

# Sudden Death in Patients With Severe Aortic Stenosis: Observations From the CURRENT AS Registry

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**Background**—The annual incidence of sudden death has been reported to be low (<1%/year) in asymptomatic patients with severe aortic stenosis (AS), and there is a paucity of data on the risk factors of sudden death in patients with severe AS.

**Methods and Results**—We evaluated the incidence and risk factors of sudden death during the median follow-up period of 1334 days in the Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis (CURRENT AS) registry enrolling 3815 consecutive patients with severe AS between 2003 and 2011. The mean age was 78 years, and the prevalences of male sex and prior myocardial infarction were 38% and 8%, respectively. Sudden death occurred in 175 patients without aortic valve replacement. The cumulative 5-year incidences of sudden death, censored at aortic valve replacement, which accounted for the competing risk, were 9.2% in symptomatic patients and 7.2% (1.4%/year) in asymptomatic patients ( $P<0.001$ ). Among 82 asymptomatic patients experiencing sudden death, 54 patients (66%) died abruptly without any preceding symptoms, and 35 (65%) of these sudden deaths occurred within 3 months of the last clinical follow-up visit. Independent risk factors for sudden death were hemodialysis (hazard ratio [HR] 3.63; 95% confidence interval [CI] 2.42-5.43), prior myocardial infarction (HR 2.11; 95% CI 1.28-3.50), body mass index <22 (HR 1.51; 95% CI 1.03-2.21), peak aortic jet velocity  $\geq 5$  m/s (HR 1.76; 95% CI 1.12-2.78), and left ventricular ejection fraction <60% (HR 1.52; 95% CI 1.08-2.14).

**Conclusions**—The incidence of sudden death in asymptomatic patients with severe AS might be higher than that reported in previous reports. Several baseline clinical and echocardiographic characteristics were associated with increased risk of sudden death.

**Clinical Trial Registration**—URL: [www.umin.ac.jp/ctr/index.htm](http://www.umin.ac.jp/ctr/index.htm). Unique identifier: UMIN000012140. (*J Am Heart Assoc.* 2018;7:e008397. DOI: 10.1161/JAHA.117.008397.)

**Key Words:** aortic stenosis • aortic valve replacement • sudden death

**A**ortic stenosis (AS) is a progressive disease, and survival during the asymptomatic phase has been reported to be similar to that of age-matched controls with a low risk of

sudden death when patients were followed prospectively and promptly report symptom onset.<sup>1-3</sup> The current guidelines generally recommend a strategy of watchful waiting until

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Accompanying Appendix S1, Data S1, Table S1, and Figure S1 are available at <http://jaha.ahajournals.org/content/7/11/e008397/DC1/embed/inline-supplementary-material-1.pdf>

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Received December 19, 2017; accepted April 12, 2018.

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## Clinical Perspective

### What Is New?

- This is the first large-scale report examining the incidence of sudden death and the risk factors associated with sudden death in a contemporary multicenter registry of consecutive patients with severe aortic stenosis.
- The incidence of sudden death in asymptomatic patients with severe aortic stenosis might be higher than that reported in previous studies. The cumulative 5-year incidence of sudden death censored at aortic valve replacement, accounting for the competing risk, was 7.2% (1.4%/year) in asymptomatic patients.
- Several clinical and echocardiographic characteristics were found to be significantly associated with the risk of sudden death, particularly hemodialysis, prior myocardial infarction, body mass index <22, peak aortic jet velocity  $\geq 5$  m/s, and left ventricular ejection fraction <60%.

### What Are the Clinical Implications?

- Identification of characteristics associated with an increased risk for sudden death might improve the understanding of potential mechanisms.
- Baseline clinical factors can help inform sudden death risk stratification. We should take these risk factors for sudden death into account when we decide the appropriate timing for surgical or transcatheter intervention.

symptoms emerge for aortic valve replacement (AVR) in asymptomatic patients with severe AS, based on the low annual incidence of sudden death (<1%/year) in asymptomatic patients with severe AS.<sup>1,3-7</sup> However, the low annual incidence of sudden death was reported mostly from small single-center studies conducted in the 1990s and 2000s. Inclusion of relatively younger patients in these studies might not allow us to extrapolate these findings to contemporary patients with more advanced age. There is a paucity of data regarding the predictive factors for an increased risk of sudden death in patients with severe AS, although nearly 70% of sudden death episodes were not preceded by any of the classical AS symptoms.<sup>3-5</sup> Therefore, we sought to investigate the incidence of sudden death and the risk factors associated with sudden death in a large contemporary multicenter registry of consecutive patients with severe AS.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study Population

The Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe Aortic Stenosis (CURRENT AS) registry is a multicenter, retrospective registry enrolling consecutive patients with severe AS among 27 centers (on-site surgical facility in 20 centers) in Japan between 2003 and 2011 (Data S1). The design and patient enrollment of the CURRENT AS registry have been described previously.<sup>6</sup> The institutional review boards in all participating centers approved the protocol. This study included 3815 patients who met the definition of severe AS (peak aortic valve velocity >4.0 m/s, mean aortic pressure gradient >40 mm Hg, or aortic valve area <1.0 cm<sup>2</sup>) for the first time during the study period.<sup>7,8</sup> Written informed consent from each patient was waived because clinical information was obtained from the routine practice, and no patient refused to participate in the study when contacted for follow-up. Among the 3815 study patients, 2618 were managed with the conservative strategy in which AVR was not planned based on the findings of the index echocardiography, and 1197 patients were managed with the initial AVR strategy in which AVR was planned based on the findings of the index echocardiography. Collection of baseline clinical information including symptomatic status was conducted through hospital chart or database review. Symptoms related to AS at baseline were classified into angina, syncope, and heart failure including both acute heart failure requiring hospitalization and chronic exertional dyspnea. Patients were deemed to be asymptomatic at baseline if they were described as asymptomatic or there were no records regarding the symptoms related to AS defined above. Among 3815 patients enrolled in the registry, there were 2005 patients with and 1808 patients without AS-related symptoms at the time of index echocardiography, excluding 2 patients whose symptomatic status was not available. Follow-up was commenced on the day of the index echocardiography.

