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ORIGINAL ARTICLE
Valvular Heart Disease

Acute Heart Failure in Patients With Severe Aortic Stenosis
— Insights From the CURRENT AS Registry —

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Background: Clinical profiles of acute heart failure (AHF) complicating severe aortic stenosis (AS) remain unclear.

Methods and Results: From a Japanese multicenter registry enrolling consecutive patients with severe AS, 3,813 patients were categorized into the 3 groups according to the symptom of heart failure (HF); No HF (n=2,210), chronic HF (CHF) (n=813) and AHF defined as hospitalized HF at enrolment (n=790). Median follow-up was 1,123 days with 93% follow-up rate at 2 years. Risk factors for developing AHF included age, female sex, lower body mass index, untreated coronary artery stenosis, anemia, history of HF, left ventricular ejection fraction <50%, presence of any combined valvular disease, peak aortic jet velocity ≥5 m/s and tricuspid regurgitation pressure gradient ≥40 mmHg, and negative risk factors included dyslipidemia, history of percutaneous coronary intervention and hemodialysis. Respective cumulative 5-year incidences of all-cause death and HF hospitalization in No HF, CHF and AHF groups were 37.1%, 41.8% and 61.8% (P<0.001) and 20.7%, 33.8% and 52.3% (P<0.001). Even in the initial aortic valve replacement (AVR) stratum, AHF was associated with excess 5-year mortality risk relative to No HF and CHF (adjusted hazard ratio [HR] 1.64; 95% confidence interval [CI]: 1.14–2.36, P=0.008; adjusted HR 1.47; 95% CI: 1.03–2.11, P=0.03, respectively).

Conclusions: AHF complicating severe AS was associated with an extremely dismal prognosis, which could not be fully resolved by AVR. Careful management to avoid the development of AHF is crucial.

Key Words: Acute heart failure; Aortic stenosis; Prognosis

Aortic stenosis (AS) is one of the most common valvular heart diseases, especially in the elderly,[1,2] so its prevalence is growing with aging of the general population.[3] Patients with severe AS often develop heart failure (HF), which is an inflexion point in the natural history of AS.[4] Some patients with severe AS initially present with symptoms of chronic HF (CHF), but others suffer from acute HF (AHF) as the initial manifestation of severe AS. A number of recent reports have comprehensively investigated the risk factors and prognosis of AHF in general,[5–8] but there have been few studies specifically evaluating AHF complicating severe AS.[9,10]

Therefore, we sought to clarify the characteristics of severe AS patients who develop AHF, to evaluate the effect of AHF on short- and long-term clinical outcomes of severe AS patients according to the initial treatment strategies,

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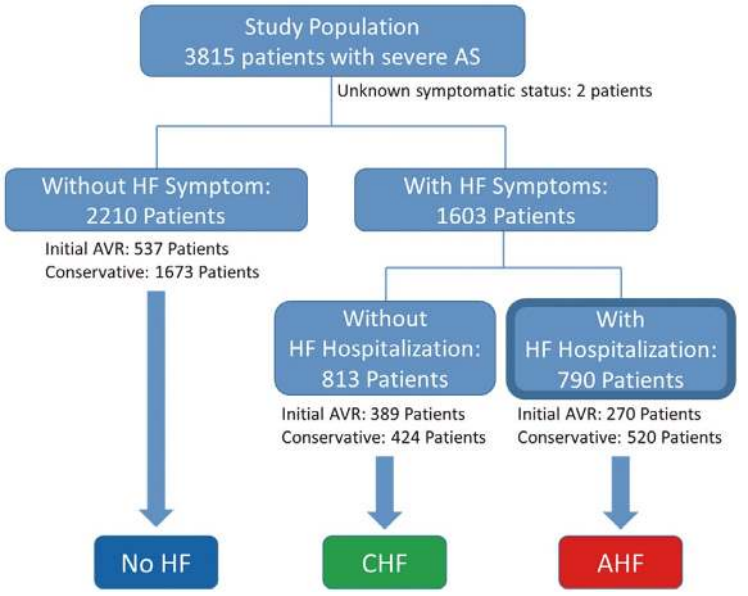

Figure 1. Study flowchart. Patients were categorized into No HF and HF groups based on the presence of HF symptoms at enrolment, excluding 2 patients whose symptomatic status was not available. The HF group was further divided into 2 groups (CHF and AHF groups) according to the need for in-hospital management of HF. The 3 groups were further stratified by the initial treatment strategy to either initial AVR stratum or conservative stratum. AHF, acute HF; AS, aortic stenosis; AVR, aortic valve replacement; CHF, chronic HF; HF, heart failure.

and to identify the determinants of initial aortic valve replacement (AVR) strategy in patients with AHF in a large Japanese observational database of consecutive patients with severe AS.

Methods

Study Population

The study design and primary results of the CURRENT AS (Contemporary Outcomes After Surgery and Medical Treatment in Patients with Severe Aortic Stenosis) registry have been previously reported.[11] Briefly, the CURRENT AS registry is a retrospective, multicenter registry that enrolled 3,815 consecutive patients with severe AS from among 27 centers in Japan between January 2003 and December 2011. We searched the hospital database of transthoracic echocardiography patients, 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 cm^2) for the first time during the study period. Collection of clinical information, including symptoms (i.e., HF, angina and syncope), medical history, diagnostic imaging, laboratory markers and other patient characteristics, was conducted through hospital chart and database review. Presence of HF was confirmed at participating hospitals by reviewing the final diagnosis, HF-related signs or symptoms and clinical course. The protocol was approved by the institutional review board or ethics committee at all 27 participating centers (**Appendix S1**). Written informed consent was waived because of the retrospective nature of the study, and none of the patients refused to participate in the study when contacted for follow-up.

In the main analysis, 3,813 study patients were categorized into No HF (n=2,210) and HF group (n=1,603) based on the presence of HF symptoms at enrolment, excluding 2 patients whose symptomatic status was not available. There were a few patients who had had HF symptoms once before enrolment, but did not have any at enrolment. We categorized those patients into the No HF group according to the definition. Thereafter, the HF group was further divided into 2 groups: AHF and CHF. In this process, because AHF is a syndrome with a wide range of conditions and acuteness, we avoided subjective categorization by not defining AHF solely on the basis of the mode of presentation or symptom onset. Instead, to keep consistency throughout the data collection and analyses, we defined the AHF and CHF groups according to whether or not hospitalized management was required. As a result, 790 patients who developed symptoms of HF requiring hospitalized management at enrolment were categorized into the AHF group, and 813 patients who had HF symptoms but did not require hospitalization were categorized into the CHF group (**Figure 1**). The 3 groups were further

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stratified by the initial treatment strategies to either the initial AVR stratum or conservative stratum. Because of the distinct clinical course of the patients who had coronary artery disease (CAD), we performed a sensitivity analysis in which patients with CAD were excluded from the entire cohort. In this analysis, the remaining patients were divided into 2 groups: AHF and No AHF rather than 3 groups to counteract the potential ambiguity of categorization of No HF and CHF groups in the main analyses. Follow-up was commenced on the day of the index echocardiography, unless specified otherwise.

Definitions of the Clinical Events

The primary outcome measures in the present analysis were all-cause death and HF hospitalization. Causes of death were classified according to VARC (Valve Academic Research Consortium) definitions, and adjudicated by a clinical event committee.[12,13] HF hospitalization was defined as hospitalization for worsening HF requiring intravenous drug therapy. Other definitions of the clinical events have been described previously[11], and clinical events were adjudicated by a clinical event committee (**Appendix S1**).

