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Severe AS patients with ≥10% decline in LVEF at 1-year follow-up had worse outcome under conservative management, using CURRENT AS registry in Japan.

Structured Abstract

Objective: This study aimed to investigate the prognostic impact of the decline in left ventricular ejection fraction (LVEF) at 1-year follow-up in patients with severe aortic stenosis (AS) managed conservatively.

Background: No previous study has explored the association between LVEF decline during follow-up and clinical outcomes in severe AS.

Methods: Among 3815 patients with severe AS enrolled in the multicenter CURRENT AS registry in Japan, we analyzed conservatively managed 839 patients who underwent echocardiography at 1-year follow-up. The primary outcome measure was a composite of AS-related deaths and hospitalization due to heart failure.

Results: There were 91 patients (10.8%) with >10% decline in LVEF and 748 patients (89.2%) without decline. LV dimensions and the prevalence of valve regurgitation and atrial fibrillation/flutter significantly increased in the decline in LVEF group. The cumulative 3-year incidence of the primary outcome measure was significantly higher in the decline in LVEF group than no decline group (44.8% vs. 28.5%, p<0.001). After adjusting for confounders, the excess risk of decline in LVEF to no decline for the primary outcome measure remained significant (hazard ratio: 1.67, 95% confidence interval: 1.10-2.53). When stratified by the LVEF at the index echocardiography (70%≤, 60 to 69%, and <60%), the risk of decline in LVEF on the primary outcome was consistently seen in all the subgroups without any interaction (P=0.77).

Conclusions: Severe AS patients with a >10% LVEF decline at 1-year after diagnosis had worse AS-related clinical outcome than those without decline in LVEF under conservative management.

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Condensed abstract

Assessing the serial changes in left ventricular ejection fraction (LVEF) might be an important aspect in the management for aortic stenosis (AS). No previous study has explored the association between LVEF during follow-up and clinical outcomes in severe AS. We revealed that patients with decline of more than 10% in LVEF at 1-year after diagnosis of severe AS had worse clinical outcome under conservative management than those without decline in LVEF, using a multicenter observational database of severe AS patients in Japan. Monitoring a decline in LVEF would be clinically useful in patients with severe AS under conservative management.

Abbreviations list

AS=aortic stenosis
AVA=aortic valve area
AVR=aortic valve replacement
CI=confidence intervals
HF =heart failure
HR=hazard ratios
LV=left ventricular
LVEF=left ventricular ejection fraction
STS= society of thoracic surgeons
TAVI=transcatheter aortic valve implantation
Vmax=peak aortic jet velocity

Introduction

Left ventricular (LV) dysfunction in aortic stenosis (AS) could be the consequence of maladaptation when wall stress exceeds the compensatory mechanism. The presence of LV dysfunction, classically defined as left ventricular ejection fraction (LVEF) <50% is a current class 1 indication for aortic valve replacement in patients with severe AS(1,2), and more recently, less severe LV dysfunction with LVEF 50-59 % has also been reported to be associated with a poor prognosis(3-6). However, assessing the serial changes in LVEF might be another important aspect in the management for AS. Previous studies that evaluated serial changes in LV function in AS patients were limited to those after surgical aortic valve replacement (SAVR)(7,8) or transcatheter aortic valve implantation (TAVI)(9). In patient with mild to moderate AS, serial measurements of LV function showed annual decline in LVEF in the patients with low ejection fraction (LVEF<50%) before the established diagnosis of severe AS(4). There is no previous study exploring the association between decline in LVEF during follow-up and subsequent clinical outcomes in patients with established severe AS. In the present study, we investigated the prognostic implication of the decline in LVEF during follow-up using a large Japanese multicenter observational database of consecutive patients with severe AS(10).

Methods

Study patients

CURRENT AS (Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis) registry is a retrospective multicenter registry that enrolled 3815 consecutive patients with severe AS from 27 centers in Japan between January 2003 and December 2011. The design, patient enrollment, and main result of the registry were previously reported in detail(10). In brief, we searched the hospital database for transthoracic echocardiography and enrolled consecutive patients who had met the criteria for severe AS (peak aortic jet velocity [Vmax] >4.0 m/s, mean aortic pressure gradient >40 mm Hg, or aortic valve area [AVA] <1.0 cm^2)(11) for the first time during the study period. Follow-up data were mainly collected via review of hospital charts; otherwise, data were collected via contact with patients, relatives, and/or referring physicians via mail with questions regarding vital status, symptoms, and subsequent hospitalizations. Based on the initial treatment strategies after the index echocardiography, the entire cohort was divided into the conservative management cohort (N=2618) and the initial aortic valve replacement (AVR) cohort (N=1197). In the present analysis, we explored the relation between the echocardiographic findings at follow-up and subsequent clinical outcomes in 2618 patients under the conservative management. We excluded those patients from the main analysis who did not undergo follow-up echocardiography (N=801) and patients who underwent follow-up echocardiography outside the 1-year time frame (N=708) (Figure 1). Among 1109 patients with follow-up echocardiography, the current study population consisted of 839 patients with

available LVEF data by follow-up echocardiography at 1-year without interim SAVR, TAVI, or heart failure (HF) hospitalization (Figure 1). The 1-year time frame for follow-up echocardiography was defined with the allowance period of 6 months (6- to 18-month after the index echocardiography).

The institutional review board of each participating center approved the study protocol. Written informed consent was waived due to the retrospective nature of the study. Patient records were anonymized prior to analysis.

Echocardiography and definitions of decline in LVEF

All patients underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation in each participating center according to the guidelines(12). Echocardiographic data were site-reported without echocardiographic core laboratory. Biplane Simpson's method of disks or the Teichholz method was used for calculating LVEF. Peak and mean aortic pressure gradient were determined using the simplified Bernoulli equation, and AVA was calculated using the standard continuity equation(13). We defined the decline in LVEF as an absolute decrease of LVEF >10%, based on the previous reports on inter-observer variability(14-16), serial changes of LVEF in dilated cardiomyopathy(17,18), and the decline in LVEF by cancer chemotherapy(19-21). The changes (delta) in LVEF were calculated according to the following equation: (the value at follow-up) – (the value at baseline).

Outcomes

The primary outcome measure for the present analysis was AS-related events defined as a composite of AS-related death and HF hospitalization after follow-up echocardiography. AS-related death included aortic valve procedure-related death, sudden death, death caused by HF potentially related to the aortic valve, and death due to aortic valve endocarditis(10,22). HF hospitalization was defined as hospitalization due to worsening HF requiring intravenous drug therapy. The causes of death were classified according to the Valve Academic Research Consortium definitions, and were adjudicated by a clinical event committee(23).

Statistical analysis

The categorical variables were expressed as numbers and percentages and were compared using a chi-square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Based on their distribution, continuous variables between the 2 groups were compared using a Student's t-test or Wilcoxon rank sum test. When we compared the clinical and echocardiographic data at baseline and at follow-up, we used paired Student's t-tests for continuous variables, sign tests for between the 2 variables and Wilcoxon signed rank test for the 3 ordinal variables for LVEF.

The cumulative incidences of the clinical events during 3 years after the follow-up

echocardiography were estimated using the Kaplan-Meier method with the between-groups difference assessed by the log-rank test. To estimate the risk of the decline in LVEF group relative to the non-decline in LVEF group, a multivariable Cox proportional hazards model was developed for the outcome measures with the results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We selected 22 clinically relevant risk-adjusting variables (Table 1 and 2) with the center incorporated as the stratification variable, which was basically consistent with our previous study, except for the addition of symptom and LVEF classification at baseline into 3 groups (LVEF<60%, 60-69%, ≥70%) as the risk-adjusting variables (10). In the subgroup analysis, we evaluated the interaction between those subgroup factors such as Vmax, symptoms, and LVEF at baseline and the effect of decline relative to no decline in LVEF for the primary outcome measure. Given the small number of patients with an event in the subgroup analysis and additional analyses, we adopted the parsimonious model incorporating 6 risk-adjusting variables for the subgroup analyses based on Vmax, symptoms, or LVEF at baseline as presented in Table 1 and 2, or Supplementary Table 1 for additional analyses. All statistical analyses were conducted by 2 physicians (E.M. and T.K.) and a statistician (T.M.) using JMP 14 or SAS 9.4 (SAS Institute Inc., Cary, North Carolina). All the reported P values were two-tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

There were 91 patients (10.8%) with >10% decline in LVEF and 748 patients (89.2%) without decline in LVEF at 1-year follow-up (Figure 1). The baseline patient characteristics were generally similar between the decline and no-decline groups except for the higher prevalence of men, current smoking, and anemia in the decline in LVEF group (Table 1).

