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Ⅲ. 研究成果の刊行物・別刷

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Comprehensive Risk Stratification of Japanese Patients With Aortic Stenosis

– A Proposal of a New Risk Score From the CHART-2 Study –

Kenjiro Sato, MD; Yasuhiko Sakata, MD, PhD; Masanobu Miura, MD, PhD; Soichiro Tadaki, MD; Ryoichi Ushigome, MD; Takeshi Yamauchi, MD; Takeo Onose, MD; Kanako Tsuji, MD; Ruri Abe, MD; Kotaro Nochioka, MD, PhD; Jun Takahashi, MD, PhD; Satoshi Miyata, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators

Background: The risk of patients with aortic stenosis (AS) should be stratified not only by AS severity but also by comorbidities.

Methods and Results: We aimed to develop a risk score for mortality in 412 patients with AS (pressure gradient ≥30 mmHg, mean age 74.9 years, male 52.4%) in the CHART-2 Study (n=10,219). During a 3-year follow-up, 73 (17.7%) patients died. Crude 3-year mortality of patients in New York Heart Association (NYHA) classes I, II, and III/IV was 9.5%, 16.5%, and 49.7%, respectively (P<0.001). Stepwise Cox regression analysis showed that the combination of 7 factors was the best model to predict the mortality of AS patients, who were scored according to their hazard ratios, including NYHA class III–IV (score 6), male sex (3), serum albumin level ≤4 g/dl (2), aortic peak flow ≥4.5 m/s (2), age ≥75 years (2), chronic kidney disease (2), and anemia (1). Receiver-operating characteristic analysis showed excellent association between the sum of the scores and 3-year mortality (area under the curve, 0.78). The multivariate Cox proportional hazard model demonstrated that the present risk score also well stratified the mortality risk.

Conclusions: The present study demonstrates that, in addition to the classical prognostic factors related to symptoms and AS severity, various comorbidities are associated with mortality. Thus, the present comprehensive risk score may be useful for risk stratification of AS patients.

Key Words: Aortic stenosis; Heart failure; Risk score

Along with the rapid aging of general population, the prevalence of valvular heart disease, particularly aortic stenosis (AS), has been increasing worldwide, especially in developed countries, which includes Japan.[1] It was reported in the 1960s that the average survival of AS patients was 2–5 years after the onset of symptoms.[2] However, there are few papers on the natural course of AS patients in the contemporary era, although they may live longer than ever before with advanced medical therapies without surgical treatments.[3,4] Considering the recent progress in the management of AS, including transcatheter interventions[5,6] and valvular surgeries,[7,8] there is an emerging need to properly stratify the mortality and morbidity risks of AS patients without a prior history of valvular surgery. However, because the present guidelines only recommend evaluating the severity of AS by symptoms and echocardiography,[9–11] they are not necessarily suitable for comprehensive risk stratification of AS patients. Although some previous studies proposed new prognostic indexes of AS using echocardiographic data[12–15] or biomarkers,[16–19] they are not widely used in current practice. Several other risk scores have been developed for patients with heart failure (HF),[20,21] but are not necessarily useful for AS patients. Moreover, considering the fact that AS reflects one aspect of systemic degenerative processes of the elderly, several comorbidities other than symptoms and AS severity should be included in the risk scores of AS. Thus, a comprehensive risk score covering not only the symptoms and severity of AS but also comorbidities of patients without surgical treatments needs to be developed based on

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Department of Cardiovascular Medicine (K.S., Y.S., M.M., S.T., R.U., T.Y., T.O., K.T., R.A., K.N., J.T., H.S.), Department of Evidence-based Cardiovascular Medicine (S.M.), Tohoku University Graduate School of Medicine, Sendai, Japan

The Guest Editor for this article was Masafumi Kitakaze, MD.

Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

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Table 1. Characteristics of Patients With AS in Japan

Age (years)	74.9±9.8
Sex (male)	216 (52.4%)
BMI (kg/m²)	23.3±3.6
SBP (mmHg)	130.4±20.8
DBP (mmHg)	70.3±12.6
Heart rate (beat/min)	73.2±15.5
Laboratory test	
Hemoglobin (g/dl)	12.6±1.8
BUN (mg/dl)	20.3±10.1
Creatinine (mg/dl)	1.1±1.1
Albumin (g/dl)	4.0±0.5
LDL-C (mg/dl)	110.7±30.3
CKD (eGFR ≤60 ml/min/1.73 m²)	193 (46.8%)
BNP ≥100 pg/ml	186 (45.1%)
Echocardiography	
LVEF ≤50%	31 (7.5%)
LVDd (mm)	47.1±7.4
IVSd (mm)	12.3±2.9
PWd (mm)	11.8±2.6
APF	
<3.5 m/s	230 (63.7%)
3.5–4.5 m/s	88 (24.4%)
≥4.5 m/s	43 (11.9%)
AVPG	
<45 mmHg	220 (60.9%)
45–60 mmHg	48 (13.3%)
≥60 mmHg	93 (25.8%)
Mitral stenosis (MVA ≤2 cm²)	26 (6.4%)
Severe MR	31 (7.5%)
Severe AR	55 (13.3%)
Medical treatment	
RAS-I	275 (66.7%)
CCB	222 (53.9%)
β-blocker	111 (26.9%)
Statin	152 (36.9%)
Loop diuretic	117 (28.4%)
Aldosterone antagonist	59 (14.3%)
NYHA class	
I	154 (37.7%)
II	208 (50.9%)
III–IV	47 (11.5%)

Results are expressed as mean±SD for continuous variables. APF, aortic peak flow; AR, aortic regurgitation; AS, aortic stenosis; AVPG, aortic valve pressure gradient; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium-channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IVSd, interventricular septum thickness; LDL-C, low density lipoprotein cholesterol; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVA, mitral valve area; NYHA, New York Heart Association; PWd, posterior left ventricular wall thickness; RAS-I, renin-angiotensin system inhibitor; SBP, systolic blood pressure.

observations from a large-scale cohort study.

Editorial p????

In the present study, we addressed this important clinical issue in a large-scale cohort study, named the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study (n=10,219).[22–24]

Methods

The CHART-2 Study

The CHART-2 Study is a large-scale prospective observational multicenter cohort study, as previously reported in detail (NCT00418041).[22–24] Briefly, the CHART-2 Study successfully enrolled patients older than 20 years of age in stages B–D of HF according to the ACC/AHA guidelines[25] and those with coronary artery disease between October 2006 and March 2010 (n=10,219).[22–24] All information, including medical history, laboratory data and echocardiography data, was obtained at the time of enrolment and annually thereafter. The CHART-2 Study was approved by each local ethics committee in the 24 participating hospitals and written informed consent was given by all patients.

Study Subjects

In the CHART-2 Study, AS was defined as ≥30 mmHg aortic valve peak pressure gradient (AVPG) by echocardiography at the time of enrolment.[22] Of the 10,219 patients enrolled in CHART-2, 482 were defined as having AS. After excluding 70 patients who had undergone valvular surgery, the remaining 412 patients were finally included in the present study.

Determination of Risk Scores

The risk scores were based on the results of multivariate Cox regression analysis. Briefly, significant variables selected from the optimal multivariate Cox regression model were assigned an integer score, which was applied just as the integer position of their hazard ratio (HR) was obtained by truncating the decimal point. For the sake of simplicity, anemia was defined as the hemoglobin (Hb) level (<13 g/dl in men and <12 g/dl in women), according to the World Health Organization definition,[26] and age and serum albumin were replaced by binary variables equal to 1 for age ≥75 years and serum albumin ≤4 g/dl, and equal to 0 otherwise. Next, the total score of each patient was calculated by the sum of each variable's score. According to the sum of the risk scores, we divided the patients into 3 groups: the low-risk group with score 0–6 (n=210), the intermediate-risk group with score 7–10 (n=112), and the high-risk group with score 11–18 (n=36).