All patients underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation in each participating center according to the guidelines.<sup>9</sup> Peak and mean aortic pressure gradient were obtained with the use of the simplified Bernoulli equation, and aortic valve area was calculated using the standard continuity equation and indexed to body surface area.

## Outcome Measures

The primary outcome measure in the current analysis was sudden death. Sudden death was defined as death that occurred suddenly and unexpectedly in previously stable patients, in whom specific causes of sudden death were not identified other than severe AS. Death was not judged as

sudden death if the death was confirmed to be due to other causes such as myocardial infarction or acute aortic dissection. The causes of death were classified according to the Valve Academic Research Consortium definitions and were adjudicated by a clinical event committee (Data S1).<sup>10,11</sup> A 3-member adjudication committee composed of 3 cardiologists reviewed the details of deaths. When the members disagreed on the causes of death, a final decision was made by consensus.

## Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were reported as the mean and SD or median and interquartile range. Cumulative incidence of sudden death in asymptomatic and symptomatic patients as well as the entire population was estimated by the Gray method, which accounted for the competing risk of death other than sudden death.<sup>12</sup> We estimated the cumulative incidence of sudden death both with and without censoring at surgical or transcatheter AVR. A multivariable Cox regression model described by Fine and Gray was developed to identify clinical and echocardiographic characteristics associated with an increased risk for sudden death with censoring at surgical or transcatheter AVR in the entire cohort, accounting for the competing risk of death other than sudden death.<sup>13</sup> Consistent with our previous report,<sup>6</sup> we used 20 clinically relevant potential factors listed in Table 1 in the multivariable Cox proportional hazard models, and the centers were incorporated as the stratification variable. We also explored the clinical characteristics associated with sudden death in asymptomatic and symptomatic patients. We constructed parsimonious models with a limited number of potential risk factors for sudden death in asymptomatic and symptomatic patients with severe AS because the number of patients with this event was too small in this subgroup. We thus selected 10 clinically relevant factors as the potential risk factors with strong evidence as listed in Table 1 for parsimonious models. This was consistent with our previous report<sup>14</sup> except for the addition of prior myocardial infarction, male sex, body mass index <22, and left ventricular ejection fraction (LVEF). We included LVEF <60% instead of the traditional LVEF <50% as a potential risk predictor because we previously reported that the negative prognostic impact of LVEF 50% to 59% was comparable to that of LVEF <50% in patients with severe AS who were managed conservatively.<sup>15</sup> As the subgroup analyses, we assessed the cumulative incidence of sudden death in patients with hemodialysis (HD) (N=405) and non-HD patients (N=3410) because we previously reported an extremely high rate of sudden death in HD patients.<sup>14</sup> We also explored the clinical characteristics associated with sudden death in non-HD patients. Statistical

analyses were conducted by a physician (T. Taniguchi) and a statistician (T. Morimoto) with the use of JMP 10.0.2 (SAS Institute Inc, Cary, NC) or SAS 9.4 (SAS Institute Inc, Cary, NC). All reported *P* values were 2 tailed, and *P*<0.05 was considered statistically significant.

## Results

### Baseline Clinical and Echocardiographic Characteristics

Among the 3815 patients with severe AS enrolled in this registry, the mean age was 77.8 years, and 1443 patients (38%) were male. Clinical and echocardiographic characteristics of the entire cohort are shown in Table 1. The prevalence of prior myocardial infarction was 8%. The peak aortic jet velocity was 4.1±0.9 m/s, and aortic valve area was 0.72±0.18 cm<sup>2</sup> (Table 1). There were 405 patients (11%) with HD, and 1808 patients (47%) were asymptomatic at baseline. Symptomatic patients at baseline were much older and more often had coronary artery disease, atrial fibrillation or flutter, or anemia than asymptomatic patients. Surgical risk scores such as Logistic EuroSCORE, EuroSCORE II, and Society of Thoracic Surgeons score were significantly higher in symptomatic patients than in asymptomatic patients. Regarding the echocardiographic parameters, symptomatic patients compared with asymptomatic patients had lower LVEF, larger left ventricular dimensions, and higher incidence of pulmonary hypertension. Symptomatic patients more often had greater AS severity and combined valvular disease such as mitral regurgitation, tricuspid regurgitation, and aortic regurgitation.

### Incidences of Sudden Death

The median follow-up period of the surviving patients in the entire cohort was 1334 (interquartile range 1019–1701) days with 93% follow-up rate at 2-years. Sudden death occurred in 175 patients and in 196 patients with and without censoring at surgical AVR or TAVI, respectively. The cumulative 5-year incidences of sudden death in the entire cohort were 8.0% and 5.7% (1.6%/year and 1.1%/year) with and without censoring at surgical AVR or transcatheter aortic valve implantation (TAVI), respectively (Figure 1).