Statistical Analysis

Categorical variables are presented as numbers and percentages, and were compared with the chi-square test or Fisher's exact test. Continuous variables are expressed as the mean and standard deviation or median and interquartile range (IQR). Continuous variables were compared using Student's t test or Wilcoxon rank-sum test based on

Table 1. Baseline Characteristics According to HF Status in the Entire Cohort

Variable	No HF (n=2,210)	CHF (n=813)	AHF (n=790)	P value
Clinical characteristics				
Age*, years	76.7±9.5	76.7±9.9	81.8±9.1	<0.001
≥80 years	897 (41)	338 (42)	494 (63)	<0.001
Male*	896 (41)	303 (37)	244 (31)	<0.001
BMI, kg/m^2	22.0±3.8	21.9±3.8	20.9±3.9	<0.001
<22 kg/m^2 *	1,281 (58)	475 (58)	570 (72)	<0.001
Hypertension*	1,533 (69)	569 (70)	565 (72)	0.51
BSA, m^2	1.47±0.18	1.46±0.19	1.40±0.19	<0.001
Current smoking*	125 (6)	36 (4)	35 (4)	0.24
History of smoking	504 (23)	172 (21)	154 (19)	0.14
Dyslipidemia	824 (37)	288 (35)	215 (27)	<0.001
On statin therapy*	597 (27)	212 (26)	161 (20)	0.001
Diabetes mellitus	537 (24)	166 (20)	194 (25)	0.06
On insulin therapy*	119 (5)	35 (4)	34 (4)	0.32
CAD*	656 (30)	232 (29)	246 (31)	0.52
Untreated significant coronary artery stenosis‡	343 (16)	137 (17)	153 (19)	0.04
Prior PCI	340 (15)	74 (9)	88 (11)	<0.001
Prior CABG	119 (5)	51 (6)	32 (4)	0.13
Prior MI*	174 (8)	60 (7)	89 (11)	0.006
Prior open heart surgery	190 (9)	78 (10)	51 (6)	0.06
Prior HF	113 (5)	297 (37)	234 (30)	<0.001
Prior symptomatic stroke*	304 (14)	89 (11)	109 (14)	0.1
History of atrial fibrillation or flutter*	397 (18)	212 (26)	219 (28)	<0.001
Aortic/peripheral vascular disease*	359 (16)	107 (13)	113 (14)	0.08
Serum creatinine, mg/dL*	0.8 (0.7–1.2)	0.9 (0.7–1.3)	1 (0.8–1.5)	<0.001
>2 mg/dL without hemodialysis	50 (2)	38 (5)	65 (8)	<0.001
Hemodialysis*	262 (12)	83 (10)	60 (8)	0.004
Hemoglobin, g/dL	12 (11–13)	12 (10–13)	11 (9–12)	<0.001
Anemia*,†	1,088 (49)	451 (55)	578 (73)	<0.001
BNP, pg/mL§	135.6 (57.2–322.5)	315.6 (132.1–787.8)	839.2 (383.9–1,634.6)	<0.001
Liver cirrhosis (Child-Pugh B or C)*	17 (1)	12 (1)	9 (1)	0.2
Malignancy	333 (15)	89 (11)	94 (12)	0.004
Currently under treatment*	105 (5)	22 (3)	22 (3)	0.007
Chronic lung disease	199 (9)	119 (15)	82 (10)	<0.001
Moderate or severe*	47 (2)	35 (4)	30 (4)	0.002
Logistic EuroSCORE, %	8.2 (5.1–13.6)	9.5 (5.5–15.6)	16.7 (10.1–28.4)	<0.001
EuroSCORE II, %	2.4 (1.4–3.5)	3.0 (1.8–4.5)	6.1 (3.8–10.2)	<0.001
STS score (PROM), %	3.2 (2.0–5.1)	3.5 (2.1–5.7)	7.1 (4.3–11.7)	<0.001
Symptoms at index echocardiography				
Asymptomatic	1,808 (82)	0 (0)	0 (0)	<0.001
Chest pain	299 (14)	106 (13)	93 (12)	0.5
Syncope	136 (6)	27 (3)	35 (4)	0.004

(**Table 1** continued the next page.)

Variable	No HF (n=2,210)	CHF (n=813)	AHF (n=790)	P value
Etiology of aortic stenosis				<0.001
Degenerative	1,941 (88)	704 (87)	732 (93)	
Congenital (Unicuspid, Bicupsid, or Quadricupsid)	174 (8)	57 (7)	23 (3)	
Rheumatic	74 (3)	46 (6)	30 (4)	
Infective endocarditis	4 (0.2)	0 (0)	3 (0.4)	
Other	17 (0.8)	6 (0.7)	2 (0.3)	
Echocardiographic variables				
V_{max}, m/s	4.0±0.9	4.4±0.9	4.2±1.0	<0.001
>5 m/s	306 (14)	217 (27)	174 (22)	<0.001
>4 m/s*	1,153 (52)	563 (69)	468 (59)	<0.001
Peak aortic PG, mmHg	68±29	81±33	74±34	<0.001
Mean aortic PG, mmHg	38±18	47±21	42±21	<0.001
AVA (equation of continuity), cm^2	0.76±0.2	0.68±0.18	0.65±0.19	<0.001
AVA index, cm^2/m^2	0.52±0.12	0.47±0.13	0.47±0.15	<0.001
Low-gradient AS‖	1,048 (47)	246 (30)	320 (41)	<0.001
LV end-diastolic diameter, mm	45±6	47±7	48±8	<0.001
LV end-systolic diameter, mm	28±6	31±9	34±9	<0.001
LVEF, %*	66±11	61±14	55±16	<0.001
<40%	62 (3)	78 (10)	153 (19)	<0.001
<50%	163 (7)	151 (19)	279 (35)	<0.001
<60%	423 (19)	283 (35)	447 (57)	<0.001
IVST in diastole, mm	11.2±2.2	11.6±2.3	11.5±2.4	<0.001
PWT in diastole, mm	10.8±2.0	11.2±2.0	11.1±2.2	<0.001
Any combined valvular disease (moderate or severe)*	680 (31)	402 (49)	475 (60)	<0.001
AR	365 (17)	209 (26)	216 (27)	<0.001
MS	56 (3)	47 (6)	30 (4)	<0.001
MR	267 (12)	196 (24)	300 (38)	<0.001
TR	249 (11)	163 (20)	216 (27)	<0.001
TRPG, mmHg	30±10	34±14	38±14	<0.001
≥40 mmHg*	205 (9)	172 (21)	229 (29)	<0.001
Clinical presentation at index UCG				
NYHA class#				<0.001
I	2,210 (100)			
II		711 (87)	135 (17)	
III		91 (11)	270 (34)	
IV			373 (47)	
III or IV	0 (0)	91 (11)	643 (81)	<0.001
Atrial fibrillation or flutter	239 (11)	133 (16)	146 (18)	<0.001
Pace maker rhythm	56 (3)	22 (3)	21 (3)	0.96
Non-invasive ventilation	0 (0)	2 (0.3)	75 (9)	<0.001
Intubation	0 (0)	1 (0)	38 (5)	<0.001
Inotrope use	0 (0)	2 (0.3)	76 (10)	<0.001
IABP/PCPS	0 (0)	0 (0)	17 (2)	<0.001
Cardiogenic shock	0 (0)	0 (0)	32 (4)	<0.001
Resuscitation	0 (0)	0 (0)	12 (2)	<0.001
Acute MI	25 (1)	4 (0.5)	32 (4)	<0.001
Therapeutic strategy				
Initial AVR	537 (24)	389 (48)	270 (34)	<0.001
Conservative	1,673 (76)	424 (52)	520 (66)	<0.001