Echocardiographic parameters

At baseline, LVEF and LV wall thickness were significantly greater and AVA was significantly smaller in the decline in LVEF group than in the no decline in LVEF, while Vmax was not significantly different between the 2 groups (Table 2, and Figure 2). During follow-up, AVA significantly decreased in both groups, while Vmax and LV mass index significantly increased in the no decline in LVEF group but not in decline in LVEF group (Table 2). From baseline to follow-up in the decline in LVEF group, LV systolic/diastolic dimensions and the prevalence of moderate or severe mitral regurgitation, aortic regurgitation, and atrial fibrillation/flutter significantly increased along with a decline in LVEF, while these changes were not observed in the no decline in LVEF group (Table 2, and Figure 2).

The patients in the decline in LVEF group had a higher prevalence of men, however,

there were no sex-specific differences for changes in LVEF, Vmax, or LV mass index over time (Supplementary Table 2).

Clinical outcomes

The median follow-up duration after the follow-up echocardiography was 875 (interquartile range: 526-1260) days, with an 83.2% follow-up rate at 2-year. The cumulative incidence of AVR/TAVI trended to be higher in the decline in LVEF group than in the no decline in LVEF group within 1 year after the follow-up echocardiography, while it was not different at 3-year between the 2 groups (Figure 3). The cumulative 3-year incidence of the primary outcome measure was significantly higher in the decline in LVEF group than in no decline in LVEF group (39.5% vs. 26.8%, P<0.001) (Figure 4A). After adjusting for confounders, the excess risk of the decline in LVEF relative to no decline in LVEF for the primary outcome measure remained significant (HR: 1.98, 95%CI: 1.29-3.06) (Table 3). The cumulative 3-year incidences of all-cause death, AS-related death, and HF hospitalization were also significantly higher in the decline in LVEF group than no decline in LVEF group (Central illustration, Figure 4B, and 4C). After adjusting for confounders, the excess risk for all-cause death, and AS-related death remained significant, while it was no longer significant for HF hospitalization.

In the decline in LVEF group, 38 out of 91 patients (42%) developed AS-related events after follow-up echocardiography. Within the decline in LVEF group, there was no

significant difference in the baseline and follow-up LVEF, nor the delta LVEF, between patients with and without AS-related events (Figure 5A). In the no decline in LVEF group, 26% of patients (191 out of 748) developed at least one event after follow-up echocardiography. In contrast to the findings in the decline in LVEF group, in the no decline in LVEF group, the ejection fraction was significantly lower both at baseline and at 1-year, among patients with an AS-related event (Figure 5B). There was no significant difference in the delta LVEF between patients with and without AS-related event in the no decline in LVEF group.

Subgroup analysis

When stratified by Vmax, symptoms, and LVEF at baseline, there were no significant interactions between the subgroup factors and the effect of decline in LVEF relative to no decline in LVEF for the primary outcome measure (Table 4).

Analysis of patients who remained asymptomatic at the time of 1-year follow-up echocardiography

In this main study population (N=839), out of 594 asymptomatic patients, 555 patients remained asymptomatic at the time of the 1-year follow-up echocardiography. There were 61 patients with >10% decline in LVEF and 494 patients without decline in LVEF at 1-year follow-up (Supplementary Table 1). The proportion of patients who remained asymptomatic at the time of the 1-year follow-up did not differ between the decline in LVEF

and no-decline in LVEF groups (88 % and 94 %, respectively, P=0.11). The outcome was fully consistent with the main analysis (Supplementary Figure 1 and Supplementary Table 3).

Additional analysis of patients not included in the main analysis

Among 1509 patients excluded from the main analysis, 241 patients underwent follow-up echocardiography within 5 months, 467 patients after 18 months, and 801 patients had no follow-up echocardiography (Supplementary Figure 2). Compared to those patients included in the main analysis, those 241 patients who had echocardiography within 5 months were older, more likely to be symptomatic, and had higher STS (society of thoracic surgeons) score, lower LVEF, lower AVA, and higher prevalence of any combined valvular disease, while those 467 patients who had echocardiography after 18 months showed no remarkable differences in the baseline characteristics and echocardiographic data (Supplementary Table 4). Out of 467 patients, 120 patients were excluded from the outcome analysis, because of interim SAVR, TAVI, or HF hospitalization. The cumulative 3-year incidence of the primary outcome measure from the follow-up echocardiography was significantly higher in the decline in LVEF group (N=51) than in the no decline group (N=296) (39.2% vs. 29.1%, P=0.03) (Supplementary Table 5 and Supplementary Figure 3). Among 801 patients without follow-up echocardiography, 497 deaths were observed (Supplementary Table 6). Among them, 212 patients (42.7%) died within 5 months (cardiovascular death: N=149; non-cardiovascular death; N=63), 132 patients (26.6%) died in the 1-year time frame

(cardiovascular death: N=71; non-cardiovascular death: N=61), and 153 patients died (30.8%) after 18 months (cardiovascular death: N=94; non-cardiovascular death: N=59).

Discussion

The main finding of this study is that patients with a decrease in LVEF at 1-year after diagnosis of severe AS had significantly higher risk for AS-related serious adverse events than those without decrease in LVEF, regardless of the baseline LVEF.

There were only a few studies reporting the decline of LVEF in patients with AS under the conservative management strategy(4,24,25). In the PARTNER trial, serial measurements of LVEF in this population showed no changes of mean LVEF during 1-year follow-up sessions, without reporting the prognostic impact of decline of LVEF(26). Although we did not collect the echocardiographic data before the index echocardiography, Ito et al. reported that in patients with LVEF of ≤50% at the diagnosis of severe AS, their LVEF had been gradually declined from the time of moderate AS(4). In addition, LVEF below 50% at the diagnosis of severe AS showed worse outcomes independently of AVR or conservative treatment(4). In a randomized study evaluating the effect of eplerenone in 65 symptomatic patients with moderate-severe AS, LVEF did not change in patients with placebo treatment with 19 months follow-up(27). Another trial involving patients with mild-to-moderate asymptomatic AS, male sex independently predicted larger reduction in LVEF during progression of AS, not consistently with our result (28). These studies evaluated the

patients with moderate AS and the progression of AS. The present study, being a large multi-center observational study, is the first to report the worse effect of the decline in LVEF on the prognosis of patients with severe AS under conservative management. In the decline in LVEF group, there were no differences in baseline, follow-up, and the delta of LVEF between patients with and without events. Moreover, there were no interactions between the LVEF classifications or the presence of symptom at baseline and the deleterious effect of the decline in LVEF. The present study suggested the clinical usefulness of monitoring a decline in LVEF. In addition, even in patients who remained asymptomatic at the time of the 1-year follow-up echocardiography, the LVEF >10% decline was a factor associated with AS-related event or all-cause death. It would suggest that a decline in LVEF of ≥10% during follow-up should potentially be a trigger to referral for valve replacement in an asymptomatic severe AS patient managed conservatively.

Progressive contractile dysfunction may represent a fundamental component of the pathogenesis of HF in severe AS, because the increasing afterload due the stenotic valve leads to the dysfunction of LV with an excessive myocardial hypertrophy(24) and progression of fibrosis(25,29), leading to poor prognosis(1-3). The present study nicely illustrated the relation between the ventricular remodeling in a time frame of the disease progression and subsequent outcomes in severe AS patients. The transition of adaptive hypertrophy to maladaptive response was clearly showed by the fact that the no decline group showed less

thickened ventricular wall than the decline group at baseline, and an increase in Vmax, LVEF, and LV mass index at follow-up. These observations were theoretically consistent with adaptive hypertrophy(30). However, the decline group did not show an increase of wall thickness despite of a smaller area of aortic valve at follow-up echocardiography, while the prevalence of mitral regurgitation, aortic regurgitation and atrial fibrillation /flatter increased at follow-up. These longitudinal changes of echocardiographic parameters in the decline group showed the progressive ventricular damage associated with severe AS(31). Our observations were consistent with progression of staging classification recently suggested(31). In the present study, we chose the follow-up duration of 1 year from baseline echocardiography, because the patient risk should be re-assessed at 1-year at the latest during watchful waiting after initial risk assessment. Further study is needed to clarify how to and when to capture the transition from adaptive ventricular response to maladaptive process in each patient with severe AS in a more sensitive manner(29,32,33).