Among 175 patients with sudden death with censoring at surgical AVR or TAVI, 139 (79%) sudden deaths occurred out of hospital. Eleven patients died suddenly while waiting for surgical AVR or TAVI, and 10 patients with HD had sudden death during dialysis. Among 82 patients with sudden death who did not have any symptoms at baseline, 54 patients (66%) died abruptly without preceding symptoms, and 35 (65%) of these sudden deaths with no

**Table 1.** Baseline Clinical and Echocardiographic Characteristics in the Entire Cohort

Variables	Whole Cohort	Symptomatic	Asymptomatic	P Value
	N=3815	N=2005	N=1808	
<b>Clinical characteristics</b>				
Age, y	77.8±9.8	78.6±9.8	76.8±9.6	<0.001
Age ≥80 y*	1729 (45%)	978 (49%)	749 (41%)	<0.001
Male*	1443 (38%)	713 (36%)	730 (40%)	0.002
BMI, kg/m <sup>2</sup>	21.8±3.8	21.6±3.8	22.0±3.8	0.01
BMI <22 kg/m <sup>2</sup> *	2326 (61%)	1268 (63%)	1057 (58%)	0.003
BSA, m <sup>2</sup>	1.46±0.18	1.44±0.19	1.47±0.18	<0.001
Hypertension*	2667 (70%)	1418 (71%)	1248 (69%)	0.25
Current smoking*	196 (5%)	101 (5%)	95 (5%)	0.76
History of smoking	830 (22%)	428 (21%)	402 (22%)	0.51
Dyslipidemia	1327 (35%)	679 (34%)	648 (36%)	0.20
On statin therapy	970 (25%)	506 (25%)	464 (26%)	0.76
Diabetes mellitus	897 (24%)	463 (23%)	434 (24%)	0.51
On insulin therapy*	188 (5%)	97 (5%)	91 (5%)	0.78
Prior myocardial infarction*	323 (8%)	172 (9%)	151 (8%)	0.80
Coronary artery disease*	1144 (30%)	656 (33%)	488 (27%)	<0.001
Prior PCI	502 (13%)	216 (11%)	286 (16%)	<0.001
Prior CABG	199 (5%)	101 (5%)	98 (5%)	0.60
Prior open-heart surgery	316 (8%)	151 (8%)	165 (9%)	0.07
Prior symptomatic stroke*	503 (13%)	249 (12%)	253 (14%)	0.15
Atrial fibrillation or flutter*	828 (22%)	490 (24%)	338 (19%)	<0.001
Aortic/peripheral vascular disease*	282 (7%)	111 (6%)	171 (9%)	<0.001
Serum creatinine, mg/dL	0.9 (0.7-1.3)	0.9 (0.7-1.3)	0.8 (0.7-1.2)	<0.001
Creatinine level >2 mg/dL	558 (15%)	309 (15%)	249 (14%)	0.15
Hemodialysis*	405 (11%)	198 (10%)	207 (11%)	0.12
Anemia*†	2117 (55%)	1254 (63%)	862 (48%)	<0.001
Liver cirrhosis (Child-Pugh B/C)	38 (1%)	27 (1%)	11 (1%)	0.02
Malignancy	517 (14%)	240 (12%)	276 (15%)	0.003
Malignancy currently under treatment*	149 (4%)	55 (3%)	94 (5%)	<0.001
Chest wall irradiation	25 (1%)	13(1%)	12 (1%)	0.95
Immunosuppressive therapy	131 (3%)	71 (4%)	60 (3%)	0.71
Chronic lung disease	400 (10%)	239 (12%)	161 (9%)	0.002
Chronic lung disease (moderate or severe)*	112 (3%)	69 (3%)	43 (2%)	0.052
Logistic EuroSCORE, %	9.7 (5.8-16.7)	11.4 (6.6-20.0)	8.4 (5.1-13.9)	<0.001
EuroSCORE II, %	2.9 (1.6-4.8)	3.6 (2.0-6.3)	2.4 (1.4-3.6)	<0.001
STS score (PROM), %	3.8 (2.2-6.6)	4.5 (2.5-8.0)	3.3 (2.0-5.2)	<0.001
Symptom related to AS*	2005 (53%)			
Chest pain	498	498	0	...
Syncope	198	198	0	...
Heart failure	1603	1603	0	...
HF hospitalization at the index echocardiography	790 (21%)	790	0	...