Statistical Analysis

All continuous variables are shown as mean±standard deviation (SD) and categorical variables are presented as number and percent. The Kaplan-Meier curves evaluated the survival time for all-cause death in AS patients. Patients who underwent surgical treatments for AS during the follow-up period were treated as censored on the day of admission for surgery. The survival curves were compared by log-rank test. To determine the independent predictors of the mortality of AS patients, univariate Cox proportional hazard regression models were applied for the following variables: age, sex, body mass index (BMI), systolic blood pressure (BP), diastolic BP, heart rate (≥90 beats/min), history of HF hospitalization, dyslipidemia, atrial fibrillation, left ventricular diastolic diameter (LVDd), interventricular septum thickness (IVSd), posterior left ventricular wall thickness (PWd), mitral stenosis (MS), defined as mitral valvular area ≤2 cm²; severe mitral regurgitation (MR) defined as grade ≥3; severe aortic regurgitation (AR) defined as grade ≥3; aortic peak flow (APF), pressure gradient, B-type natriuretic peptide (≥100 pg/dl), Hb level, serum albumin, chronic

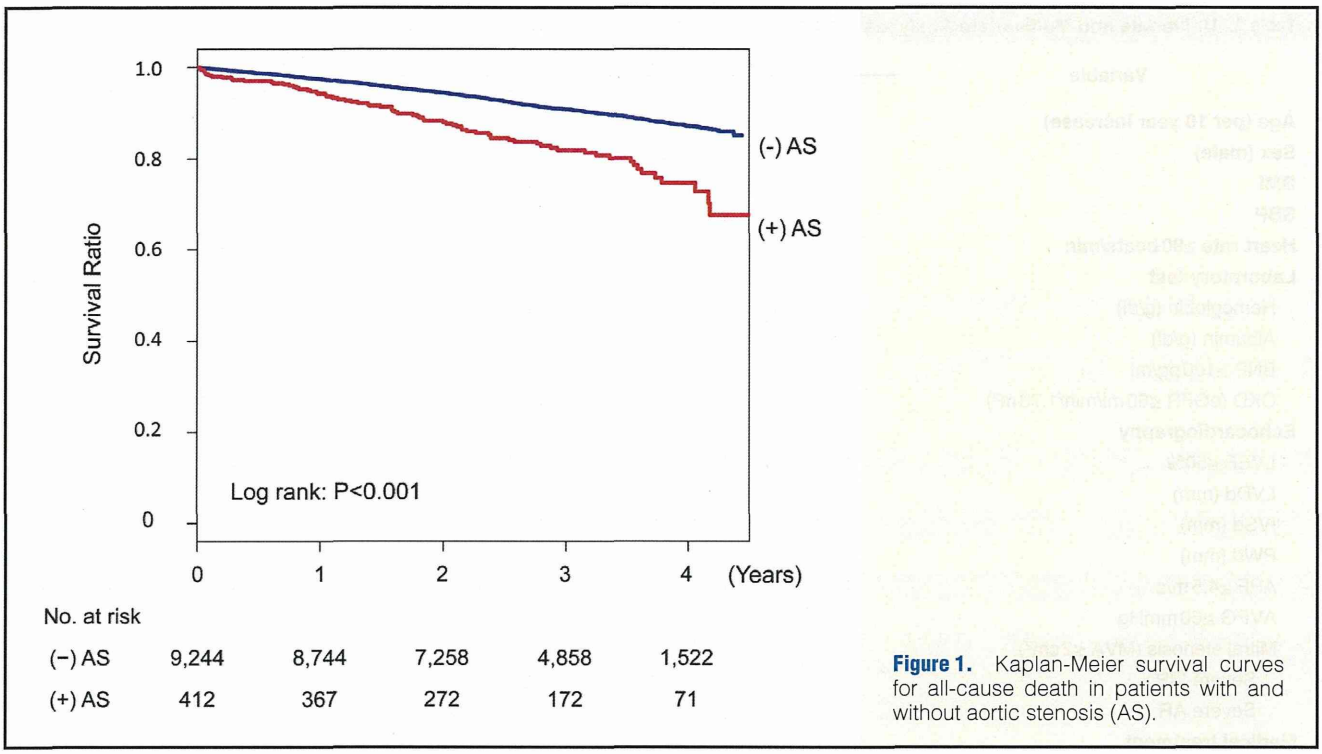

Figure 1. Kaplan-Meier survival curves for all-cause death in patients with and without aortic stenosis (AS).

kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m^2, use of calcium-channel blocker, loop diuretic, statin or antiplatelet drug, and New York Heart Association (NYHA) class. The variables showing P<0.5 in the univariate Cox proportional hazard regression model were entered into the multivariate Cox regression model followed by stepwise variable selection to achieve the optimal combination of covariates. The Kaplan-Meier curves were plotted for each risk group to evaluate the outcomes of all-cause death, cardiovascular (CV) death and non-CV death. For all steps, P<0.05 was considered to be statistically significant. All statistical analysis was performed by the statistical computing software R version 3.0.3.