Limitations

First, the main limitation of the present study is that only 839 of 3815 (22%) patients identified with severe AS were included in the current analysis. This truly affects the generalizability of the findings. The present study was retrospectively performed without pre-specified echocardiographic follow-up protocol. Thus, data regarding the follow-up

echocardiography was obtained only in patients who were followed regularly in each participating center. Therefore, the follow-up data during one year was not available in all patients in the registry. However, the trend was fully consistent when we analyzed the patients (N=347) with a follow-up echocardiography after 18 months (beyond the time frame of 1-year follow-up echocardiography). Second, we did not collect detailed clinical information including the changes of symptoms at the follow-up echocardiography. Thus, we could not investigate the link between the development or worsening of symptoms and the decline in LVEF. Third, the baseline LVEF was higher in the decline in LVEF group than in the no decline in LVEF group. In patients with low LVEF, absolute values of decline may be small, even if they actually had decline in LVEF. We cannot deny the possibility that those patients might have been included in the no decline in LVEF group despite the presence of substantial worsening of LVEF, which could have diluted the difference in outcomes between the 2 groups. However, the decline in LVEF group showed worse prognosis than the no decline in LVEF group in the present study, despite higher baseline LVEF in the decline in LVEF group. Fourth, we developed multivariable Cox proportional hazard models using baseline characteristics noted at enrollment. As the survival analysis started at the time of follow-up echocardiography, the data at follow-up echocardiography might be more appropriate for evaluation. Fifth, echocardiographic measurement was not performed in a core laboratory, but in each participating center. Finally, information about the cardiac output

and stress echocardiography was not obtained in this study.

Conclusions

Patients with decline of more than 10% in LVEF at 1-year after diagnosis of severe AS had worse clinical outcome under conservative management than those without decline in LVEF. Monitoring a decline in LVEF would be clinically useful in patients with severe AS under conservative management.

Clinical Perspectives

What is next? (what is needed to improve our knowledge base).

Monitoring a decline in LVEF at the 1-year follow-up would be clinically useful in patients with severe AS under conservative management. Further study is needed to clarify how to and when to capture the transition from adaptive ventricular response to maladaptive process in each patient with severe AS in a more sensitive manner.

What is new? (What did this study add;)

In the present study, we investigated the prognostic implication of the decline in LVEF during follow-up using a large multicenter observational database of consecutive patients with severe AS in Japan. We showed that the patients with a >10% decline of LVEF at the 1-year follow-up echocardiography had a worse prognosis compared with those without decline in LVEF, regardless of the baseline LVEF. The present study nicely illustrated the relation between the ventricular remodeling in a time frame of the disease progression and subsequent outcomes in severe AS patients.

What is known? (what is the background that generates the question that is being addressed); In patient with mild to moderate AS, serial measurements of LV function showed annual decline in LVEF in the patients with low ejection fraction (LVEF<50%)

before the established diagnosis of severe AS. There is no previous study exploring the association between decline in LVEF during follow-up and subsequent clinical outcomes in patients with established severe AS.

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Figure legends

Figure 1. Study patient flow.

The 1-year time frame was defined with the allowance period of 6 months (6- to 18-month after the index echocardiography).

CURRENT AS=Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis, Vmax=peak aortic jet velocity, PG=pressure gradient, AVA=aortic valve area, AVR=aortic valve replacement, TAVI=transcatheter aortic valve implantation, and LVEF=left ventricular ejection fraction.

Figure 2. Changes in echocardiographic parameters other than LVEF

(A) Vmax, (B) AVA, (C) LVDd, and (D) LVMI comparing between the 2 groups with and without decline in LVEF.

The error bars represent standard deviation.

LVDd=left ventricular end-diastolic dimension, and LVMI=left ventricular mass index.

Figure 3. Cumulative incidences of AVR or TAVI represent Kaplan-Meier estimates at 1, 2, and 3 years after follow-up echocardiography.

Figure 4. Cumulative incidences of primary and secondary outcome measure represent Kaplan-Meier estimates at 1, 2, and 3 years after follow-up echocardiography. (A) Primary outcome measure that was a composite of AS-related death or HF hospitalization (B) AS-related death, and (B) HF hospitalization. AS=aortic stenosis, and HF=heart failure.

Central illustration. Cumulative incidences of all-cause death represent Kaplan-Meier estimates at 1, 2, and 3 years after follow-up echocardiography. The decline in LVEF was defined as an absolute decrease of LVEF >10%.

Figure 5. Changes in LVEF at 1-year

(A) Decline in LVEF group, and (B) No decline in LVEF group

AS-related event was defined as a composite of AS-related death or HF hospitalization

1 **Table 1. Baseline patient characteristics: With or without decline in LVEF**

	Decline in LVEF group ¶ (N=91)	No decline in LVEF group (N=748)	P value
Age, years *#	78.1±7.0	76.9±9.5	0.24
Men*	42 (46)	261 (35)	0.03
BMI<22* ‖	53 (58)	444 (59)	0.84
Hypertension*	59 (65)	552 (74)	0.07
Current smoking*	11 (12)	30 (4)	0.002
Dyslipidemia	32 (35)	305 (41)	0.30
On statin therapy	23 (25)	217 (29)	0.46
Diabetes mellitus	27 (30)	185 (25)	0.31
On insulin therapy*	6 (7)	33 (4)	0.35
Prior myocardial infarction*	11 (12)	77 (10)	0.60
Coronary artery disease*	33 (36)	219 (29)	0.17
Prior PCI	21 (23)	126 (17)	0.14
Prior CABG	5 (5)	50 (7)	0.67
Prior open heart surgery	12 (13)	92 (12)	0.81

Prior stroke*	20 (22)	111 (15)	0.08
History of Atrial fibrillation or flutter*#	28 (31)	163 (22)	0.054
Aortic/peripheral vascular disease*	9 (10)	60 (8)	0.54
Serum creatinine, mg/dl	0.9 (0.73-1.21)	0.87 (0.7-1.2)	0.57
Serum creatinine>0.83mg/dl *‡	50 (55)	334 (45)	0.06
Hemodialysis*	11 (12)	70 (9)	0.41
Hemoglobin	11.5 (10.3-12.9)	12 (10.6-13.2)	0.29
Anemia *§	54 (59)	329 (44)	0.006
Liver cirrhosis (Child B or C) *	0	3 (0.4)	1.00
Chronic lung disease (moderate or severe) *	5 (5)	23 (3)	0.22
Malignancy under treatment*#	2 (2)	37 (5)	0.42
Chest wall irradiation	1 (1)	8 (1)	1.00
Logistic EuroSCORE	9.2 (6.2-15.2)	8.5 (5.5-15.2)	0.45
EuroSCORE	2.7 (1.9-4.3)	2.7 (1.6-4.3)	0.99

STS score	3.9 (2.2-5.5)	3.6 (2.3-5.7)	0.38
Symptoms *#	22 (24)	223 (30)	0.26
Heart failure	20 (20)	179 (24)	
Syncope	2 (2)	15 (2)	
Chest pain	8 (9)	50 (7)	
HF hospitalization at index UCG	7 (8)	71 (9)	0.58

Baseline patient characteristics indicated those at time of the index echocardiography.

Values are number (%), mean ± standard deviation, or median with interquartile range.

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

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

Risk-adjusting variables selected for the parsimonious Cox proportional hazard models.

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

‡ Serum creatinine was divided by the mean value.

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

¶ Decline in LVEF was defined as >10% absolute decrease in LVEF at 1-year follow-up echocardiography.

LVEF=left ventricular ejection fraction, BMI=body mass index, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, STS=society of thoracic surgeons, and HF=heart failure.

