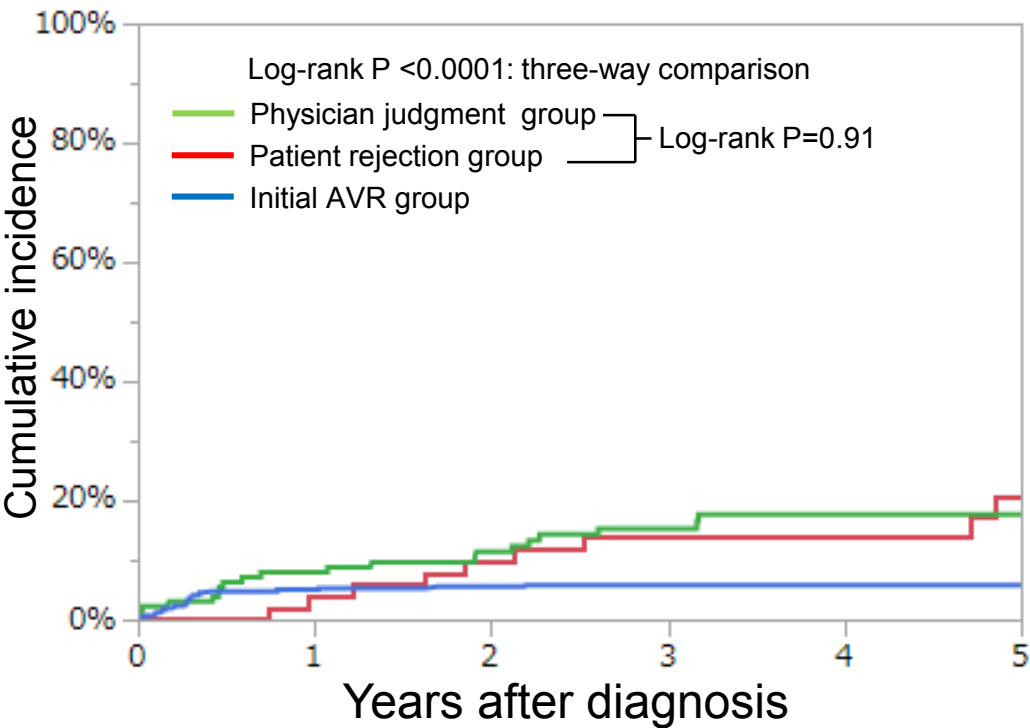
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		3	10	18	20
N of patients at risk	133	128	111	75	34
Cumulative incidence		2.3%	7.9%	15.3%	17.7%
Patient rejection group					
N of patients with at least 1 event		0	2	7	9
N of patients at risk	55	54	51	38	25
Cumulative incidence		0.0%	3.9%	14.0%	20.5%
Initial AVR group					
N of patients with at least 1 event		3	21	24	24
N of patients at risk	427	423	374	274	111
Cumulative incidence		0.7%	5.0%	5.8%	5.8%