Results

Patient Characteristics

Mean age of the AS patients was 74.9±9.8 years and females accounted for 47.6% (Table 1). The echocardiographic data showed that they had relatively preserved ejection fraction and mild left ventricular hypertrophy. A relatively low APF (<3.5 m/s) was observed in 230 patients (63.7%) and 220 (60.9%) had a relatively low AVPG (<45 mmHg). In addition to AS, 26 (6.4%), 31 (7.5%), and 55 (13.3%) of the patients had MS, severe MR, and severe AR, respectively. The prevalence of CKD was 46.8%. For the medical treatments of AS, renin-angiotensin system inhibitors and β-blockers were prescribed in 66.7% and 26.9%, respectively. As for the functional class in HF, 154 patients (37.7%) were NYHA class I and 208 (50.9%) were class II.

3-Year Mortality and Prognostic Factors

Among the 412 patients with AS, 73 (17.7%) died during the 3-year follow-up period. Crude 3-year mortality of patients with NYHA class I, II, and III/IV was 9.5%, 16.5%, and 49.7%, respectively (P<0.001). The Kaplan-Meier curves for all-cause death showed that AS patients had significantly worse prognosis than those without it (Figure 1). The causes of death are shown in Table 2. Among the 73 deaths, 43 (58.9%) were CV, including 23 (31.5%) from HF and 9 (12.3%) sudden deaths.

Table 2. Cause of Death Among Patients With AS in Japan

Cause of death	n (%)
Cardiovascular death	43 (58.9)
Heart failure	23 (31.5)
Sudden death	9 (12.3)
AMI	3 (4.1)
Stroke	2 (2.7)
Other	6 (8.2)
Noncardiovascular death	25 (34.2)
Cancer	8 (11.0)
Other	17 (23.3)
Unknown	5 (6.8)
Total	73

AS, aortic stenosis; AMI, acute myocardial infarction.

Table 3 shows the prognostic factors for all-cause death. In the univariate analysis, age, Hb level, serum albumin level, CKD, APF ≥4.5 m/s, AVPG ≥60 mmHg, severe MR, statins, loop diuretics, and NYHA class ≥III were significantly associated with 3-year mortality, but the cardiac remodeling parameters by echocardiography, such as IVSd, PWd or LVDd, were not. Among the valvular insufficiencies, severe MR was a significant prognostic factor (P=0.039) for all-cause death, but severe AR (P=0.262) and MS (P=0.284) were not. Finally, however, the stepwise multivariate analysis identified age, male sex, Hb level, serum albumin, CKD, APF ≥4.5 m/s, and NYHA class ≥III as prognostic factors (Table 3). Interestingly, male sex was associated with increased 3-year mortality in the multivariate analysis, but not in the univariate analysis, indicating that the

Table 3. Univariate and Multivariate Analyses for All-Cause Death of Patients With AS in Japan

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (per 10 year increase)	2.26	1.62–3.14	<0.001	2.13	1.49–3.06	<0.001
Sex (male)	1.21	0.76–1.92	0.426	3.20	1.86–6.37	<0.001
BMI	0.95	0.89–1.02	0.145	–	–	–
SBP	0.99	0.98–1.00	0.232	–	–	–
Heart rate ≥90 beats/min	1.68	0.92–3.06	0.091	1.82	0.85–3.90	0.122
Laboratory test						
Hemoglobin (g/dl)	0.70	0.62–0.79	<0.001	0.82	0.70–0.97	0.019
Albumin (g/dl)	0.31	0.20–0.47	<0.001	0.38	0.21–0.67	0.001
BNP ≥100 pg/ml	1.56	0.98–2.48	0.059	–	–	–
CKD (eGFR ≤60 ml/min/1.73 m²)	3.82	2.25–6.51	<0.001	2.08	1.02–4.26	0.044
Echocardiography						
LVEF ≤50%	1.18	0.51–2.73	0.697	–	–	–
LVDd (mm)	1.01	0.98–1.04	0.494	–	–	–
IVSd (mm)	1.05	0.97–1.13	0.232	–	–	–
PWd (mm)	1.09	1.00–1.19	0.062	–	–	–
APF ≥4.5 m/s	2.40	1.27–4.53	0.007	2.37	1.13–4.99	0.023
AVPG ≥60 mmHg	1.76	1.02–3.01	0.041	–	–	–
Mitral stenosis (MVA ≤2 cm²)	1.56	0.72–3.42	0.262	2.63	0.93–7.44	0.068
Severe MR	2.09	1.04–4.20	0.039	–	–	–
Severe AR	1.39	0.76–2.54	0.284	–	–	–
Medical treatment						
RAS-I	1.15	0.69–1.91	0.593	–	–	–
Statin	0.47	0.27–0.81	0.007	–	–	–
Loop diuretic	2.77	1.75–4.39	<0.001	–	–	–
CCB	0.84	0.53–1.33	0.456	–	–	–
NYHA class						
II	1.56	0.87–2.81	0.134	1.38	0.67–2.84	0.382
III–IV	5.94	3.08–11.45	<0.001	6.53	2.81–15.14	<0.001