Continued

Table 1. Continued

Variables	Whole Cohort	Symptomatic	Asymptomatic	P Value
	N=3815	N=2005	N=1808	
<b>Echocardiographic variables</b>				
$V_{max}$ , m/s	4.1±0.9	4.3±0.9	3.9±0.8	<0.001
$V_{max} \geq 5$ m/s*	698 (18%)	490 (24%)	207 (11%)	<0.001
$V_{max} \geq 4$ m/s	2185 (57%)	1320 (66%)	864 (48%)	<0.001
Peak aortic PG, mm Hg	72±32	78±33	65±28	<0.001
Mean aortic PG, mm Hg	41±20	45±21	36±17	<0.001
AVA (equation of continuity), cm <sup>2</sup>	0.72±0.18	0.67±0.19	0.77±0.17	<0.001
Indexed AVA, cm <sup>2</sup> /m <sup>2</sup>	0.50±0.13	0.47±0.13	0.53±0.12	<0.001
LV end-diastolic diameter, mm	45.9±7.0	47.0±7.6	44.8±6.0	<0.001
LV end-systolic diameter, mm	30.2±7.9	31.9±8.8	28.4±6.2	<0.001
LVEF, %	62.8±13.5	59.9±14.9	65.9±10.9	<0.001
LVEF <50%	593 (16%)	451 (22%)	142 (8%)	<0.001
LVEF <60%*	1153 (30%)	798 (40%)	355 (20%)	<0.001
IVST in diastole, mm	11.3±2.3	11.6±2.4	11.1±2.2	<0.001
PWT in diastole, mm	11.0±2.0	11.2±2.1	10.7±2.0	<0.001
Any combined valvular disease (moderate or severe)*	1558 (41%)	997 (50%)	560 (31%)	<0.001
Moderate or severe AR	791 (21%)	497 (25%)	293 (16%)	<0.001
Moderate or severe MS	133 (3%)	84 (4%)	49 (3%)	0.01
Moderate or severe MR	763 (20%)	550 (27%)	213 (12%)	<0.001
Moderate or severe TR	628 (16%)	412 (21%)	216 (12%)	<0.001
TR pressure gradient $\geq 40$ mm Hg*	606 (16%)	433 (22%)	173 (10%)	<0.001
<b>Treatment strategy</b>				
Initial AVR strategy	1197 (31%)	905 (45%)	291 (16%)	<0.001
Conservative strategy	2618 (69%)	1100 (55%)	1517 (84%)	

Comparison between symptomatic and asymptomatic patients was performed after excluding 2 patients whose symptomatic status was not available. Abbreviations: 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; HF, heart failure; IVST, interventricular septum thickness; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; PCI, percutaneous coronary intervention; PG, pressure gradient; PROM, predicted risk of mortality; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation;  $V_{max}$ , peak aortic jet velocity.

\*Potential independent variables selected for the Cox proportional hazard model.

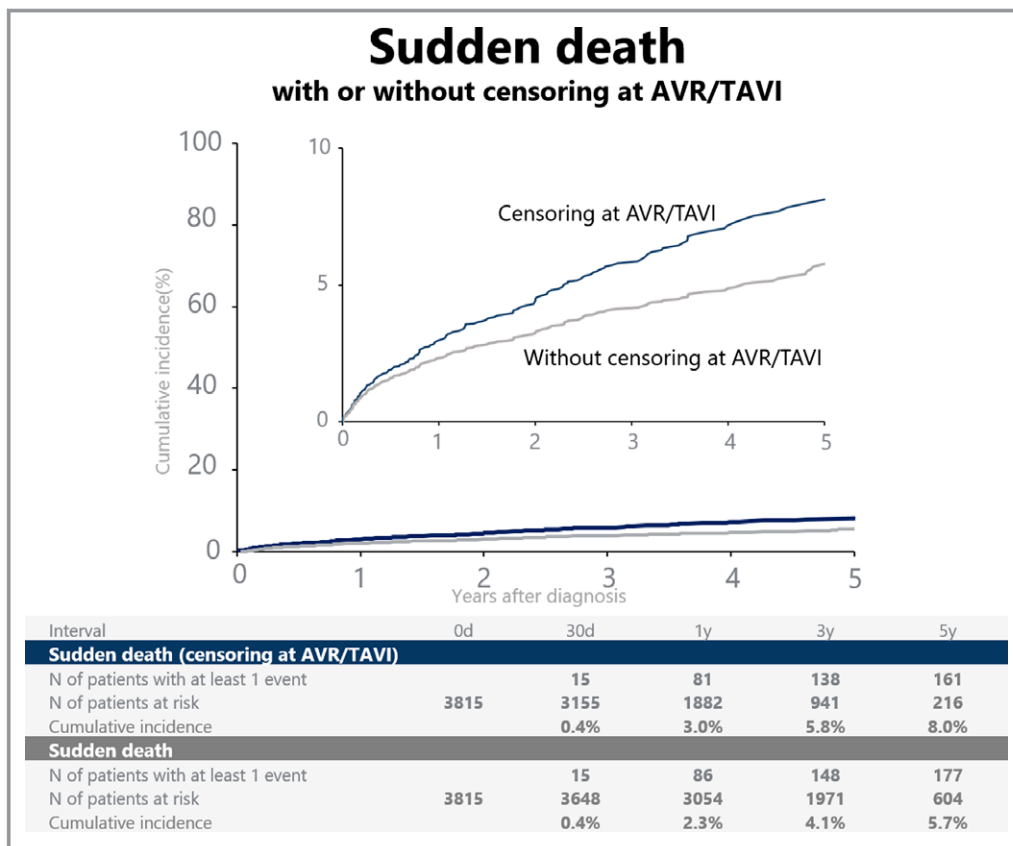
†Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

preceding symptoms occurred within 3 months of the last clinical follow-up visit.

The cumulative 5-year incidence of sudden death was significantly higher in symptomatic patients than in asymptomatic patients (9.2% [N=93/2005] versus 7.2% [N=82/1808],  $P=0.008$ ; 1.8%/year and 1.4%/year) (Figure 2). The cumulative 5-year incidence of sudden death in asymptomatic patients with severe AS was 5.8% without censoring at surgical AVR or TAVI. The cumulative 5-year incidence of sudden death was markedly higher in the HD group than in the non-HD group (23.3% versus 6.5%,  $P<0.001$ ; 4.7%/year and 1.3%/year) (Figure S1).