B. Age >=75

Aortic valve related death
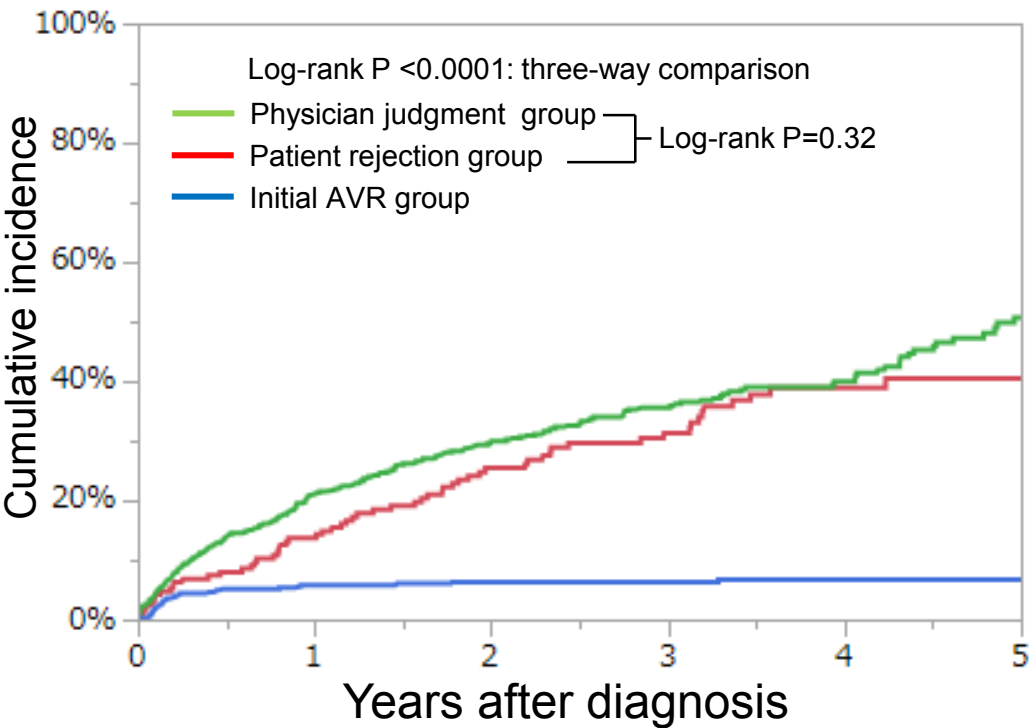
Cumulative incidence vs Years after diagnosis

Log-rank P <0.0001: three-way comparison

— Physician judgment group ⎤
— Patient rejection group ⎬— Log-rank P=0.32
— Initial AVR group   ⎦

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		25	129	197	226
N of patients at risk	711	640	424	216	54
Cumulative incidence		3.6%	21.0%	35.6%	50.7%
Patient rejection group					
N of patients with at least 1 event		6	25	52	61
N of patients at risk	201	182	148	81	27
Cumulative incidence		3.1%	13.7%	31.3%	40.4%
Initial AVR group					
N of patients with at least 1 event		6	27	29	30
N of patients at risk	478	471	406	258	65
Cumulative incidence		1.3%	5.8%	6.3%	6.7%

Supplementary Figure 7

A. Age <75

Non-cardiac death
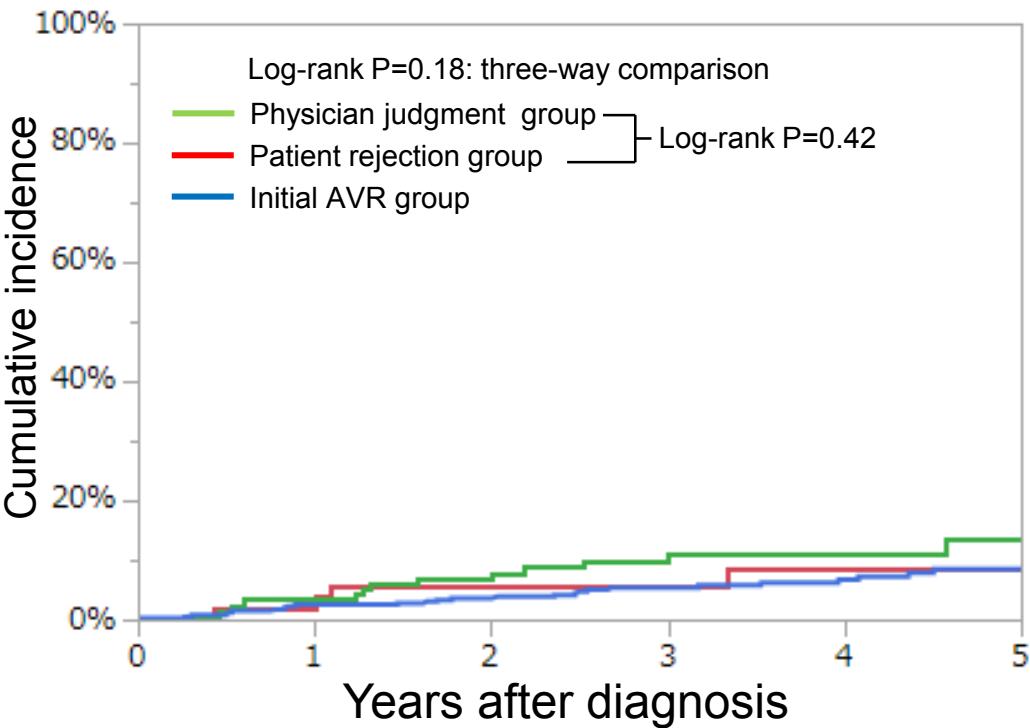
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		0	4	12	13
N of patients at risk	133	128	111	75	34
Cumulative incidence		0.0%	3.4%	11.1%	13.4%
Patient rejection group					
N of patients with at least 1 event		0	1	3	5
N of patients at risk	55	54	51	38	23
Cumulative incidence		0.0%	1.9%	5.8%	8.4%
Initial AVR group					
N of patients with at least 1 event		1	10	20	26
N of patients at risk	427	423	374	274	111
Cumulative incidence		0.2%	2.5%	5.4%	8.5%