Values are mean±SD, median (interquartile range), or number (%). *Potential risk-adjusting variables selected for Cox proportional hazards models. †Anemia as defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women; <13.0 g/dL in men). ‡Coronary angiography was performed in 982 (44%) patients in the No HF group, 484 (60%) patients in the CHF group, and 378 (48%) patients in the AHF group. §B-type natriuretic peptide values obtained in 1,824 (47.8%) patients (No HF group: n=910 [41%], CHF group: n=455 [56%], AHF group: n=459 [58%]). ‖V_{max} <4.0 m/s and mean aortic PG <40 mmHg, but AVA <1.0 cm^2. #Data not available in 23 (0.6%) patients. AHF, acute HF; AR, aortic regurgitation; AS, aortic stenosis; 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; CHF, chronic HF; HF, heart failure; IABP, intra-aortic balloon pumping; IVST, interventricular septum thickness; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; PG, pressure gradient; PROM, predicted risk of mortality; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; TRPG, tricuspid regurgitation pressure gradient; V_{max}, peak aortic jet velocity.

Table 2. Risk Factors for Developing AHF

Variables	Univariate analysis				Multivariable analysis		
	AHF		OR	P value	OR	95% CI	P value
	Yes [n=790]	No [n=3,023]					
Clinical characteristics							
Age ≥80 years	494 (63)	1,233 (41)	2.42	<0.001	1.69	1.39–2.05	<0.001
Male	244 (31)	1,199 (40)	0.68	<0.001	0.69	0.56–0.84	<0.001
BMI <22 kg/m^2	570 (72)	1,755 (58)	1.87	<0.001	1.29	1.05–1.57	0.01
Hypertension	565 (72)	2,101 (69)	1.10	0.27	1.20	0.98–1.47	0.08
Current smoking	35 (4)	161 (5)	0.82	0.3	1.30	0.84–1.96	0.24
Dyslipidemia	215 (27)	1,112 (37)	0.64	<0.001	0.73	0.60–0.90	0.003
Diabetes on insulin therapy	34 (4)	154 (5)	0.84	0.36	0.95	0.61–1.46	0.82
Untreated coronary artery stenosis*	153 (19)	480 (16)	1.27	0.02	1.55	1.21–1.98	<0.001
Prior HF	234 (30)	410 (14)	2.68	<0.001	1.46	1.17–1.81	<0.001
Prior MI	89 (11)	234 (8)	1.51	0.002	1.21	0.85–1.71	0.3
Prior PCI	88 (11)	414 (14)	0.79	0.06	0.69	0.49–0.95	0.02
Prior CABG	32 (4)	170 (6)	0.71	0.07	0.64	0.40–1.01	0.06
Prior symptomatic stroke	109 (14)	394 (13)	1.07	0.57	0.92	0.70–1.19	0.5
History of atrial fibrillation or flutter	219 (28)	609 (20)	1.52	<0.001	1.16	0.94–1.43	0.2
Creatinine level >2 mg/dL without hemodialysis	65 (8)	88 (3)	3.00	<0.001	1.43	0.97–2.09	0.07
Hemodialysis	60 (8)	345 (11)	0.64	0.001	0.50	0.35–0.69	<0.001
Anemia†	578 (73)	1,538 (51)	2.63	<0.001	2.07	1.70–2.52	<0.001
Chronic lung disease (moderate or severe)	30 (4)	82 (3)	1.42	0.12	1.27	0.78–2.00	0.33
Echocardiographic variables							
V_{max} ≥5 m/s	174 (22)	523 (17)	1.35	0.003	1.45	1.16–1.80	<0.001
LVEF <50%	279 (35)	314 (10)	4.71	<0.001	4.88	3.91–6.10	<0.001
Any combined valvular disease (moderate or severe)	475 (60)	1,082 (36)	2.70	<0.001	1.85	1.53–2.24	<0.001
TRPG ≥40 mmHg	229 (29)	377 (12)	2.90	<0.001	1.73	1.38–2.15	<0.001

Values are number (%). *Coronary angiography was performed in 378 (48%) patients in the AHF group and 1,466 (49%) patients in the No AHF group. †Anemia as defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women; <13.0 g/dL in men). CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

their distributions.

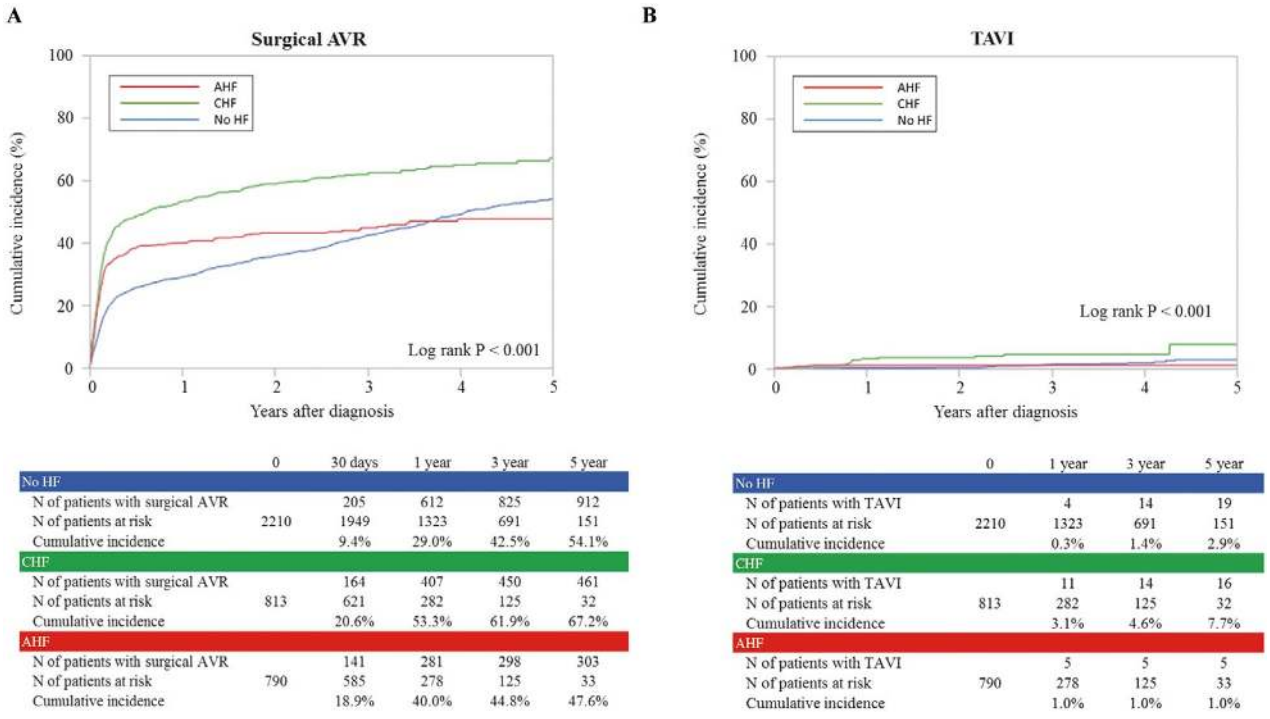
Independent risk factors for developing AHF and determinants of initial AVR strategy were identified among clinically relevant factors by means of univariate and multivariable logistic regression analyses, following the dichotomization of continuous variables by median values or clinically meaningful reference values. The risk factors for developing AHF in the entire cohort were analyzed by dividing the entire cohort into 2 groups: AHF (n=790) and No AHF (a combined group of CHF and No HF groups: n=3,023). The results are expressed as odds ratios (ORs) and their 95% confidence intervals (CIs).