Table 2. Echocardiographic parameters at baseline and follow-up in the decline and no decline in LVEF groups

	Decline in LVEF group (N=91)				No decline in LVEF group (N=748)				Comparison between the 2 groups		
	Baseline	Follow-up	Delta	P value (Paired)	Baseline	Follow-up	Delta	P value (Paired)	P value (Baseline)	P value (Follow-up)	P value (Delta)
Atrial fibrillation or flutter	17 (19)	23 (25)		0.01	120 (16)	123 (16)		0.63	0.52	0.04	
Vmax (m/s)	3.9±0.8	4.0±0.9	0.1±0.5	0.12	3.8±0.8	3.9±0.8	0.17±0.5	<0.001	0.08	0.51	0.21
Vmax ≥4 m/s *#	42 (46)	45 (49)		0.53	308 (41)	343 (46)		0.001	0.36	0.57	
Peak aortic PG (mmHg)	64.6±28.0	67.2±29.5	3.1±18.1	0.11	59.7±24.7	64.9±27.5	5.2±16.0	<0.001	0.08	0.47	0.25
Mean aortic PG (mmHg)	35.3±15.5	38.8±17.3	3.5±9.2	0.003	34.0±15.3	36.8±17.0	2.8±9.3	<0.001	0.49	0.34	0.60
Aortic valve area (cm^2)	0.74±0.17	0.70±0.22	-0.04±0.17	0.03	0.79±0.16	0.78±0.20	-0.02±0.16	0.005	0.009	0.001	0.17
LV diastolic dimension (mm)	45.0±6.5	46.4±7.7	1.3±5.3	0.02	45.5±6.5	45.3±6.4	-0.2±4.1	0.16	0.54	0.13	0.001
LV systolic dimension (mm)	28.0±7.1	33.5±8.4	5.5±4.5	<0.001	29.5±7.1	28.9±6.9	-0.6±4.0	<0.001	0.06	<0.001	<0.001

LVEF (%)	69.1±11.7	52.9±13.8	-16.3±6.8	<0.001	64.2±11.7	65.9±10.9	1.7±7.1	<0.001	<0.001	<0.001	<0.001
LVEF <60% *#	16 (18)	55 (60)			182 (24)	154 (21)					
LVEF 60~69% *#	26 (29)	30 (33)		<0.001	332 (44)	313 (42)		<0.001	<0.001	<0.001	
LVEF ≥70% *#	49 (54)	6 (7)			234 (31)	281 (38)					
LVMI (g/m^2)	130±34	135±36	5.0±26.8	0.06	118±37	119±35	1.7±23.2	0.10	0.006	<0.001	0.28
IVST (mm)	11.8±2.2	11.7±2.2	-0.03±1.79	0.87	10.8±2.1	10.9±2.1	0.14±1.44	0.008	<0.001	<0.001	0.30
Any combined valvular disease *#	36 (40)	46 (51)		0.01	270 (36)	275 (40)		0.03	0.52	0.008	
Moderate or severe AR	14 (15)	21 (23)		0.02	136 (18)	136 (20)		0.36	0.51	0.43	
Moderate or severe MS	2 (2)	2 (2)		1.00	22 (3)	28 (4)		0.03	0.69	0.39	
Moderate or severe MR	12 (13)	23 (25)		<0.001	103 (14)	113 (16)		0.15	0.88	0.03	
Moderate or severe TR	20 (22)	21 (24)		0.76	110 (15)	117 (17)		0.10	0.07	0.12	

TRPG >40mmHg*	17 (19)	18 (24)		0.47	99 (13)	97 (17)		0.68	0.16	0.12	

The categorical variables were expressed as numbers and percentages and were compared using a chi-square test or Fisher's exact test.

Continuous variables were expressed as mean ± standard deviation and were compared between the two groups using the Student's t-test.

When we compared the data at baseline and at follow-up, we used paired Student's t-tests for continuous variables, sign tests for between the 2 variables and Wilcoxon signed rank test for the 3 ordinal variables for LVEF.

Delta was calculated according to the following equation: (the value at follow-up) – (the value at baseline).

High LVMI was defined as >115 g/m^2 in men, and >95g/m^2 in women.

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

Risk-adjusting variables selected for the parsimonious Cox proportional hazard models.

LVEF=left ventricular ejection fraction, Vmax=peak aortic jet velocity, PG=pressure gradient, LV=left ventricular, LVMI=left ventricular mass index, IVST=interventricular septal thickness, AR=aortic regurgitation, MS=mitral stenosis, MR=mitral regurgitation, TR=tricuspid regurgitation, and TRPG=tricuspid regurgitation pressure gradient.

Table 3. Clinical Outcomes comparing between the decline and no decline in LVEF groups.

	Decline in LVEF group N=91	No decline in LVEF group N=748	Unadjusted HR	P value	Adjusted HR	P value
	N of patients with event (Cumulative 3-year incidence)	N of patients with event (Cumulative 3-year incidence)	(95%CI)		(95%CI)	
Primary outcome measure: A composite of AS-related death or HF hospitalization	38 (39.5%)	191 (26.8%)	2.09 (1.45-2.92)	<0.001	1.98 (1.29-3.06)	0.002
All-cause death	45 (43.4%)	238 (28.3%)	1.95 (1.40-2.66)	<0.001	2.37 (1.61-3.49)	<0.001

AS-related death	25 (22.9%)	103 (14.9%)	2.52 (1.59-3.84)	<0.001	3.46 (1.98-6.06)	<0.001
HF hospitalization	27 (29.4%)	145 (21.1%)	1.97 (1.28-2.91)	0.001	1.67 (1.00-2.77)	0.051

LVEF=left ventricular ejection fraction, HR=hazard ratio, CI=confidence interval, AS=aortic stenosis, and HF=heart failure.

Table 4. Subgroup analysis for the effect of decline in LVEF relative to no decline in LVEF on the primary outcome measure.

	Decline in LVEF group N=91	No decline in LVEF group N=748			
	N of patients with event /N of patients at risk (Cumulative 3-year incidence)	N of patients with event /N of patients at risk (Cumulative 3-year incidence)	Adjusted HR (95%CI)	P value	P value for interaction
Vmax at baseline					
Vmax≧4m/s	19/42 (39.8%)	84/308 (25.9%)	2.13 (1.12-4.04)	0.02	0.55
Vmax<4m/s	19/49 (39.8%)	107/440 (28.1%)	3.85 (2.14-6.90)	<0.001	
Symptoms at baseline					
Symptomatic	8/22 (44.2%)	84/223 (39.9%)	2.50 (1.01-6.23)	0.048	0.49

Asymptomatic	30/69 (37.8%)	107/525 (21.3%)	2.73 (1.66-4.51)	<0.001	
LVEF at baseline					
LVEF≧70%	19/49 (30.8%)	41/234 (17.5%)	2.64 (1.34-5.20)	0.005	
LVEF 60-69%	11/26 (42.9%)	74/332 (21.7%)	2.85 (1.32-6.14)	0.007	0.66
LVEF<60%	8/16 (63.6%)	76/182 (49.9%)	3.67 (1.50-8.99)	0.004	

LVEF=left ventricular ejection fraction, HR=hazard ratio, CI=confidence interval, and Vmax=peak aortic jet velocity.