Supplementary Figure 7

B. Age >=75

Non-cardiac death
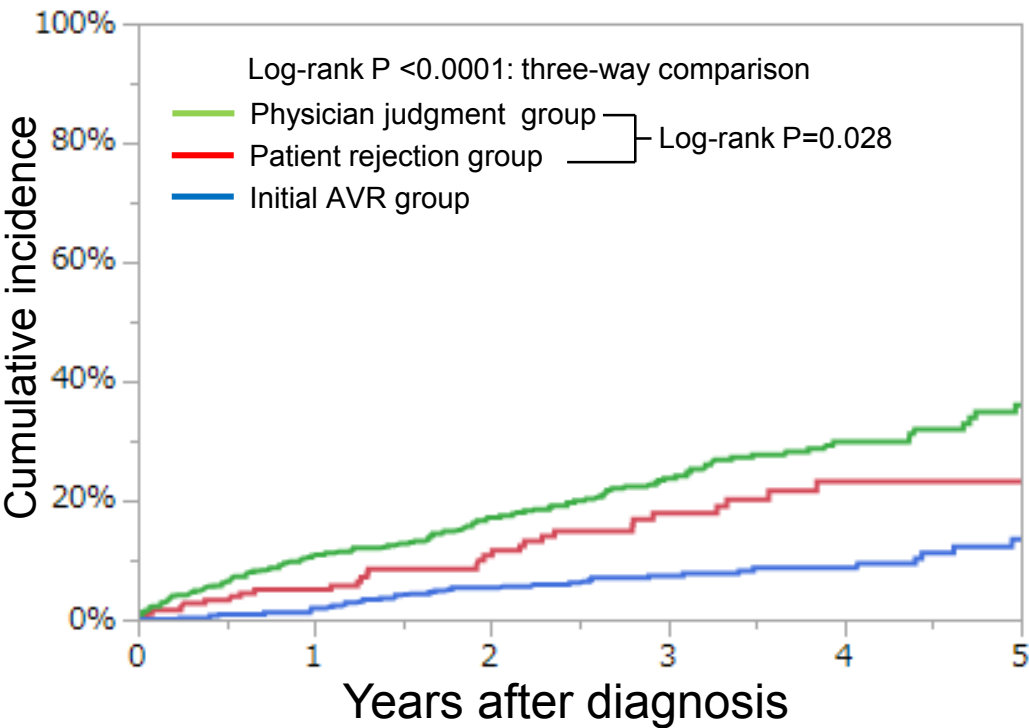
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		15	63	111	132
N of patients at risk	711	640	424	216	54
Cumulative incidence		2.2%	10.9%	23.7%	36.0%
Patient rejection group					
N of patients with at least 1 event		3	9	25	29
N of patients at risk	201	182	148	81	27
Cumulative incidence		1.6%	5.1%	17.8%	23.2%
Initial AVR group					
N of patients with at least 1 event		0	8	29	37
N of patients at risk	478	471	406	258	65
Cumulative incidence		0.0%	1.9%	7.4%	13.5%