Cumulative incidences of clinical events were estimated by the Kaplan-Meier method, and the differences among the groups were assessed with the log-rank test. The risks of AHF relative to No HF and CHF, respectively, for the clinical endpoints were estimated by Cox proportional hazard models and expressed as hazard ratios (HRs) and their 95% CIs. In consistent with our previous report,[11] the 21 clinically relevant factors listed in **Table 1** were included as the risk-adjusting variable in the multivariable Cox proportional hazard models and the centers were incorporated as the stratification variable. All statistical analyses were performed with the statistical software program JMP 10.0.0 (SAS Institute Inc., Cary, NC, USA) or SAS 9.4 (SAS Institute). All reported P-values are 2-tailed; P<0.05 was considered statistically significant.

Results

Baseline Characteristics

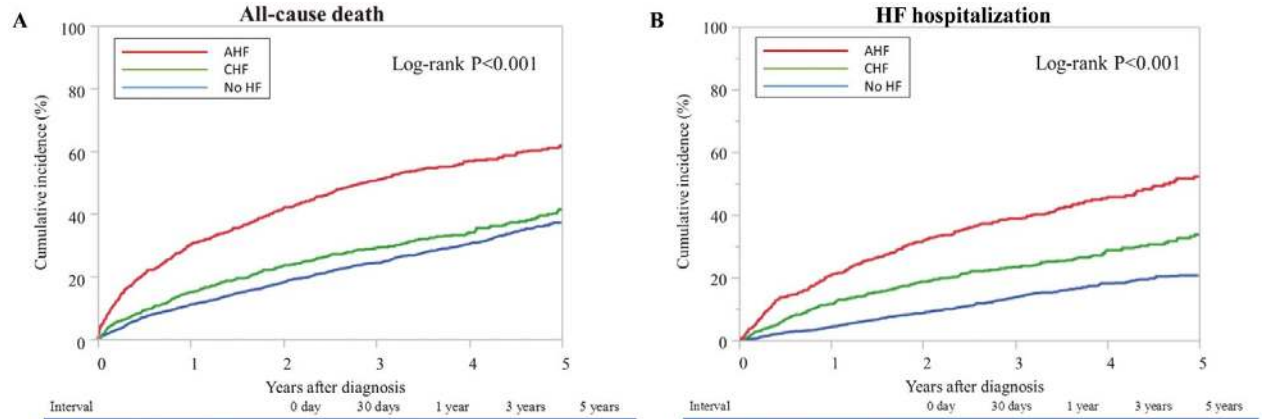
According to the baseline characteristics of the 3 groups, patients in the AHF group were characterized by older age, smaller body mass index (BMI), and higher prevalence of women, untreated significant coronary artery stenosis, prior myocardial infarction, atrial fibrillation/flutter, renal dysfunction, and anemia (**Table 1**). The values for B-type natriuretic peptide (BNP) level obtained in 1,824 patients were significantly higher in the AHF group than in the CHF and No HF groups (**Table 1**). Proportion of patients with chest pain was not different among the 3 groups, although patients with syncope were more often found in the No HF group. Regarding the echocardiographic parameters, the prevalence of very severe AS, defined as V_{max} ≥5 m/s, was higher in the CHF and AHF groups than in the No HF group. The AHF group had lower left ventricular ejection fraction (LVEF), higher prevalence of concomitant valvular diseases, and higher tricuspid regurgitation pressure gradient (TRPG) than the CHF and No HF groups (**Table 1**). In terms of clinical presentation, 81% of patients in the AHF group were in NYHA class III or IV, 14% required respiratory support and 10% required



	0	30 days	1 year	3 year	5 year
No HF					
N of patients with surgical AVR		205	612	825	912
N of patients at risk	2210	1949	1323	691	151
Cumulative incidence		9.4%	29.0%	42.5%	54.1%
CHF					
N of patients with surgical AVR		164	407	450	461
N of patients at risk	813	621	282	125	32
Cumulative incidence		20.6%	53.3%	61.9%	67.2%
AHF					
N of patients with surgical AVR		141	281	298	303
N of patients at risk	790	585	278	125	33
Cumulative incidence		18.9%	40.0%	44.8%	47.6%

	0	1 year	3 year	5 year
No HF				
N of patients with TAVI		4	14	19
N of patients at risk	2210	1323	691	151
Cumulative incidence		0.3%	1.4%	2.9%
CHF				
N of patients with TAVI		11	14	16
N of patients at risk	813	282	125	32
Cumulative incidence		3.1%	4.6%	7.7%
AHF				
N of patients with TAVI		5	5	5
N of patients at risk	790	278	125	33
Cumulative incidence		1.0%	1.0%	1.0%

Figure 2. Cumulative incidence of surgical AVR (**A**) or TAVI (**B**) among the AHF, CHF, and No HF groups. TAVI, transcatheter aortic valve implantation. Other abbreviations as in Figure 1.



Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with event		31	238	504	642
N of patients at risk	2210	2143	1891	1257	370
Cumulative incidence		1.4%	11.1%	24.3%	37.1%
CHF					
N of patients with event		20	119	222	270
N of patients at risk	813	780	654	427	140
Cumulative incidence		2.5%	15.2%	29.2%	41.8%
AHF					
N of patients with event		51	227	370	416
N of patients at risk	790	724	511	287	95
Cumulative incidence		6.5%	29.9%	50.5%	61.8%

Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with at least 1 event		11	87	247	311
N of patients at risk	2210	2135	1837	1156	341
Cumulative incidence		0.5%	4.3%	13.7%	20.7%
CHF					
N of patients with at least 1 event		8	85	158	188
N of patients at risk	813	774	604	360	111
Cumulative incidence		1.0%	11.7%	23.4%	33.8%
AHF					
N of patients with at least 1 event		18	135	225	257
N of patients at risk	790	707	446	227	65
Cumulative incidence		2.4%	20.8%	38.8%	52.3%

Figure 3. Cumulative incidences of the primary outcome measures among the AHF, CHF, and No HF groups. (**A**) All-cause death, and (**B**) HF hospitalization. Abbreviations as in Figure 1.

inotrope use.

In the entire study population, an initial AVR strategy was selected in 1,196 patients (31%), and the remaining 2,617 patients were managed conservatively. Patients in the AHF group were less often referred to an initial AVR strategy than patients in the CHF group. Surgical risk scores were significantly higher in the AHF group than in the CHF and No HF groups (**Table 1**).

Risk Factors for Developing AHF

The independent risk factors for developing AHF included advanced age, female sex, lower BMI, presence of untreated coronary artery stenosis, history of prior HF and anemia in addition to echocardiographic parameters of V_{max} ≥5 m/s, LVEF <50%, coexistence of any combined valvular disease, and TRPG ≥40 mmHg; the negative predictors included dyslipidemia, prior history of percutaneous coronary intervention and hemodialysis (**Table 2**).