Figure 1

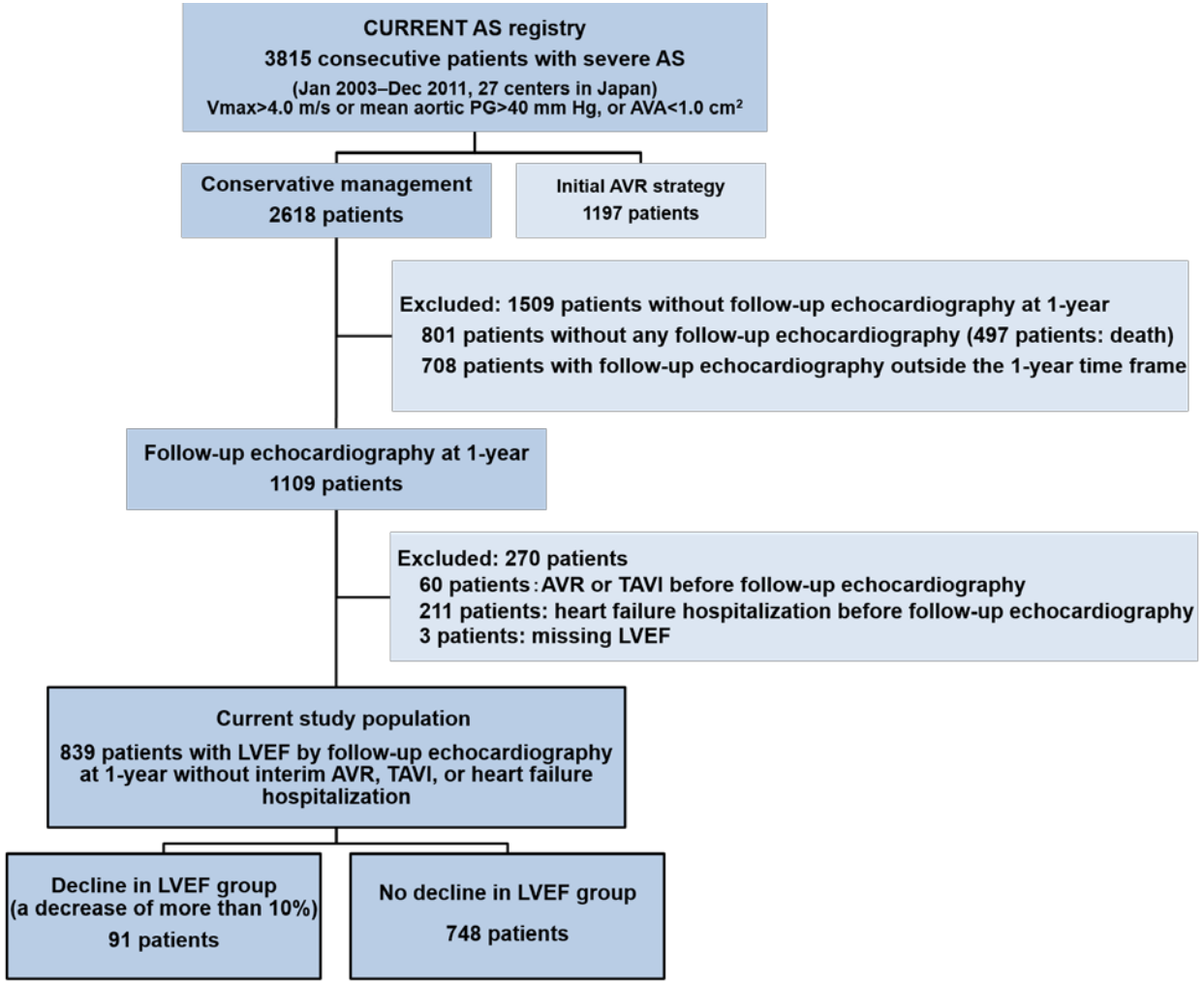
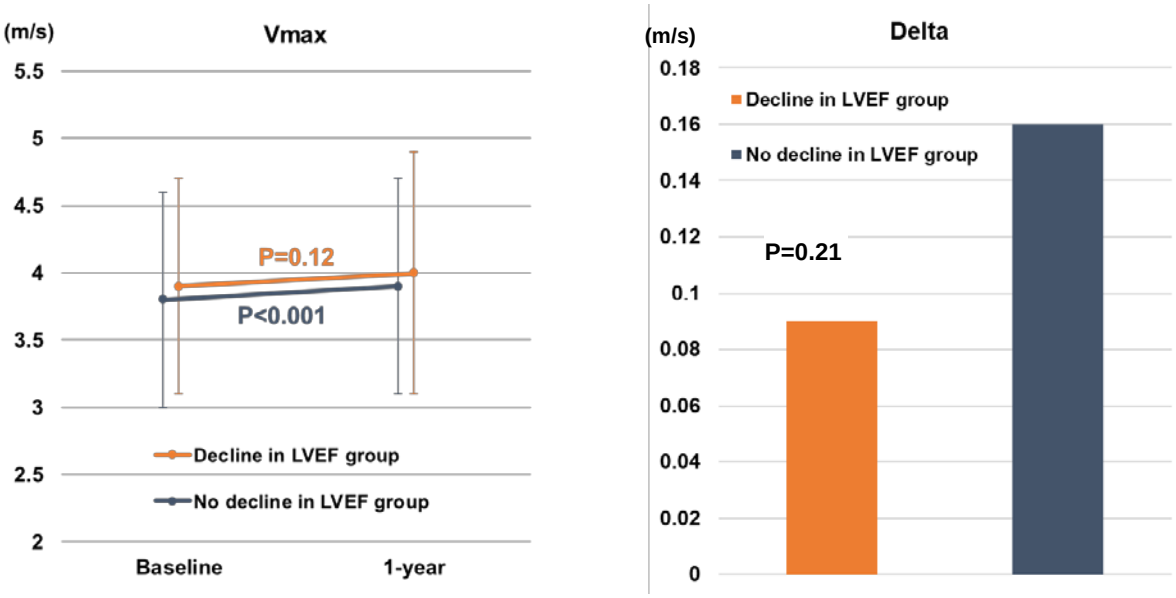


Figure 2

A)



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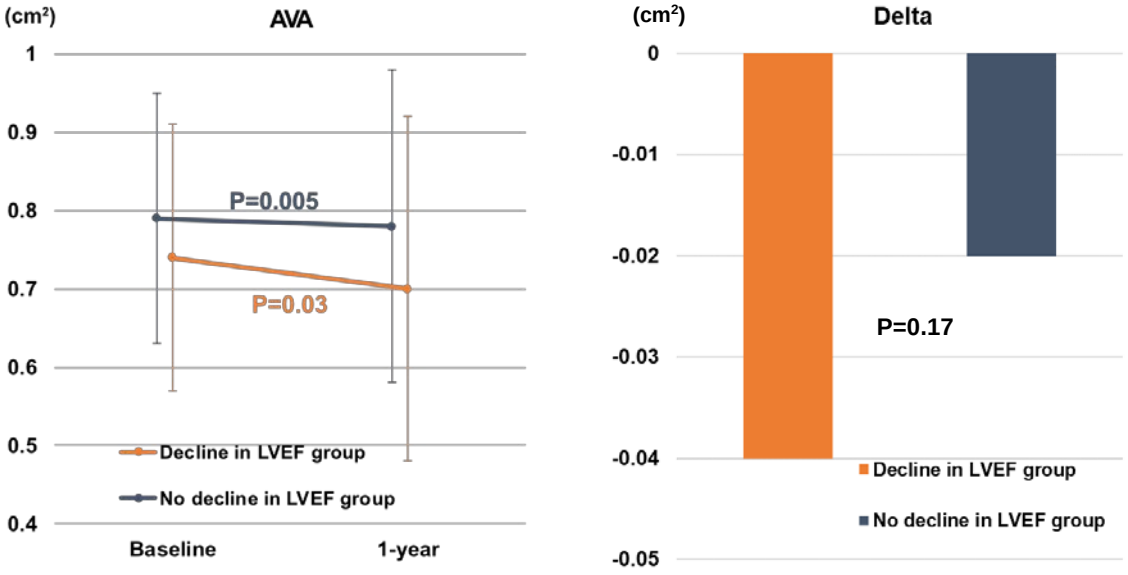

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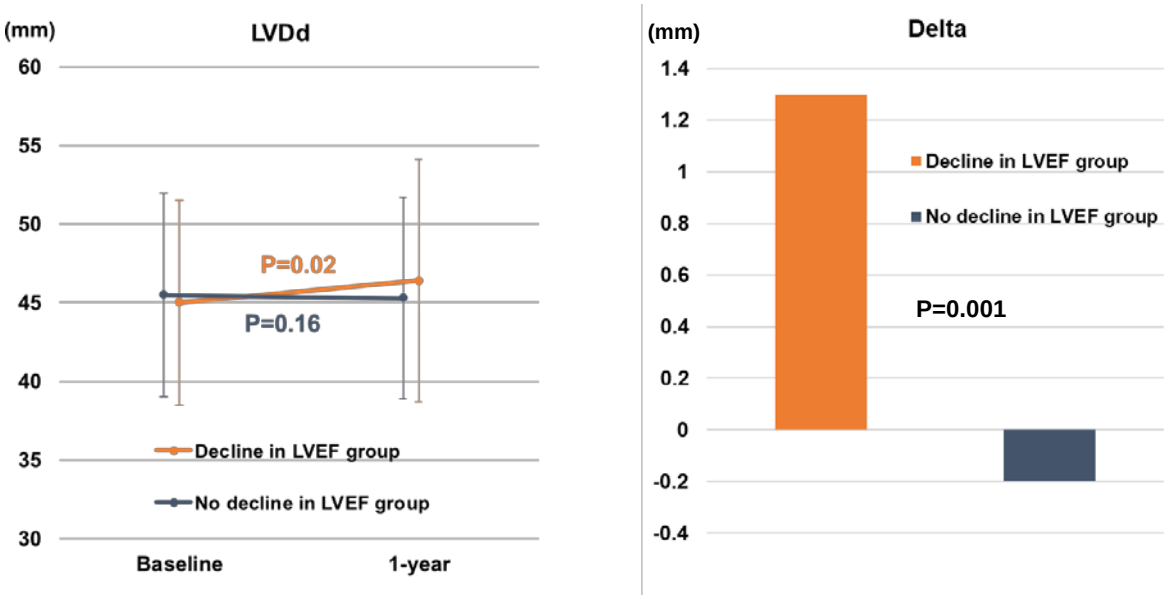