A. Age <75

Heart failure hospitalization
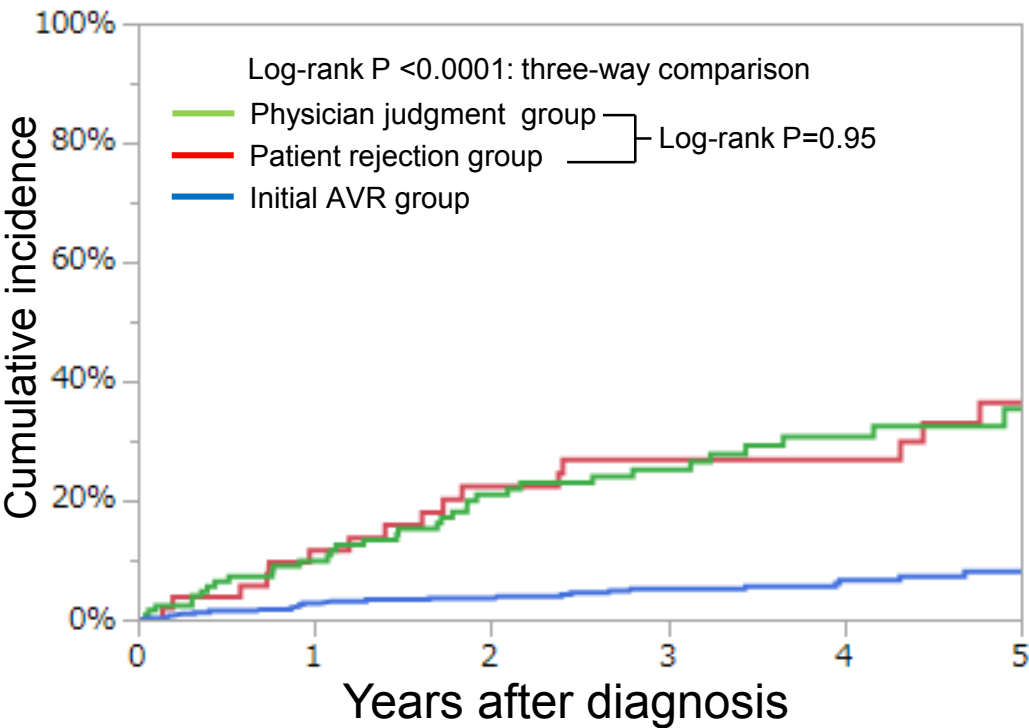
interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		2	12	28	34
N of patients at risk	133	126	104	61	23
Cumulative incidence		1.6%	9.9%	25.2%	35.4%
Patient rejection group					
N of patients with at least 1 event		0	6	13	16
N of patients at risk	55	54	45	29	20
Cumulative incidence		0.0%	11.6%	26.8%	36.4%
Initial AVR group					
N of patients with at least 1 event		1	11	19	24
N of patients at risk	427	422	365	267	104
Cumulative incidence		0.2%	2.8%	5.2%	8.0%