## Clinical Characteristics Associated With Sudden Death

Independent predictors associated with a higher risk for sudden death included HD (hazard ratio [HR] 3.63; 95% confidence interval [CI] 2.42-5.43), prior myocardial infarction (HR 2.11; 95% CI 1.28-3.50), body mass index <22 (HR 1.51; 95% CI 1.03-2.21), peak aortic jet velocity  $\geq 5$  m/s (HR 1.76; 95% CI 1.12-2.78), and LVEF<60% (HR 1.52; 95% CI 1.08-2.14) (Table 2). The results after exclusion of HD patients were consistent with those from the main analysis set (Table S1). Independent predictors for sudden death in



**Figure 1.** Kaplan-Meier curves for sudden death in the entire cohort with and without censoring at AVR/TAVI. Cumulative incidence of sudden death was estimated by the Gray method, taking the competing risk of death other than sudden death. AVR indicates aortic valve replacement; TAVI, transcatheter aortic valve implantation.

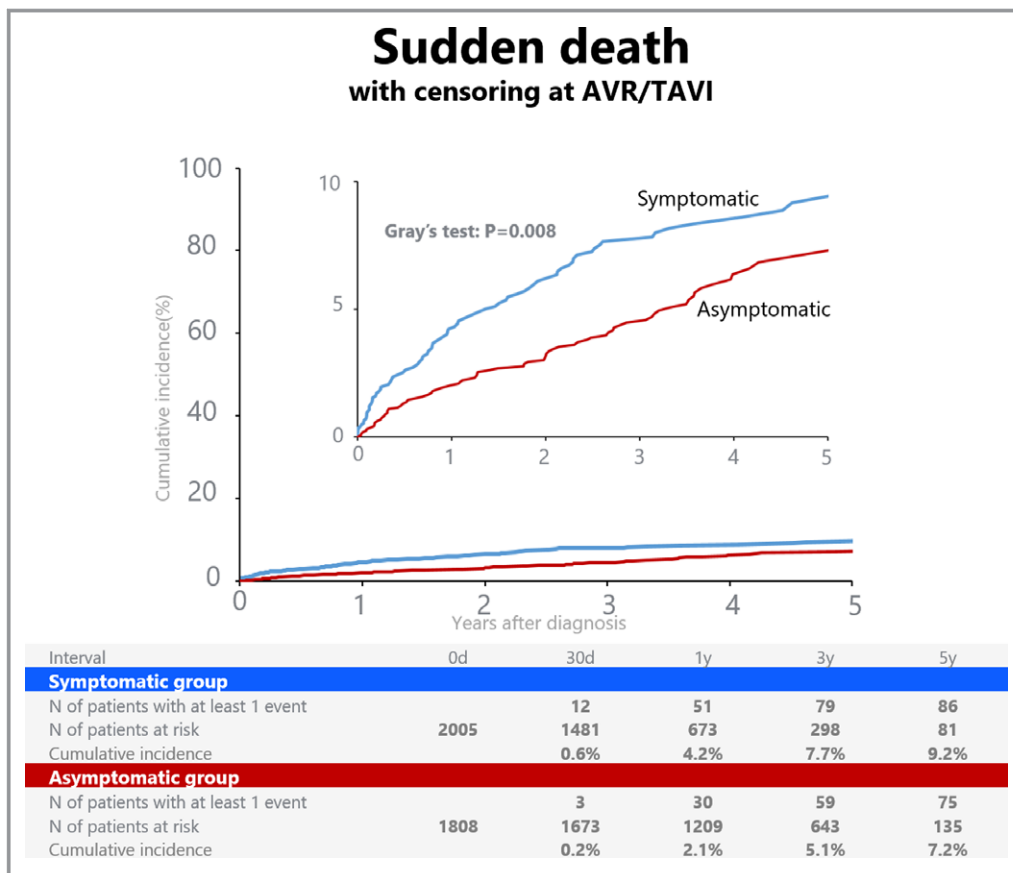
asymptomatic and symptomatic patients were consistent with those identified in the entire cohort (Table 3).

## Discussion

The main findings of the present study were the following: (1) the incidence of sudden death in asymptomatic patients with severe AS might be higher than that reported in previous studies; (2) we identified several baseline clinical characteristics as well as echocardiographic parameters that were associated with increased risk of sudden death in patients with severe AS, including potent predictors such as HD, prior myocardial infarction, and modest predictors such as body mass index  $<22$ , baseline peak aortic valve velocity  $\geq 5$  m/s, and LVEF  $<60\%$ .