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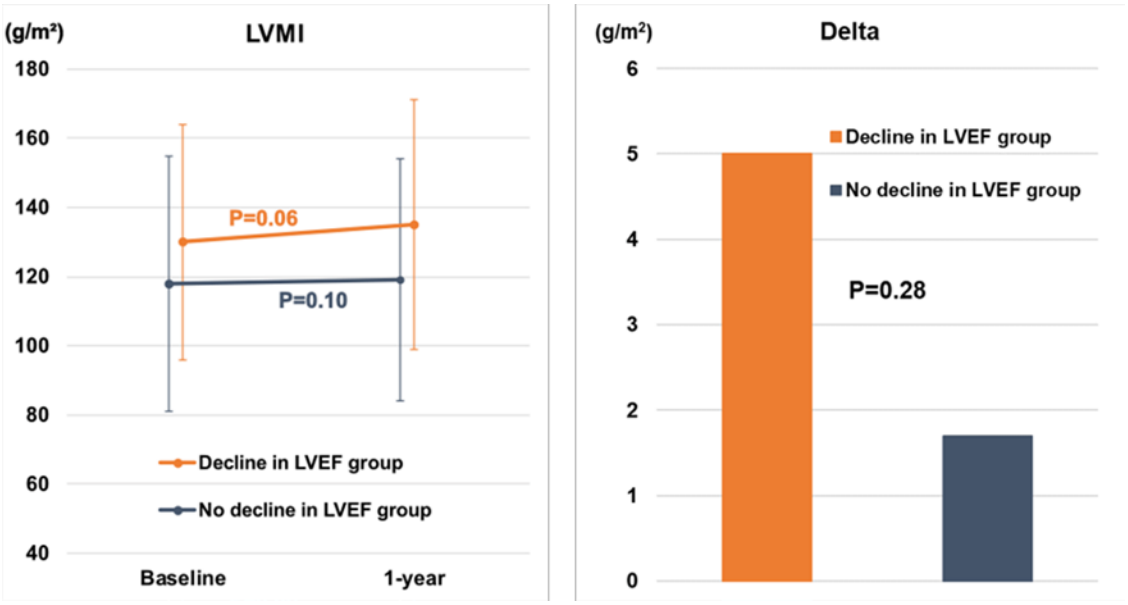
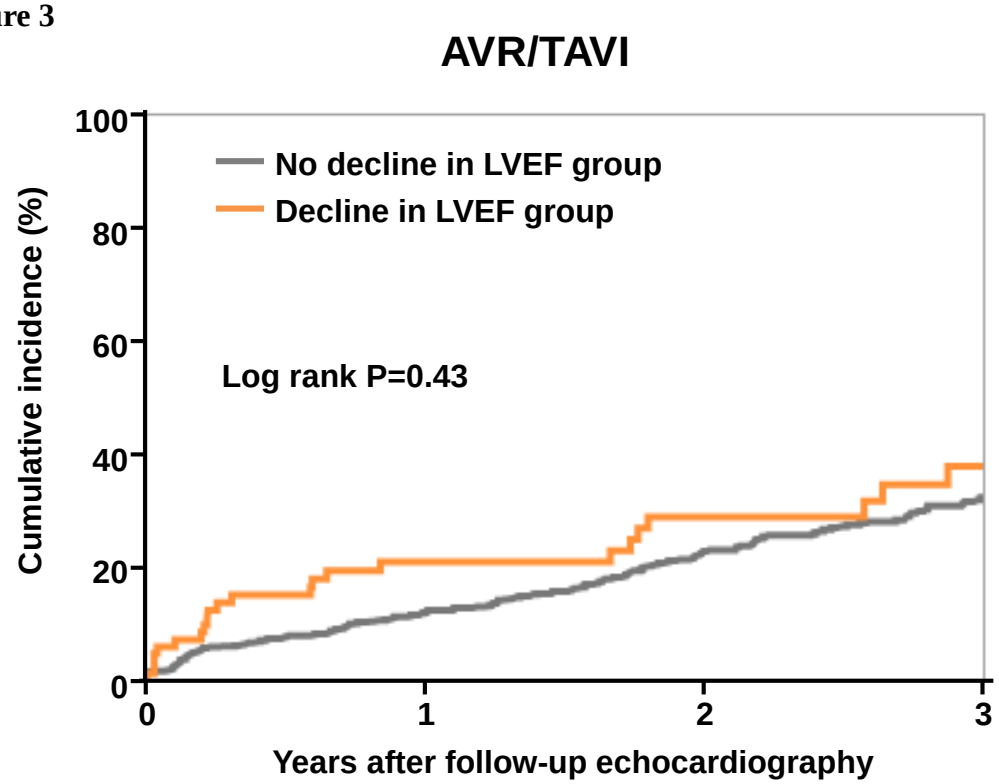
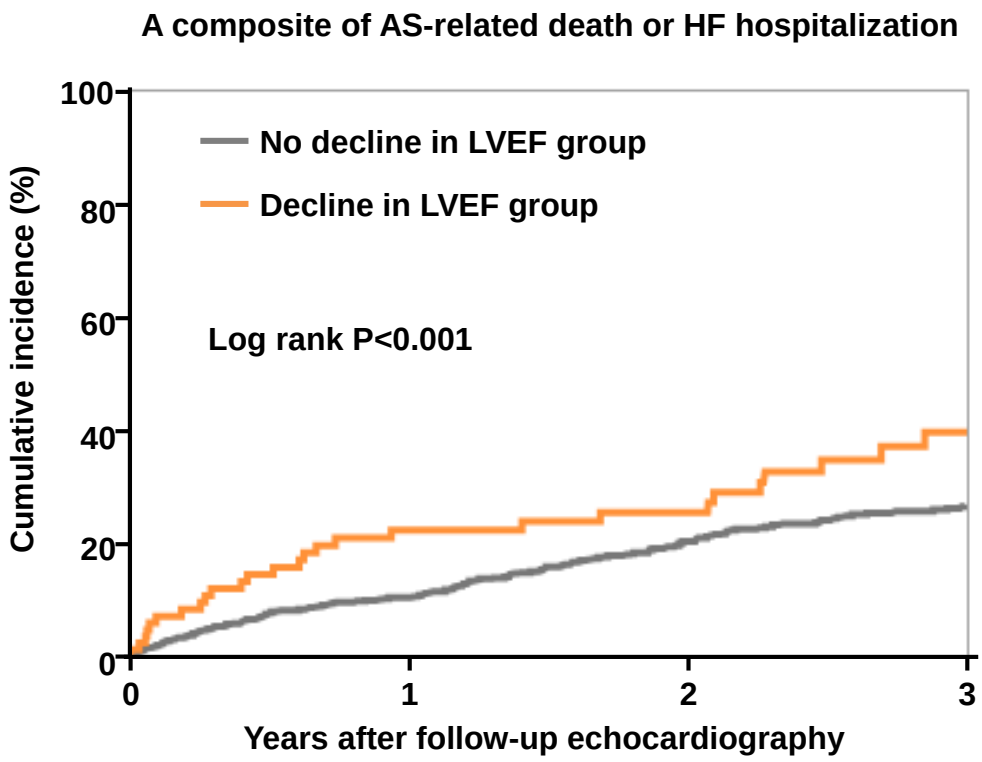