Clinical Outcomes in the Entire Cohort

Among the 1,196 patients who were assigned to an initial AVR strategy, 1,173 (98.1%) actually underwent surgical AVR (n=1,162) or transcatheter aortic valve implantation (TAVI: n=11). The median interval between the index echocardiography and the AVR procedure was 36 days (IQR: 16–61). Among the 2,617 patients who were initially assigned to a conservative strategy, 569 (21.7%) eventually underwent surgical AVR (n=541) or TAVI (n=29) with a median interval of 838 days (IQR: 307–1,308) from the index echocardiography. Therefore, during a median

Table 3. Crude and Adjusted Effects of AHF Relative to No HF or CHF for Long-Term Clinical Outcomes

	No HF	CHF	AHF		AHF vs. No HF				AHF vs. CHF			
	Total no. of patients with at least 1 event (cumulative 5-year incidence) (%)			Log-rank P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Entire cohort: n=3,813 (No HF: 2,210, CHF: 813, AHF: 790)												
All-cause death	703 (37.1)	304 (41.8)	441 (61.8)	<0.001	2.34 (2.08–2.63)	<0.001	1.83 (1.59–2.10)	<0.001	1.91 (1.65–2.21)	<0.001	1.43 (1.22–1.67)	<0.001
Cardiovascular death	426 (24.8)	201 (29.9)	325 (49.2)	<0.001	2.83 (2.44–3.26)	<0.001	2.05 (1.73–2.43)	<0.001	2.11 (1.77–2.52)	<0.001	1.55 (1.29–1.87)	<0.001
Aortic valve-related death	253 (16.1)	113 (17.4)	243 (39.2)	<0.001	3.53 (2.96–4.21)	<0.001	2.64 (2.14–3.27)	<0.001	2.79 (2.24–3.50)	<0.001	2.02 (1.59–2.55)	<0.001
Sudden death*	108 (6.7)	35 (5.2)	53 (11.4)	<0.001	1.81 (1.29–2.50)	<0.001	NA	NA	1.97 (1.29–3.05)	0.002	NA	NA
Noncardiovascular death*	278 (16.4)	103 (16.5)	116 (24.7)	<0.001	1.58 (1.27–1.96)	<0.001	NA	NA	1.51 (1.16–1.97)	0.002	NA	NA
HF hospitalization	344 (20.7)	200 (33.8)	268 (52.3)	<0.001	3.30 (2.81–3.86)	<0.001	2.60 (2.15–3.15)	<0.001	1.87 (1.56–2.25)	<0.001	1.26 (1.04–1.53)	0.02
Aortic valve-related death or HF hospitalization	465 (26.5)	241 (37.6)	366 (39.5)	<0.001	3.22 (2.81–3.70)	<0.001	2.65 (2.25–3.12)	<0.001	2.07 (1.76–2.44)	<0.001	1.51 (1.27–1.79)	<0.001
Conservative group: n=2,617 (No HF: 1,673, CHF: 424, AHF: 520)												
All-cause death	620 (43.4)	228 (57.2)	365 (75.3)	<0.001	2.85 (2.50–3.24)	<0.001	1.84 (1.58–2.15)	<0.001	1.74 (1.47–2.95)	<0.001	1.36 (1.14–1.63)	<0.001
Cardiovascular death	373 (29.5)	153 (43.8)	275 (63.2)	<0.001	3.55 (3.03–4.15)	<0.001	2.15 (1.78–2.59)	<0.001	1.95 (1.60–2.38)	<0.001	1.50 (1.22–1.86)	<0.001
Aortic valve-related death	228 (20.2)	93 (29.5)	220 (55.7)	<0.001	4.66 (3.87–5.61)	<0.001	2.90 (2.31–3.63)	<0.001	2.58 (2.03–3.30)	<0.001	1.98 (1.54–2.56)	<0.001
Sudden death*	97 (7.9)	25 (7.1)	47 (16.5)	<0.001	2.31 (1.62–3.26)	<0.001	NA	NA	2.03 (1.26–3.34)	0.003	NA	NA
Noncardiovascular death*	247 (19.6)	75 (22.6)	90 (32.9)	<0.001	1.77 (1.39–2.25)	<0.001	NA	NA	1.31 (0.97–1.79)	0.08	NA	NA
HF hospitalization	320 (26.4)	160 (54.4)	230 (70.4)	<0.001	4.35 (3.67–5.16)	<0.001	2.49 (2.03–3.06)	<0.001	1.68 (1.38–2.06)	<0.001	1.22 (0.98–1.51)	0.08
Aortic valve-related death or HF hospitalization	417 (32.5)	183 (57.7)	307 (77.9)	<0.001	4.31 (3.71–5.00)	<0.001	2.75 (2.30–3.29)	<0.001	1.92 (1.60–2.31)	<0.001	1.21 (1.47–1.79)	<0.001

(**Table 3** continued the next page.)

	No HF	CHF	AHF		AHF vs. No HF				AHF vs. CHF			
	Total no. of patients with at least 1 event (cumulative 5-year incidence) (%)			Log-rank P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Initial AVR group: n=1,196 (No HF: 537, CHF: 389, AHF: 270)												
All-cause death	84 (17.3)	76 (25.2)	76 (33.0)	<0.001	2.12 (1.55–2.89)	<0.001	1.64 (1.14–2.36)	0.008	1.63 (1.18–2.24)	0.003	1.47 (1.03–2.11)	0.03
Cardiovascular death	53 (11.1)	48 (16.3)	50 (22.8)	<0.001	2.16 (1.47–3.18)	<0.001	1.49 (0.95–2.35)	0.08	1.66 (1.12–2.47)	0.01	1.44 (0.92–2.27)	0.1
Aortic valve-related death	25 (5.0)	20 (5.5)	23 (9.0)	0.04	1.96 (1.11–3.46)	0.02	1.15 (0.58–2.27)	0.7	1.74 (0.95–3.19)	0.07	1.30 (0.65–2.60)	0.5
Sudden death*	11 (3.0)	10 (3.5)	6 (4.3)	0.8	1.25 (0.43–3.28)	0.67	NA	NA	0.95 (0.32–2.57)	0.9	NA	NA
Aortic valve procedure-related death*	18 (3.3)	15 (4.0)	17 (6.8)	0.1	2.00 (1.02–3.90)	0.04	NA	NA	1.70 (0.85–3.45)	0.1	NA	NA
Noncardiovascular death*	31 (7.0)	28 (10.7)	26 (13.1)	0.02	2.04 (1.20–3.43)	0.009	NA	NA	1.58 (0.92–2.70)	0.1	NA	NA
HF hospitalization	24 (4.8)	40 (13.9)	38 (23.2)	<0.001	3.89 (2.33–6.49)	<0.001	3.20 (1.75–5.83)	<0.001	1.58 (1.01–2.47)	0.04	1.35 (0.81–2.27)	0.3
Aortic valve-related death and HF hospitalization	48 (10.1)	58 (18.0)	59 (27.5)	<0.001	2.86 (2.00–4.19)	<0.001	2.00 (1.29–3.11)	0.002	1.63 (1.13–2.34)	0.009	1.36 (0.90–2.05)	0.1

*Multivariable analysis was not performed because of insufficient number of patients with event. HR, hazard ratio; NA, not assessed. Other abbreviations as in Table 1.

follow-up duration of 1,123 days (IQR: 559–1,577), 1743 patients (45.7%) actually underwent surgical AVR (n=1703) or TAVI (n=40). The cumulative 5-year incidence of surgical AVR or TAVI was smaller in the AHF group than in the CHF group (**Figure 2A**,**B**). Notably, in the AHF group, surgical AVR was very rarely performed beyond 6 months after the index echocardiography. There were 17 patients for whom AVR or TAVI was performed as an emergency (no delay in providing operative intervention; n=3), urgently (surgery within 24 h of referral, n=12) or as a salvage (cardiopulmonary resuscitation en route to operating theatre or during anesthesia; n=2). Patients in the AHF group showed higher prevalence of emergency/urgent/salvage status as compared with the other groups (0.6% vs. 0.6% vs. 2.6% in the No HF, CHF and AHF groups, respectively, P=0.02).