Sudden death in patients with severe AS is a clinically important issue. Previous studies have reported relatively low annual risk of sudden death ( $<1\%/year$ ) in asymptomatic patients with severe AS (Rosenhek et al, 1 out of 106 patients [0.42%/year], mean age of 57 years<sup>1</sup>; Pellikka et al, 11 out of 270 patients [0.75%/year], mean age of 72 years<sup>3</sup>; Kang

et al, 9 out of 95 patients [1.9%/year], mean age of 63 years<sup>16</sup>; and Rosenhek et al, 1 out of 116 patients [0.3%/year], mean age of 67 years<sup>2</sup>). In the present contemporary multicenter study, however, the annual risk of sudden death censored at surgical or transcatheter AVR (1.4%/year) was numerically higher than those reported in previous studies in asymptomatic patients with severe AS. One of the possible reasons for the seemingly higher rate of sudden death might be related to the more advanced age in the present study population, who often have multiple comorbidities such as HD and prior myocardial infarction predisposing to sudden death. Another possible reason might be the difference in the modes of clinical follow-up between the single-center and multicenter studies. In smaller single-center studies, patients might have been followed more closely than in larger multicenter studies. Closer follow-up would make it possible to detect emergence of symptoms earlier. Pellikka et al reported that no patient had sudden death unpreceded by symptoms in their earlier small study (N=113).<sup>17</sup> However, in their later study with a larger cohort, 11 out of 270 patients who did not undergo surgical AVR experienced sudden death



**Figure 2.** Kaplan-Meier curves for sudden death: symptomatic and asymptomatic patients with severe AS after excluding 2 patients whose symptomatic status was not available. Cumulative incidence of sudden death was estimated by the Gray method, taking the competing risk of death other than sudden death. AS indicates aortic stenosis; AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

without any preceding symptoms.<sup>3</sup> In the present study as well as in the aggregates of the previous studies, sudden death often occurs without any preceding symptoms in asymptomatic patients with severe AS. Absence of the preceding symptoms might be related to the difficulties in interpreting mild symptoms as aortic valve–related symptoms in elderly patients with a sedentary lifestyle. Therefore, the strategy of watchful waiting for the emergence of symptoms might not be very effective in preventing sudden death.

It would be important to identify those asymptomatic severe AS patients who are at high risk for sudden death. The strengths of the present study include (1) assessment of the incidence of sudden death in consecutive patients both with or without AS-related symptoms, (2) inclusion of large numbers of patients enough to explore the baseline characteristics independently associated with sudden death, and (3) a contemporary multicenter cohort of patients with severe AS including hemodialysis patients. Several baseline clinical characteristics as well as echocardiographic parameters such as HD, and prior myocardial infarction as well as greater peak

aortic valve velocity, lower LVEF, and smaller body mass index were significantly associated with increased risk of sudden death in patients with severe AS. This is the first large-scale contemporary multicenter study reporting the incidence of sudden death and the clinical factors independently associated with sudden death in consecutive patients with severe AS. We should take these risk factors for sudden death into account when we decide the appropriate timing for the surgical or transcatheter intervention. In this regard, it is essential to balance the natural risk of severe AS with the risk of surgical or transcatheter AVR. Improved surgical techniques have led to lower operative mortality, and TAVI outcomes have also improved with experience and device development. Therefore, the risk of sudden death in some high-risk patients with asymptomatic severe AS might outweigh the procedural mortality risk in the contemporary clinical practice. Early surgical or transcatheter intervention might be able to prevent sudden death, which is under investigation in the ongoing EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to

**Table 2.** Clinical Factors Associated With Sudden Death in the Entire Cohort in the Univariate and Multivariable Analyses

Variables	Unadjusted HR* (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Hemodialysis	5.35 (3.78-7.46)	<0.001	3.63 (2.42-5.43)	<0.001
Prior myocardial infarction	2.68 (1.84-3.81)	<0.001	2.11 (1.28-3.50)	0.004
BMI <22	1.85 (1.32-2.65)	<0.001	1.51 (1.03-2.21)	0.03
LVEF <60%	2.84 (2.10-3.82)	<0.001	1.52 (1.08-2.14)	0.02
V <sub>max</sub> ≥5 m/s	1.58 (1.02-2.36)	0.04	1.76 (1.12-2.78)	0.01
Symptoms related to AS	1.90 (1.41-2.57)	<0.001	1.28 (0.90-1.82)	0.17
Age ≥80 y	1.38 (1.02-1.87)	0.03	1.09 (0.77-1.53)	0.64
Male	1.75 (1.30-2.36)	<0.001	1.34 (0.95-1.89)	0.09
TRPG ≥40 mm Hg	1.55 (1.05-2.22)	0.03	1.17 (0.75-1.81)	0.49
Any valvular disease (moderate-severe)	1.25 (0.92-1.68)	0.15	1.07 (0.75-1.51)	0.72
Prior symptomatic stroke	1.07 (0.69-1.60)	0.74	0.78 (0.50-1.22)	0.28
Atrial fibrillation or flutter	1.02 (0.71-1.44)	0.91	0.91 (0.63-1.33)	0.64
Chronic lung disease (moderate-severe)	1.07 (0.42-2.20)	0.88	0.93 (0.41-2.09)	0.85
Malignancy currently under treatment	1.21 (0.51-2.39)	0.63	0.85 (0.38-1.88)	0.68
Aortic/peripheral disease	2.11 (1.33-3.22)	0.002	1.05 (0.64-1.70)	0.85
Current smoking	0.71 (0.30-1.41)	0.36	0.83 (0.38-1.80)	0.64
Diabetes mellitus on insulin	1.79 (0.97-3.03)	0.06	1.16 (0.61-2.19)	0.65
Coronary artery disease	1.81 (1.33-2.45)	<0.001	0.91 (0.60-1.37)	0.64
Anemia	2.03 (1.49-2.80)	<0.001	0.92 (0.65-1.32)	0.66
Hypertension	1.36 (0.96-1.95)	0.08	1.30 (0.90-1.88)	0.16

Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation; TRPG, tricuspid regurgitation pressure gradient; V<sub>max</sub>, peak aortic jet velocity.