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

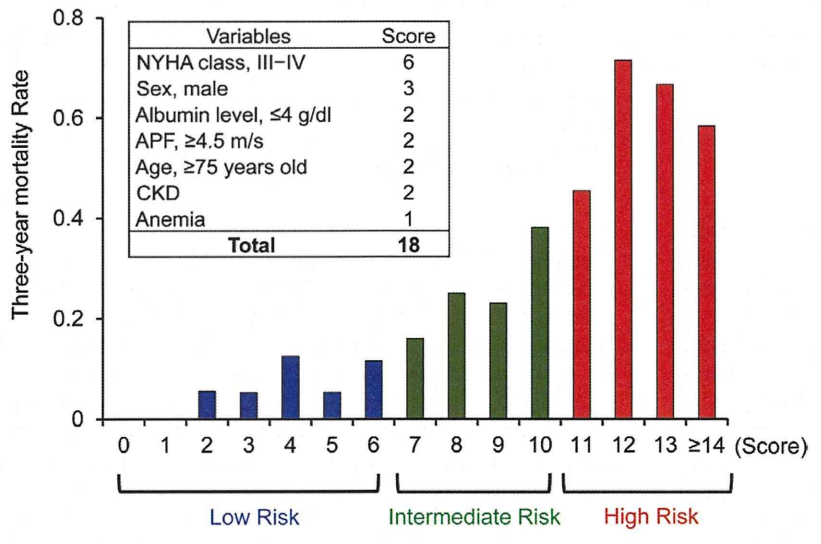

Figure 2. Scoring system and incidence of all-cause death. APF, aortic peak flow; CKD, chronic kidney disease; NYHA, New York Heart Association.

mortality risk of male sex was uncovered by adjusting for clinical background. Furthermore, among the echocardiographic parameters, APF ≥4.5 m/s was the only significant prognostic factor identified by the stepwise method.

Deviation of the Risk Score

The risk scores were given to the prognostic predictors based on their HR derived in the multivariate Cox regression analysis included NYHA class III–IV (score 6), male sex (3), serum

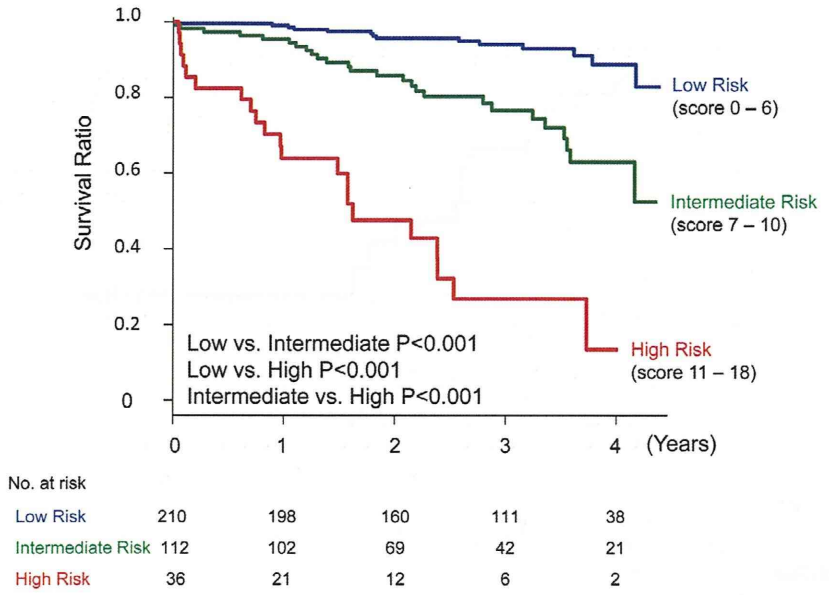

Figure 3. Kaplan-Meier survival curves for all-cause death in the 3 risk groups.