B. Age >=75

Heart failure hospitalization
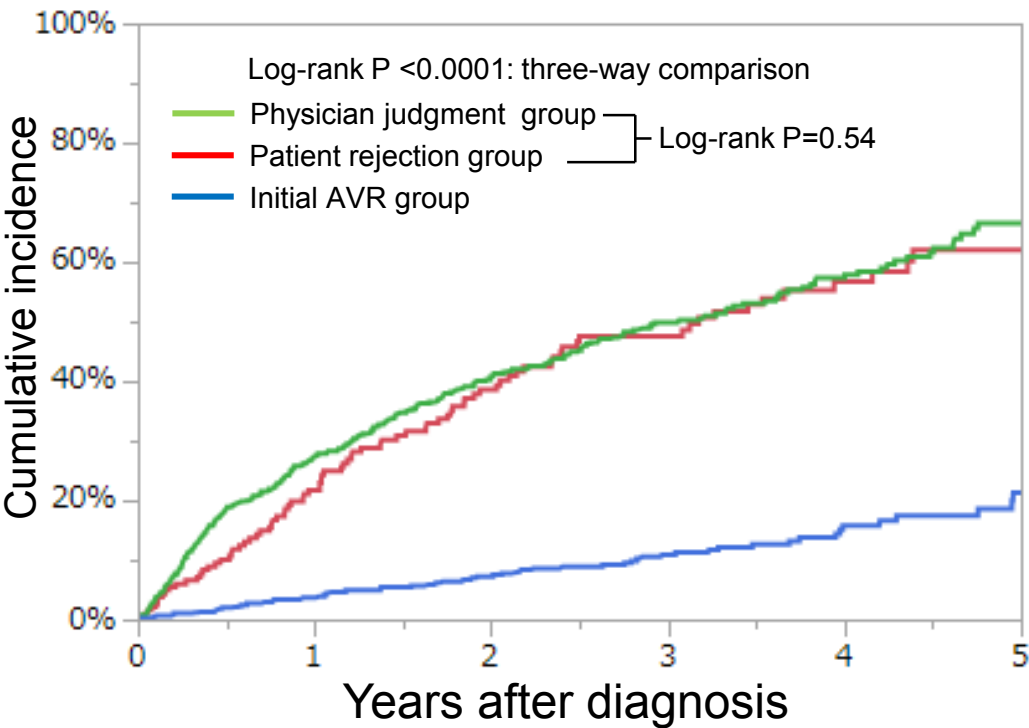
Log-rank P <0.0001: three-way comparison

Physician judgment group ⎤
Patient rejection group ⎥— Log-rank P=0.54
Initial AVR group ⎦

interval	0-day	30-day	1-year	3-year	5-year
Physician judgment group					
N of patients with at least 1 event		19	156	249	279
N of patients at risk	711	621	355	148	32
Cumulative incidence		2.9%	27.4%	49.9%	66.6%
Patient rejection group					
N of patients with at least 1 event		4	37	73	84
N of patients at risk	201	178	124	53	17
Cumulative incidence		2.1%	21.7%	47.6%	62.0%
Initial AVR group					
N of patients with at least 1 event		2	16	42	56
N of patients at risk	478	469	392	240	57
Cumulative incidence		0.4%	3.7%	10.9%	21.3%

<u>**Supplementary Figure Legends**</u>

Supplementary Figure 1. Kaplan-Meier curves showing the timing of AVR/TAVI during follow-up across the 3 study groups. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Supplementary Figure 2. Kaplan-Meier curves for all-cause death in the patient rejection group stratified by AVR/TAVI during follow-up. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Supplementary Figure 3. Kaplan-Meier curves for all-cause death after AVR/TAVI across the 3 study groups. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Supplementary Figure 4. Kaplan-Meier curves for AVR or TAVI according to age (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Supplementary Figure 5. Kaplan-Meier curves for all-cause death according to age (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

Supplementary Figure 6. Kaplan-Meier curves for aortic valve-related death according to age (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

Supplementary Figure 7. Kaplan-Meier curves for non-cardiac death according to age (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

Supplementary Figure 8. Kaplan-Meier curves for heart failure hospitalization according to age (**A**) <75 years, and (**B**) ≥75 years. The cumulative incidence of events was estimated by the Kaplan-Meier method. AVR, aortic valve replacement.