\*Competing risk of death other than sudden death was not taken into account in the univariate analysis, but it was taken into account in the multivariable analysis. Patients who had AVR or TAVI were censored at AVR/TAVI.

Surveillance for Patients With Asymptomatic Severe Aortic Stenosis) trial (NCT03042104).

## Study Limitations

This study had several limitations. First, patient follow-up in this multicenter study might have been less close than the follow-up in previous single-center studies. However, it would be important to note that 65% of sudden death occurred within 3 months of the last clinical follow-up visit among 54 patients experiencing sudden death without any symptoms. Second, not all sudden death could be attributed to severe AS, although clinical events were adjudicated according to the Valve Academic Research Consortium definitions by a clinical events committee. Third, we did not collect information on exercise testing, thereby leaving the possibility of unrecognized symptoms in some patients due to sedentary lifestyle. Although the current guidelines recommend an exercise test to confirm symptomatic status in asymptomatic patients with severe AS, exercise testing cannot be commonly performed in a satisfactory manner in many

patients with severe AS because of their advanced age, limited exercise capacities, frailties, and comorbidities. Fourth, we could not deny residual confounding and selection bias for AVR, although we performed the extensive multivariable analysis for the risk factors of sudden death. Actually, the cumulative incidence of sudden death in symptomatic patients was relatively low, because symptomatic patients, as compared with asymptomatic patients, were more often referred to surgical or transcatheter AVR after diagnosis of severe AS with the index echocardiography. Finally, we did not collect data on ECG features such as QRS duration and QRS morphology, which were reported to be associated with sudden death in asymptomatic patients with mild to moderate AS.<sup>18</sup>

## Conclusions

The incidence of sudden death in asymptomatic patients with severe AS might be higher than that reported in previous reports. Several baseline clinical characteristics as well as



**Table 3.** Clinical Factors Associated With Sudden Death in Asymptomatic and Symptomatic Patients With Severe AS in the Univariate and Multivariable Analyses

Variables	Unadjusted HR* (95% CI)	P Value	Adjusted HR (95% CI)	P Value
<b>Asymptomatic patients (N=1808)</b>				
Hemodialysis	7.79 (4.85-12.3)	<0.001	4.23 (2.48-7.22)	<0.001
Prior myocardial infarction	2.76 (1.56-4.60)	<0.001	1.75 (0.97-3.16)	0.07
BMI <22	1.79 (1.12-2.95)	0.01	1.47 (0.87-2.48)	0.15
LVEF <60%	3.33 (2.11-5.18)	<0.001	1.76 (1.08-2.87)	0.02
V <sub>max</sub> ≥5 m/s	1.62 (0.72-3.19)	0.22	2.36 (1.09-5.14)	0.03
Age ≥80 y	1.10 (0.71-1.71)	0.66	0.97 (0.61-1.53)	0.89
Male	1.77 (1.15-2.74)	0.01	1.20 (0.72-1.99)	0.48
Any valvular disease (moderate-severe)	0.97 (0.60-1.54)	0.90	1.06 (0.65-1.73)	0.80
Atrial fibrillation or flutter	1.07 (0.60-1.80)	0.81	0.78 (0.43-1.40)	0.40
Malignancy currently under treatment	1.66 (0.58-3.73)	0.31	1.01 (0.36-2.82)	0.99
<b>Symptomatic patients (N=2005)</b>				
Hemodialysis	3.87 (2.25-6.32)	<0.001	3.11 (1.73-5.59)	<0.001
Prior myocardial infarction	2.54 (1.51-4.09)	<0.001	2.30 (1.31-4.07)	0.004
BMI <22	1.65 (1.02-2.82)	0.04	1.62 (0.94-2.80)	0.08
LVEF <60%	2.04 (1.35-3.08)	<0.001	1.32 (0.84-2.07)	0.23
V <sub>max</sub> ≥5 m/s	1.24 (0.72-2.04)	0.42	1.51 (0.87-2.60)	0.14
Age ≥80 y	1.46 (0.96-2.28)	0.08	1.28 (0.76-2.17)	0.35
Male	2.02 (1.33-3.06)	0.001	1.48 (0.94-2.34)	0.09
Any valvular disease (moderate-severe)	1.20 (0.80-1.82)	0.39	1.21 (0.78-1.87)	0.40
Atrial fibrillation or flutter	0.85 (0.52-1.34)	0.50	0.99 (0.60-1.61)	0.95
Malignancy currently under treatment	0.90 (0.15-2.86)	0.88	0.52 (0.12-2.20)	0.37

Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation; V<sub>max</sub>, peak aortic jet velocity.

\*Competing risk of death other than sudden death was not taken into account in the univariate analysis, whereas it was taken into account in the multivariable analysis. Patients who had AVR or TAVI were censored at AVR/TAVI.

echocardiographic parameters were associated with increased risk of sudden death in patients with severe AS.

## Sources of Funding

This work was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan).

## Disclosures

None.

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# **SUPPLEMENTAL MATERIAL**

## **Appendix:**

### **CURRENT AS Registry Investigators**

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**A clinical event committee**

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## **Data S1.**

### **Definitions of the clinical events**

Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Sudden death was defined as unexplained death in previously stable patients. Any death during the hospitalization for aortic valve replacement or transcatheter aortic valve implantation was regarded as aortic valve procedure-related death. Aortic valve-related death included aortic valve procedure-related death, sudden death, and death due to heart failure related to aortic stenosis. Heart failure hospitalization was defined as hospitalization due to worsening heart failure requiring intravenous drug therapy.