albumin level ≤4 g/dl (2), APF ≥4.5 m/s (2), age ≥75 years (2), CKD (2), and anemia (1) (**Figure 2**). There was a significant correlation between the sum of the risk scores and the incidence of all-cause death, and the mortality rate increased with an increase in the sum of the scores (**Figure 2**). There was excellent connectivity between the risk score and mortality (area under the curve=0.784).

Based on the sum of the risk scores, we stratified the mortality risk into 3 groups: low risk (score 0–6, n=210), intermediate risk (score 7–10, n=112) and high risk (score 11–18, n=36). The Kaplan-Meier curves for all-cause death showed significant differences in all-cause, CV, and non-CV mortality among the 3 groups (**Figures 3,4**). The multivariate Cox proportional hazard model demonstrated that the intermediate- and high-risk groups had significantly increased all-cause mortality compared with the low-risk group (served as a reference) with HR of 4.49 (95% confidence interval (CI), 2.23–8.43; P<0.001) and 18.34 (95% CI, 9.18–36.63; P<0.001), respectively (**Figure 3**). Similarly, the HR for CV death in the intermediate- and high-risk groups was 4.04 (95% CI, 1.58–10.23; P<0.001) and 25.30 (95% CI, 10.09–63.46; P<0.001), respectively (**Figure 4A**), and for non-CV death it was 4.82 (95% CI, 1.80–10.23; P<0.001) and 8.77 (95% CI, 4.51–31.73; P<0.001), respectively (**Figure 4B**).

Incidence and Prediction of Surgery and Cause of Death After Aortic Valve Replacement (AVR)

During the follow-up period, 38 patients (9.2%) had surgical treatments, including AVR in 36, AVR with mitral valve replacement in 3, surgical aortic valvuloplasty in 1, and percutaneous transluminal aortic valvuloplasty in 1. Among these patients, 3 with AVR died during the follow-up period from non-CV causes (2) and acute myocardial infarction (1). These 38 patients with surgical treatments were characterized, as compared with those who did not receive them, by younger age and more advanced stage of AS on echocardiography but comparable NYHA class (**Table S1**). Even after excluding these 38 patients, the Kaplan-Meier curves still showed that the 3 groups had significant differences in mortality risk (**Figure S1**).

Discussion

The present study demonstrated that in addition to the classical prognostic factors, such as NYHA class and AS severity, other comorbidities (ie, age, male sex, nutrition (as evidenced by serum albumin), renal dysfunction and anemia) are associated with mortality of AS patients, suggesting that these new prognostic factors should be taken into consideration when evaluating the long-term prognosis of AS patients in the current era. Furthermore, using these variables, we were able to develop a comprehensive risk score that could effectively stratify the mortality risk of AS patients.

Characteristics and Prognosis of AS Patients in Japan

To the best of our knowledge, this is the largest cohort study of AS patients in Japan. In the present study, 482 of 10,219 patients enrolled in the CHART-2 Study were initially screened by the criteria of either AVPG ≥30 mmHg at the time of enrolment or prior history of surgical operations. Subsequently, after excluding 70 patients with a prior history of AVR, a total of 412 patients were examined in the present study. The mean age was 74.5 years and females accounted for 47.6%. Although AVPG and/or APF were modest compared with previous studies,[3,4,7,8] two-thirds of the patients were symptomatic and 73 (17.7%) of the 412 AS patients died during the 3-year follow-up period. The present study demonstrates that the 3-year mortality of symptomatic AS patients is better than in previous reports; crude 3-year mortality was 21.2% in the present study (16.5% for NYHA class II and 49.7% for NYHA III/IV) compared with 53.8–73.0% in the previous studies.[27–29] It is widely known that in 1968 Ross and Braunwald reported that the prognosis of AS patients from the onset of HF, syncope, and