The cumulative incidences of all-cause death and HF hospitalization were markedly higher in the AHF group than in the CHF and No HF groups (**Figure 3**, **Table 3**). After adjusting confounders, the excess risks of AHF relative to CHF and No HF, respectively, for all-cause death and HF hospitalization remained highly significant (**Table 3**). Similarly, the risks for other endpoints such as cardiovascular death, aortic valve-related death, and sudden death were significantly higher in the AHF group than in the CHF and No HF groups (**Table 3**).

Clinical Outcomes According to the Initial Treatment Strategy

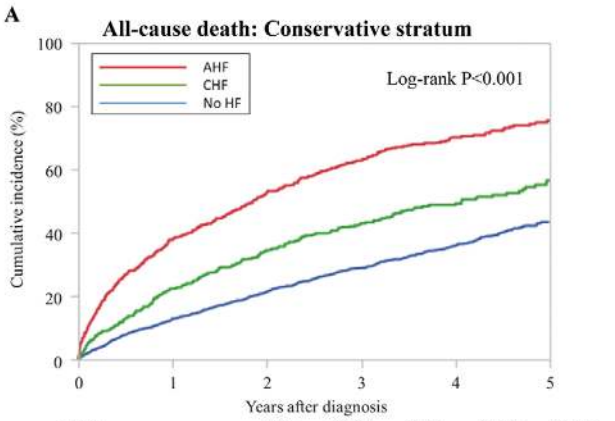
Regardless of the initial treatment strategy (initial AVR or conservative), the cumulative incidences of all-cause death and HF hospitalization were markedly higher in the AHF group than in the CHF and No HF groups, although the outcomes of AHF patients were remarkably better in the AVR stratum than those in the conservative stratum (**Figure 4**, **Table 3**). Even after adjusting for confounders, the excess risks of AHF relative to No HF for all-cause death and HF hospitalization remained highly significant in both the initial AVR and conservative strata (**Table 3**). The excess adjusted risk of AHF relative to CHF remained significant for all-cause death, but was no more significant for HF hospitalization in both the initial AVR and conservative strata (**Table 3**).

Determinants of the Choice for Initial AVR Strategy in the AHF Group

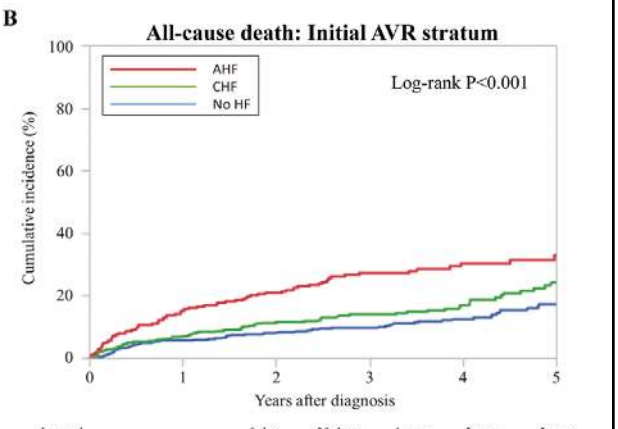
Initial AVR strategy, as opposed to a conservative strategy, was more likely to be chosen for AHF patients with low surgical risk scores (logistic EuroSCORE: 13.7 [IQR: 8.4–23.4]% vs. 18.3 [IQR: 11.4–30.5]%, P<0.001; EuroSCORE II: 5.3 [IQR: 2.9–8.8]% vs. 6.7 [IQR: 4.3–11.6]%, P<0.001; STS score: 6.3 [IQR: 3.7–10.4]% vs. 8.1 [IQR: 4.9–12.5]%, P<0.001). The independent predisposing factors for the choice of initial AVR strategy included very severe AS with V_{max} ≥5 m/s, while the independent predisposing factors for the choice of conservative strategy included advanced age, low BMI, hypertension, prior history of HF, prior history of coronary artery bypass grafting (CABG), liver cirrhosis, moderate to severe lung disease, and TRPG ≥40 mmHg (**Table 4**).

Sensitivity Analysis

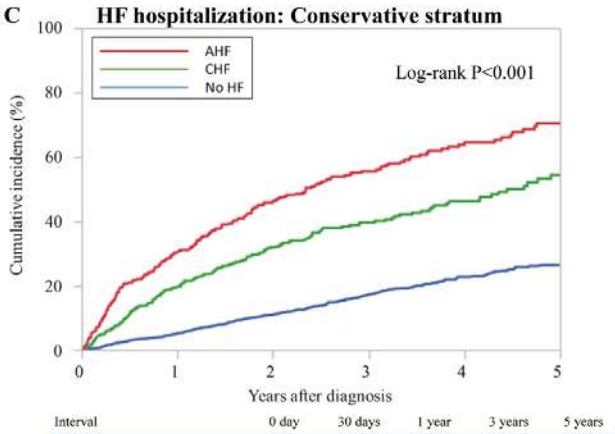
When patients who had CAD were excluded from the entire cohort and the remaining patients were divided into



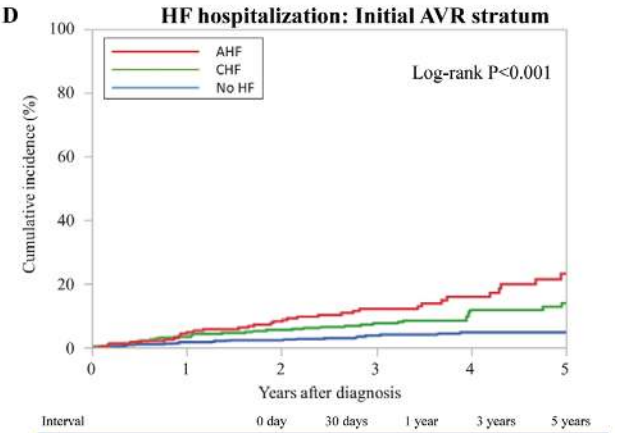
Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with event		30	209	455	575
N of patients at risk	1673	1613	1399	912	245
Cumulative incidence		1.8%	12.9%	28.9%	43.4%
CHF					
N of patients with event		17	91	171	202
N of patients at risk	424	395	313	189	61
Cumulative incidence		4.3%	22.6%	43.0%	57.2%
AHF					
N of patients with event		45	188	302	342
N of patients at risk	520	460	297	149	50
Cumulative incidence		8.8%	38.0%	63.0%	75.3%



Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with event		2	30	50	68
N of patients at risk	537	532	490	346	125
Cumulative incidence		0.4%	5.7%	9.7%	17.3%
CHF					
N of patients with event		3	27	51	67
N of patients at risk	389	385	341	238	79
Cumulative incidence		0.8%	7.4%	14.0%	25.2%
AHF					
N of patients with event		5	39	68	74
N of patients at risk	270	264	214	137	44
Cumulative incidence		2.2%	15.4%	27.2%	33.0%



Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with at least 1 event		10	79	230	291
N of patients at risk	1673	1606	1354	821	220
Cumulative incidence		0.6%	5.2%	17.2%	26.4%
CHF					
N of patients with at least 1 event		6	73	133	154
N of patients at risk	424	391	274	135	38
Cumulative incidence		1.5%	19.8%	39.7%	54.4%
AHF					
N of patients with at least 1 event		18	125	200	223
N of patients at risk	520	443	240	97	26
Cumulative incidence		3.8%	30.5%	55.6%	70.4%



Interval	0 day	30 days	1 year	3 years	5 years
No HF					
N of patients with at least 1 event		1	8	17	20
N of patients at risk	537	530	484	336	122
Cumulative incidence		0.2%	1.6%	3.7%	4.8%
CHF					
N of patients with at least 1 event		2	12	25	34
N of patients at risk	289	383	330	225	73
Cumulative incidence		0.5%	3.6%	7.5%	13.9%
AHF					
N of patients with at least 1 event		0	10	25	34
N of patients at risk	270	265	206	130	39
Cumulative incidence		0.0%	4.8%	12.1%	23.2%

Figure 4. Cumulative incidences of the primary outcome measures among the AHF, CHF, and No HF groups stratified by the initial therapeutic strategy. (**A**) All-cause death in the conservative stratum, (**B**) All-cause death in the initial AVR stratum, (**C**) HF hospitalization in the conservative stratum, and (**D**) HF hospitalization in the initial AVR stratum. Abbreviations as in Figure 1.

Table 4. Determinants of Initial AVR Strategy in AHF Group

Variables	Univariate analysis				Multivariate analysis		
	Initial AVR (n=270)	Conservative (n=520)	OR [Initial AVR vs. conservative]	P value	OR [Initial AVR vs. conservative]	95% CI	P value
Clinical characteristics							
Age ≥80 years	93 (34)	401 (77)	0.16	<0.001	0.14	0.09–0.21	<0.001
Male	110 (41)	134 (26)	1.98	<0.001	1.41	0.94–2.11	0.1
BMI <22 kg/m^2	171 (63)	399 (77)	0.52	<0.001	0.63	0.42–0.96	0.03
Hypertension	174 (64)	391 (75)	0.6	0.002	0.57	0.38–0.86	0.007
Current smoking	19 (7)	16 (3)	2.38	0.01	0.85	0.35–2.05	0.71
Dyslipidemia	85 (31)	130 (25)	1.38	0.05	1.5	0.99–2.27	0.06
Diabetes on insulin therapy	13 (5)	21 (4)	1.2	0.61	1.29	0.52–3.07	0.57
Prior HF	42 (16)	192 (37)	0.31	<0.001	0.31	0.20–0.48	<0.001
Prior MI	20 (7)	69 (13)	0.52	0.01	0.73	0.36–1.45	0.37
Prior PCI	21 (8)	67 (13)	0.57	0.03	0.67	0.32–1.35	0.26
Prior CABG	5 (2)	27 (5)	0.34	0.02	0.29	0.08–0.87	0.03
Prior symptomatic stroke	24 (9)	85 (16)	0.5	0.003	0.87	0.48–1.53	0.63
History of atrial fibrillation or flutter	55 (20)	164 (32)	0.56	<0.001	0.65	0.42–1.0	0.052
Aortic/peripheral vascular disease	44 (16)	69 (13)	1.27	0.25	1.33	0.77–2.27	0.31
Creatinine level >2 mg/dL without hemodialysis	5 (2)	60 (12)	0.14	<0.001	0.58	0.27–1.20	0.15
Hemodialysis	28 (10)	32 (6)	1.76	0.04	0.81	0.41–1.58	0.54
Anemia*	165 (61)	413 (79)	0.41	<0.001	0.83	0.56–1.25	0.38
Liver cirrhosis	1 (0.4)	8 (2)	0.23	0.11	0.05	0.002–0.37	0.002
Malignancy currently under treatment	8 (3)	14 (3)	1.1	0.83	0.87	0.28–2.52	0.8
Chronic lung disease (moderate or severe)	6 (2)	24 (5)	0.47	0.08	0.32	0.1–0.9	0.03
Echocardiographic variables							
V_{max} ≥5 m/s	89 (33)	85 (16)	2.52	<0.001	2.65	1.72–4.12	<0.001
LVEF <50%	109 (40)	170 (33)	1.39	0.03	1.42	0.96–2.10	0.08
Any combined valvular disease (moderate or severe)	148 (55)	327 (63)	0.72	0.03	1.01	0.69–1.49	0.95
TRPG ≥40 m/s	64 (24)	165 (32)	0.67	0.02	0.63	0.41–0.96	0.03

Values are number (%). *Anemia as defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women; <13.0 g/dL in men). Abbreviations as in Tables 1,2.

2 groups [viz. AHF group (n=544) and No AHF group (n=2,137)], cumulative 5-year incidences of all-cause death and HF hospitalization were markedly higher in the AHF group as compared with the No AHF group, confirming the dismal prognosis of AHF associated with severe AS observed in the main analysis (all-cause death: 59.1% vs. 36.0%, P<0.001, HF hospitalization: 48.8% vs. 21.2% in the AHF group and No AHF group, respectively) (**Figure S1A,B**).

Discussion

The main findings in the present study were as follows: (1) the prognosis of patients with severe AS complicated by AHF was poor, with extremely high rates of all-cause death and HF hospitalization; (2) AHF patients as compared with CHF patients less frequently underwent AVR, and had higher long-term mortality rates even after AVR; (3) several clinical and echocardiographic factors were found to predispose to the development of AHF, which might help identify appropriate candidates for early AVR before the emergence of AHF.

Large-scale cohort studies in this decade have demonstrated that AHF in general is disruptive with high mortality and morbidity.[5–8] Management of AHF complicating severe AS is particularly challenging because patients easily develop severe congestion or acute decline in cardiac output because of high afterload and an obstructive valve. Serious clinical conditions from multiple comorbidities may also contribute to the worse prognosis of AHF complicating severe AS. Furthermore, AHF may be evoked as a result of long-standing high afterload in the left ventricle in patients with severe AS. For those patients, irreversible pathological changes caused by high mechanical stress may lead to a sustained high risk of adverse events even after AVR. Indeed, using cardiac magnetic resonance imaging, Barone et al reported that approximately 30% of patients with AS showed focal replacement myocardial fibrosis before AVR, which had postoperative and long-term prognostic value.[14] Therefore, once AHF develops in patients with severe AS, it often leads to a dismal outcome regardless of the chosen therapeutic strategies. To improve the clinical outcomes of patients with severe AS, an early AVR strategy before emergence of AHF is warranted.