Figure 3



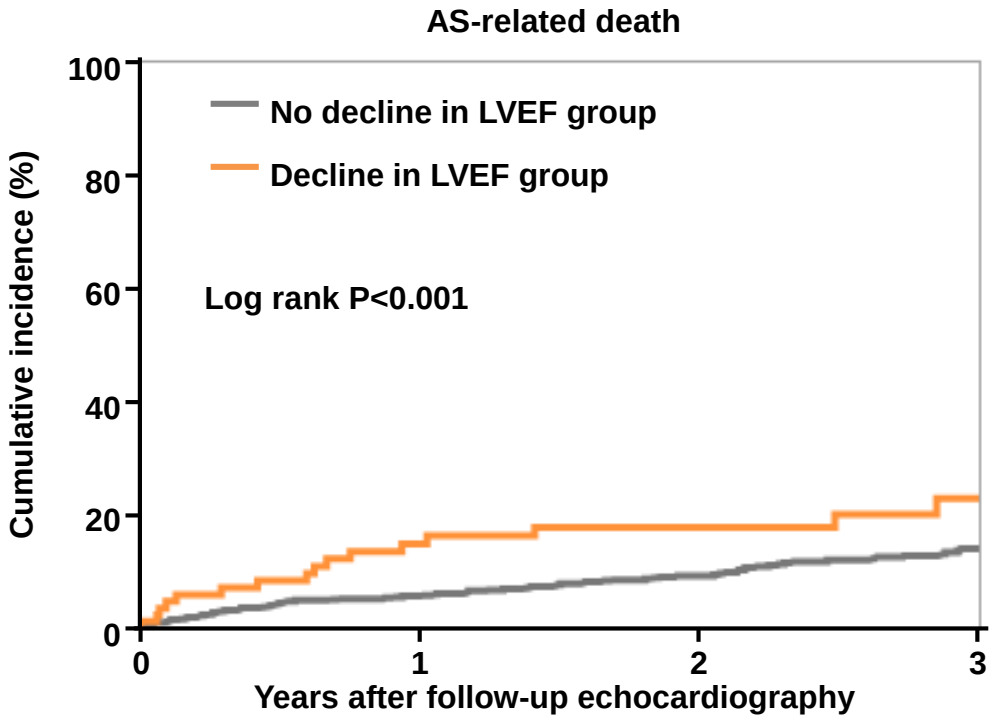
	Interval (years)	0	1	2	3
No decline in LVEF group	N of patients with AVR/TAVI		82	141	175
	N of patients at risk	748	546	360	186
	Cumulative incidence		12.0%	22.8%	32.2%
Decline in LVEF group	N of patients with AVR/TAVI		16	20	23
	N of patients at risk	91	48	34	16
	Cumulative incidence		20.9%	28.8%	37.8%

Figure 4 A)



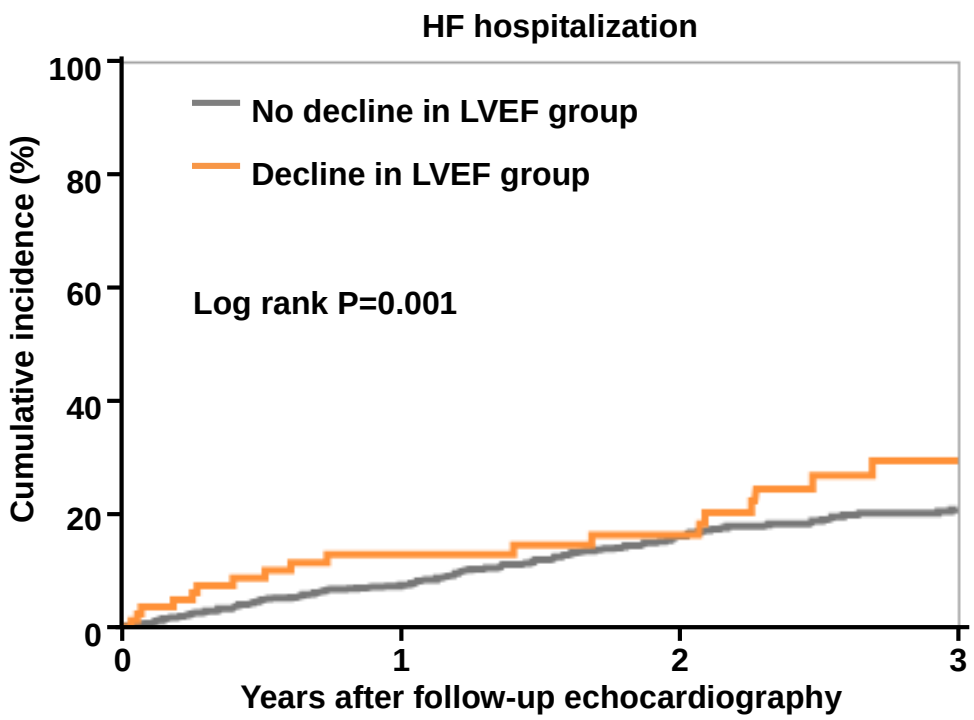
	Interval (years)	0	1	2	3
No decline in LVEF group	N of patients with at least 1 event		73	134	162
	N of patients at risk	748	593	416	233
	Cumulative incidence		10.3%	20.3%	26.8%
Decline in LVEF group	N of patients with at least 1 event		18	20	27
	N of patients at risk	91	56	44	22
	Cumulative incidence		22.2%	25.4%	39.5%

Figure 4 B)



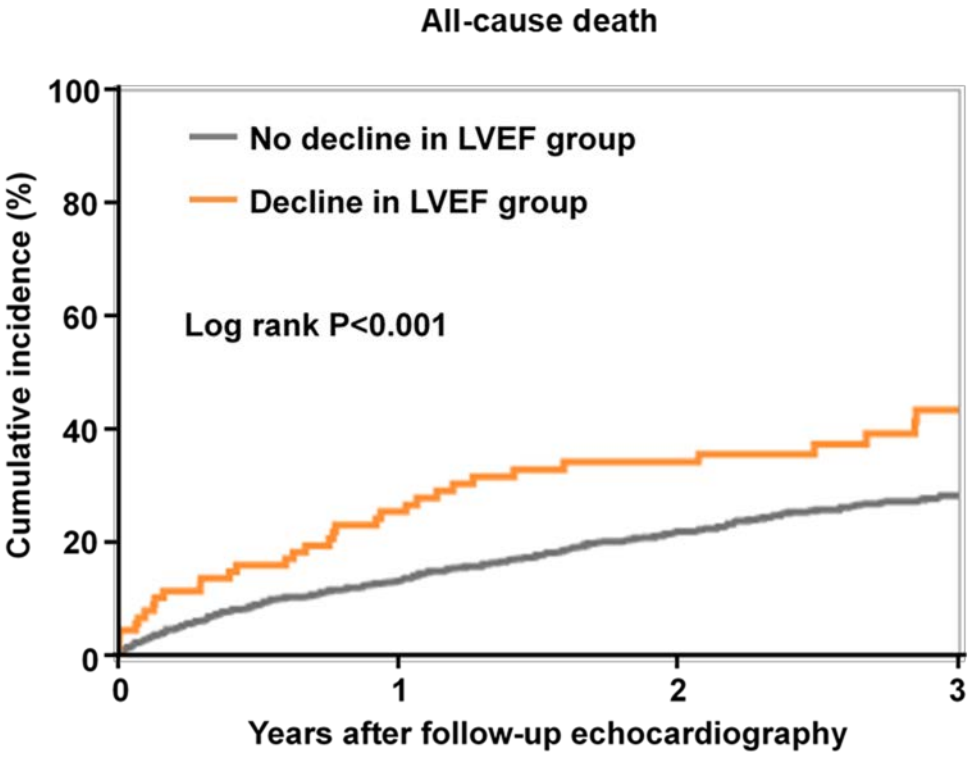
	Interval (years)	0	1	2	3
No decline in LVEF group	N of patients with event		40	62	82
	N of patients at risk	748	621	466	274
	Cumulative incidence		5.7%	9.2%	14.0%
Decline in LVEF group	N of patients with event		12	14	16
	N of patients at risk	91	62	47	24
	Cumulative incidence		14.9%	17.8%	22.9%

C)



	Interval (years)	0	1	2	3
No decline in LVEF group	N of patients with at least 1 event		50	102	122
	N of patients at risk	748	593	416	233
	Cumulative incidence		7.3%	16.1%	21.1%
Decline in LVEF group	N of patients with at least 1 event		10	12	18
	N of patients at risk	91	56	44	22
	Cumulative incidence		12.9%	16.3%	29.4%