Supplementary Table 1. Logistic regression analyses for predictors of AVR/TAVI

	Patient rejection			Physician judgment			Patient rejection & Physician judgment		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	0.90	0.86-0.95	0.0002	0.90	0.88-0.93	<0.0001	0.90	0.88-0.92	<0.0001
Women	1.41	0.62-3.18	0.41	1.42	0.83-2.43	0.20	1.42	0.92-2.19	0.11
BMI <22	0.50	0.25-0.99	0.048	0.47	0.29-0.77	0.003	0.47	0.32-0.70	0.0002
Peak aortic jet velocity ≥4 m/s	1.48	0.66-3.33	0.34	1.63	0.999-2.67	0.051	1.82	1.23-2.70	0.003
Coronary artery disease	0.78	0.32-1.92	0.59	2.93	1.65-5.19	0.0002	1.80	1.13-2.87	0.01
Creatinine level >0.83 mg/dl	1.04	0.49-2.20	0.91	0.82	0.49-1.36	0.44	0.85	0.57-1.27	0.43
Malignancy current under treatment	1.47	0.09-23.1	0.78	0.13	0.01-1.07	0.06	0.24	0.05-1.13	0.07
Anemia	0.50	0.25-1.03	0.06	0.74	0.44-1.24	0.26	0.60	0.40-0.90	0.01
Ejection fraction <68%	0.55	0.28-1.09	0.09	0.64	0.39-1.07	0.09	0.57	0.39-0.85	0.005
Chronic lung disease	5.62	1.05-30.0	0.04	0.64	0.20-2.03	0.45	1.24	0.56-2.78	0.59
Dyslipidemia	1.84	0.91-3.72	0.09	0.99	0.59-1.65	0.96	1.25	0.83-1.87	0.28
Prior myocardial infarction	0.87	0.19-4.02	0.86	0.44	0.19-0.99	0.047	0.53	0.26-1.09	0.08
Prior symptomatic stroke	0.46	0.13-1.62	0.23	1.14	0.59-2.20	0.69	0.89	0.50-1.56	0.67
Aortic/peripheral vascular disease	0.90	0.15-5.52	0.91	0.60	0.24-1.52	0.28	0.66	0.30-1.47	0.31
Any combined valvular disease	0.63	0.31-1.29	0.21	1.15	0.69-1.90	0.59	0.91	0.61-1.35	0.64
TR pressure gradient ≥40 mmHg	1.47	0.67-3.20	0.34	0.80	0.43-1.47	0.47	1.05	0.67-1.67	0.82

Based on the results of univariate analyses, we used the 16 clinically relevant risk-adjusting variables in the logistic regression models (age, male, body mass index (BMI) <22 kg/m^2, peak aortic jet velocity ≥4 m/s, coronary artery disease, creatinine level >0.83 mg/dl, malignancy current under treatment, anemia, ejection fraction <68%, chronic lung disease, Dyslipidemia, prior myocardial infarction, prior symptomatic stroke, aortic/peripheral vascular disease, any combined valvular disease, and tricuspid regurgitation pressure gradient ≥40 mm Hg).

BMI was calculated as weight in kilograms divided by height in meters squared.

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

AVR=aortic valve replacement; TAVI=transcatheter aortic valve implantation; BMI=Body mass index; TR=tricuspid regurgitation; and OR=odds ratio.

Supplementary Table 2. Effects of AVR/TAVI during the follow-up group on primary endpoint

Time-updated covariate	Adjusted HR	95% CI	P-value
AVR/TAVI during the follow-up	0.27	0.16-0.44	<0.001

Adjusted HR and 95%CI for primary endpoint was estimated by the multivariable Cox proportional hazard model. We incorporated the time-updated covariate as well as the same 21 clinically relevant factors as the main analysis into the multivariable Cox proportional hazard model, and estimated the hazard ratio of AVR/TAVI during the follow-up for the primary endpoint.

HR=hazard ratio; CI=confidence interval; AVR=aortic valve replacement; TAVI=transcatheter aortic valve implantation.