Factors Associated With Development of AHF Complicating Severe AS

Regarding clinical symptoms, we found that patients with

syncope were less often found in the AHF group as compared with the No HF group. This reflects the complex pathophysiology of severe AS in which a narrowed aortic valve causes distinct clinical manifestations such as elevated global LV afterload, decreased tissue perfusion, inappropriate reflex vasodilation and primary cardiac arrhythmia.[15]

Very severe AS with V_{max} ≥5 m/s and low LVEF were among the echocardiographic parameters related to development of AHF. This result is consistent with previous reports showing that asymptomatic patients with very severe AS and/or low LVEF showed a poor prognosis and supports the current recommendation of AVR in asymptomatic patients with very severe AS and/or low LVEF.[16–18]

Prevalence of anemia in the AHF group was 73%, which was much higher than in the CHF group (55%) or in a previous report on patients with severe AS (57%).[19] The link between anemia and poor outcome in HF is well established.[20,21] Several underlying mechanisms, such as iron deficiency, chronic kidney disease (CKD) and bone marrow dysfunction, have been postulated as the background for anemia in patients with congestive HF.[22–24] Heyde's syndrome could also be an important mechanism for anemia in patients with severe AS.[25] Correction of anemia might be a therapeutic option in the medical management of severe AS.

Our study also identified lower BMI as a risk factor for developing AHF. One possible explanation for this is that lower BMI in our study represented 'cardiac cachexia' in which metabolic, neurohormonal and immune abnormalities evoked by hemodynamic alteration lead to negative energy balance and poor prognosis.[26,27] Alternatively, the result may be related to the protective effect of adiposity known as the 'obesity paradox', although its validity is still under debate.[28–30]

CKD is a well-established risk factor of HF.[31,32] In the present study, although an elevated creatinine level showed a trend towards being related to the development of AHF, hemodialysis was a negative predictor for developing AHF. Strict body fluid control under hemodialysis may cancel the potential risk of acute congestion with CKD. Nonetheless, advanced CKD is known to be associated with a rapid progression of AS and poor outcome after surgical AVR or TAVI.[33–36] Further studies of better risk stratification and treatment strategy in this high-risk category are needed.

Decision-Making for Patients With AHF Complicating Severe AS

Advanced age, low BMI, hypertension, prior history of HF, prior history of CABG, liver cirrhosis, moderate to severe lung disease, and TRPG ≥40 mmHg were identified as independent predisposing factors to the choice of a conservative strategy. Some patients with these factors might have been deemed to be inoperable. However, considering the present results of a dismal prognosis in conservatively managed patients, careful assessment of the operative risks and clinical benefits of AVR among these high-risk patients is required. It should be acknowledged that most of the data in the present study were from the period before the introduction of TAVI. Further studies are needed to evaluate whether this less-invasive strategy could improve the prognosis of patients with severe AS complicated by AHF.

Study Limitations

In this study, a significant proportion of patients were enrolled as severe AS based solely on AVA <1.0 cm^2. Those patients with low-gradient AS might well represent a heterogeneous population in whom the indication of AVR is still controversial. However, excluding patients with low-gradient AS would be inappropriate in evaluating severe AS patients with AHF, because transaortic PG tends to decrease with worsening LV pump function.[37] Second, because of the retrospective study design, not all the information regarding biomarkers, hemodynamic parameters and medications possibly related to AHF were available.[38–40] Third, retrospectively confirming the diagnosis of CHF and AHF based on the types of symptoms could potentially lead to incomplete or inaccurate categorization. Therefore, we categorized AHF and CHF according to whether or not hospitalized management was required to avoid the ambiguity of symptom-based categorization. Our results for NYHA and BNP, which were closely related with the time course and severity of HF, were consistent with the previous large cohorts of AHF.[38,41] Furthermore, we consistently found a dismal prognosis of AHF associated with severe AS in the sensitivity analysis. Therefore, we believe that the patients in each group would appropriately represent the clinical profiles of AHF, CHF, and No HF associated with severe AS. Fourth, the low prevalence of an initial AVR strategy in AHF patients would indicate suboptimal practice non-compliant with current guidelines, although it may well represent real clinical practice.[18] Finally, it should also be acknowledged that the risk factors identified as predisposing to AHF did not disclose causality.

Conclusions

In this observational registry of patients with severe AS, AHF was associated with a dismal prognosis with extremely high mortality rate, which could not be fully resolved by AVR after AHF. Careful management to avoid development of AHF is crucial for patients with severe AS.

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Disclosures

None.

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Supplementary Files

Supplementary File 1

Supplementary Methods

Appendix S1. List of Investigators

Figure S1. Sensitivity analysis.

Please find supplementary file(s);
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Supplementary File

Acute Heart Failure in Patients With Severe Aortic Stenosis
— Insights From the CURRENT AS Registry —

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Supplementary File 1

Supplementary Methods

Definitions of the Clinical Events

Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. Aortic valve procedure-related death was defined as any death during the hospitalization for surgical aortic valve replacement or transcatheter aortic valve implantation. Aortic valve-related death included aortic valve procedure-related death, sudden death, and death from HF presumably related to aortic stenosis.

Appendix S1. List of Investigators

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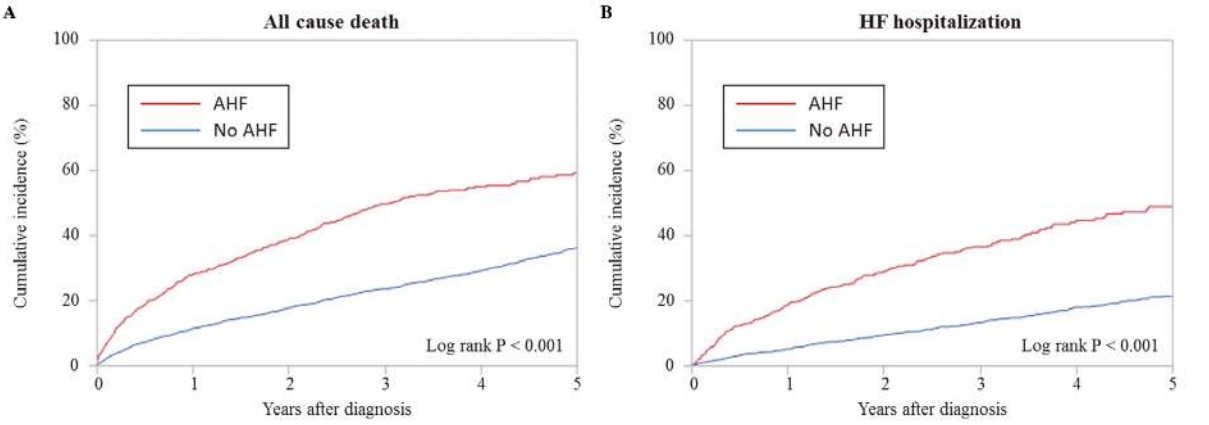

Interval	0 day	30 days	1 year	3 years	5 years
No AHF					
N of patients with event		34	234	469	600
N of patients at risk	2137	2064	1804	1233	410
Cumulative incidence		1.6%	11.3%	23.5%	36.0%
AHF					
N of patients with event		30	144	246	273
N of patients at risk	544	500	361	194	69
Cumulative incidence		5.6%	27.7%	49.5%	59.1%

Interval	0 day	30 days	1 year	3 years	5 years
No AHF					
N of patients with at least 1 event		16	99	233	304
N of patients at risk	2137	2052	1751	1143	371
Cumulative incidence		0.8%	5.1%	13.2%	21.2%
AHF					
N of patients with at least 1 event		10	84	146	169
N of patients at risk	544	491	318	164	54
Cumulative incidence		1.9%	18.6%	36.4%	48.8%

Figure S1. Sensitivity analysis. Cumulative incidence of (**A**) all-cause death and (**B**) HF hospitalization when patients without coronary artery disease were divided into 2 groups: acute heart failure (AHF) group (n=544) and No AHF group (n=2,137).