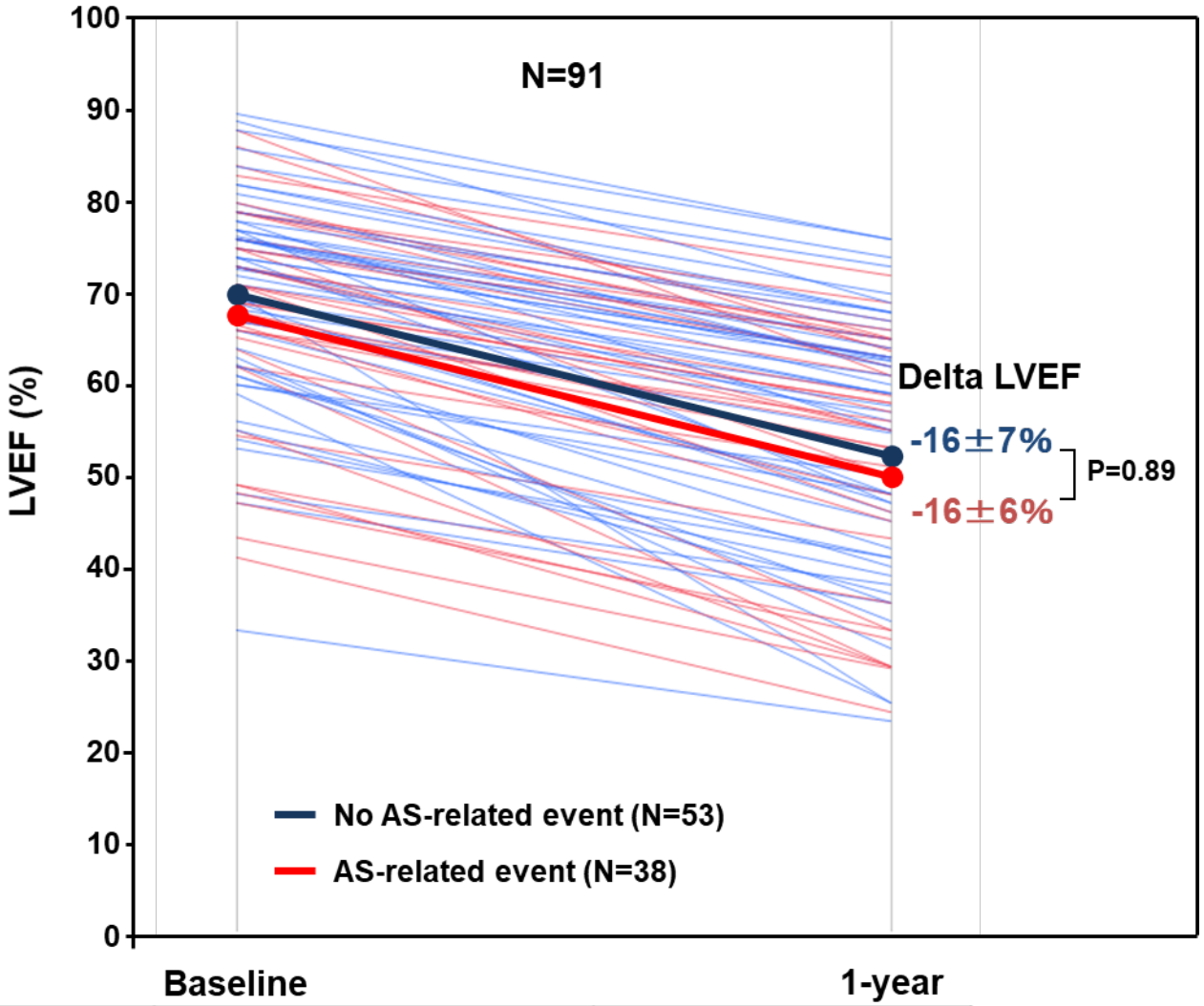
Central illustration



	Interval (years)	0	1	2	3
No decline in LVEF group	N of patients with event		97	156	188
	N of patients at risk	748	621	466	274
	Cumulative incidence		13.2%	21.9%	28.3%
Decline in LVEF group	N of patients with event		22	29	34
	N of patients at risk	91	62	47	24
	Cumulative incidence		25.4%	34.2%	43.4%

Figure 5

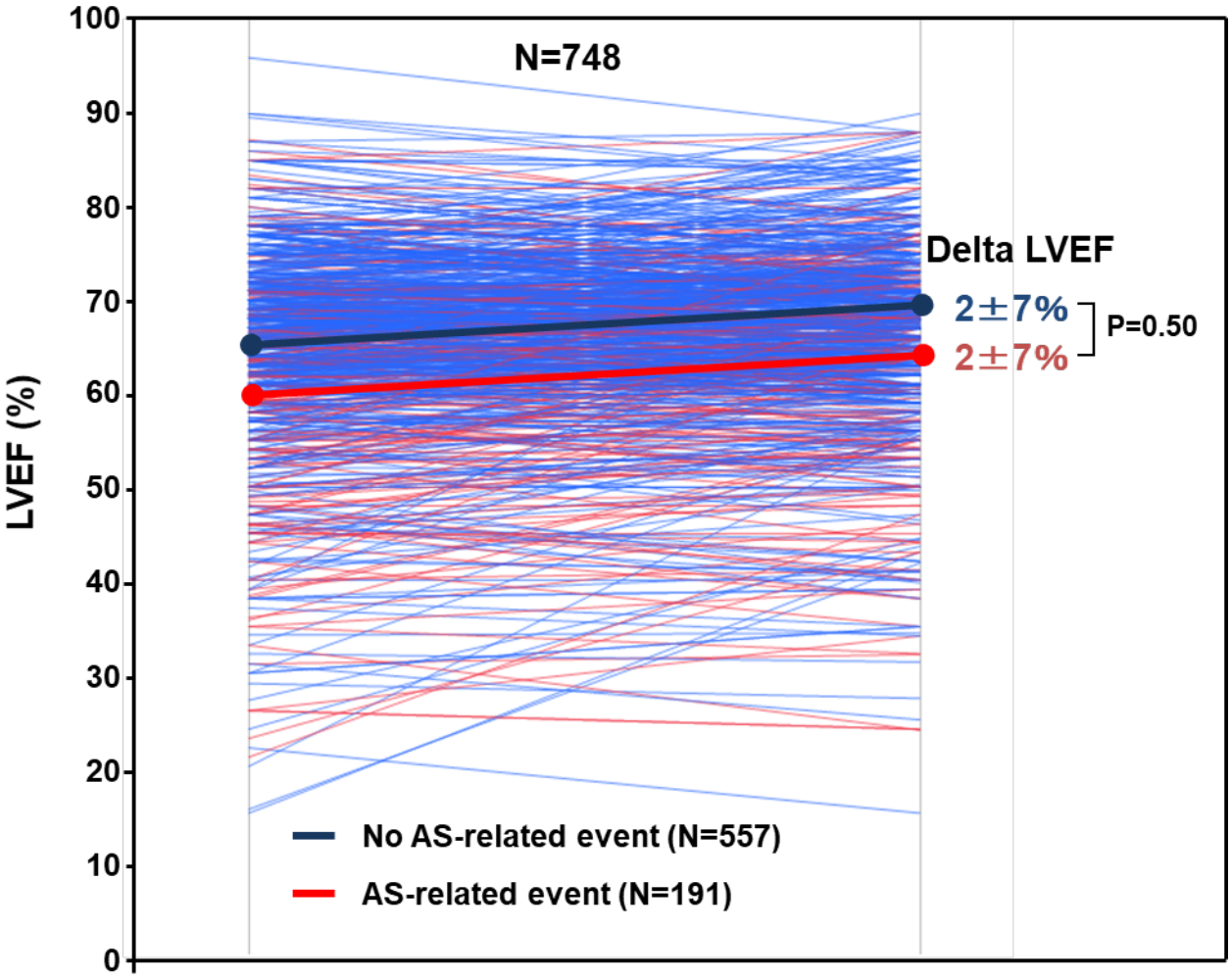
A)



No AS-related event	70±11%	P=0.41	54±14%	P=0.44
AS-related event	68±12%		52±14%	

Figure 5

B)



	Baseline		1-year	
No AS-related event	65±11%	P<0.001	67±10%	P<0.001
AS-related event	60±13%		62±12%	