**Table S1. Clinical factors associated with sudden death in the non-HD cohort in the univariate and multivariable analyses.**

Variables	Unadjusted HR* (95% CI)	P value	Adjusted HR (95% CI)	P value
Prior myocardial infarction	2.95 (1.90-4.43)	<0.001	3.25 (1.59-6.61)	0.001
BMI <22	1.87 (1.26-2.85)	0.002	1.53 (0.98-2.41)	0.06
LVEF <60%	2.71 (1.90-3.85)	<0.001	1.56 (1.04-2.35)	0.03
Vmax ≥5m/s	1.67 (1.002-2.63)	0.049	1.50 (0.91-2.49)	0.11
Symptoms related to AS	2.34 (1.65-3.36)	<0.001	1.40 (0.93-2.12)	0.11
Age ≥80	2.13 (1.47-3.12)	<0.001	1.19 (0.78-1.82)	0.42
Male	1.52 (1.06-2.16)	0.02	1.53 (1.04-2.24)	0.03
TRPG ≥40 mmHg	1.71 (1.09-2.60)	0.02	1.16 (0.69-1.94)	0.58
Any valvular disease (moderate-severe)	1.37 (0.96-1.94)	0.08	1.01 (0.67-1.52)	0.98
Prior symptomatic stroke	1.18 (0.71-1.86)	0.50	0.95 (0.58-1.56)	0.84
Atrial fibrillation or flutter	1.07 (0.70-1.59)	0.75	1.01 (0.66-1.55)	0.95
Chronic lung disease (moderate-severe)	1.18 (0.42-2.60)	0.72	0.82 (0.33-1.99)	0.65
Malignancy currently under treatment	1.47 (0.57-3.07)	0.38	1.01 (0.44-2.36)	0.98
Aortic/peripheral disease	1.06 (0.45-2.12)	0.88	0.79 (0.35-1.74)	0.55
Current smoking	0.84 (0.33-1.75)	0.67	0.94 (0.41-2.19)	0.89
Diabetes on insulin	1.83 (0.86-3.39)	0.11	1.26 (0.60-2.63)	0.54
Coronary artery disease	1.47 (0.998-2.12)	0.052	0.60 (0.33-1.11)	0.10
Anemia	1.87 (1.31-2.69)	<0.001	0.96 (0.65-1.43)	0.85
Hypertension	1.51 (1.004-2.33)	0.048	1.45 (0.94-2.24)	0.09

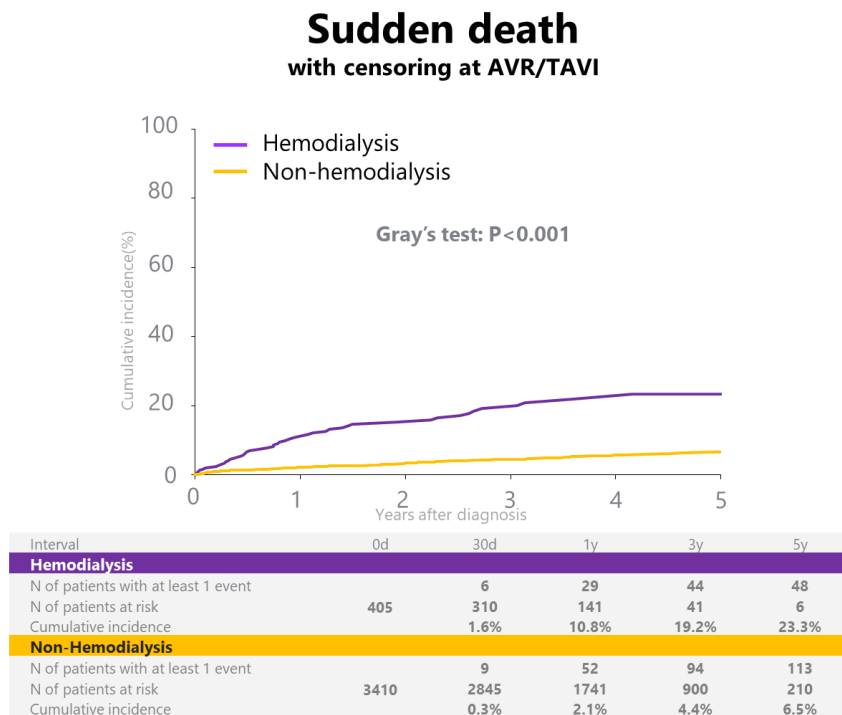
\* Competing risk of death other than sudden death was not taken into account in the univariate analysis, while it was taken into account in the multivariable analysis. Patients who had AVR or TAVI were censored at AVR/TAVI.

CI=confidence interval; HR=hazard ratio; TAVI=transcatheter aortic valve implantation. Other abbreviations were same as in Table 1.



**Figure S1. Cumulative incidence of sudden cardiac death in HD and non-HD patients with severe**

**AS.**



Cumulative incidence of sudden death was estimated by the Gray method, taking the competing risk

of death other than sudden death. AVR=aortic valve replacement; HD=hemodialysis;

TAVI=transcatheter aortic valve implantation.