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 $\geq 30$ 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 $\leq 4$ g/dl (2), aortic peak flow $\geq 4.5$ m/s (2), age $\geq 75$ 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. (Circ J 2015; 79: 1631–1638)

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. It was reported in the 1960's that the average survival of AS patients was 2–5 years after the onset of symptoms. 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. Considering the recent progress in the management of AS, including transcatheter interventions and valvular surgeries, 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, 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 or biomarkers, they are not widely used in current practice. Several other risk scores have been developed for patients with heart failure (HF), 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...
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

#### 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.23 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 as grade 1; aortic peak flow (APF), pressure gradient, B-type natriuretic peptide (BNP), and serum albumin were assigned as grade 2; severe aortic regurgitation (AR) defined as grade 3; myocardial infarction, history of myocardial infarction, history of heart failure, and atrial fibrillation were assigned as grade 4. For the sake of simplicity, the total score of each variable 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 (SBP), diastolic BP (DBP), heart rate (≥90 beats/min), history of HF hospitalization, dyslipidemia, atrial fibrillation, left ventricular diastolic diameter (LVDD), left atrial diameter (LA), left ventricular mass (LVM), and serum albumin. The independent predictors of mortality were further analyzed using a stepwise Cox proportional hazard regression analysis. 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.
Comprehensive Risk Stratification of AS

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 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 2. Cause of Death Among Patients With AS in Japan

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

AS, aortic stenosis; AMI, acute myocardial infarction.

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

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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (per 10 year increase)</td>
<td>2.26</td>
<td>1.62–3.14</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.21</td>
<td>0.76–1.92</td>
</tr>
<tr>
<td>BMI</td>
<td>0.95</td>
<td>0.89–1.02</td>
</tr>
<tr>
<td>SBP</td>
<td>0.99</td>
<td>0.98–1.00</td>
</tr>
<tr>
<td>Heart rate ≥90 beats/min</td>
<td>1.68</td>
<td>0.92–3.06</td>
</tr>
<tr>
<td><strong>Laboratory test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.70</td>
<td>0.62–0.79</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>0.31</td>
<td>0.20–0.47</td>
</tr>
<tr>
<td>BNP ≥100 pg/ml</td>
<td>1.56</td>
<td>0.98–2.48</td>
</tr>
<tr>
<td><strong>CKD (eGFR ≤60 ml/min/1.73 m²)</strong></td>
<td>3.82</td>
<td>2.25–6.51</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ≤50%</td>
<td>1.18</td>
<td>0.51–2.73</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>1.01</td>
<td>0.98–1.04</td>
</tr>
<tr>
<td>IVSD (mm)</td>
<td>1.05</td>
<td>0.97–1.13</td>
</tr>
<tr>
<td>PWd (mm)</td>
<td>1.09</td>
<td>1.00–1.19</td>
</tr>
<tr>
<td>APF ≥4.5 m/s</td>
<td>2.40</td>
<td>1.27–4.53</td>
</tr>
<tr>
<td>AVPG ≥80 mmHg</td>
<td>1.76</td>
<td>1.02–3.01</td>
</tr>
<tr>
<td>Mitral stenosis (MVA ≤2 cm²)</td>
<td>1.56</td>
<td>0.72–3.42</td>
</tr>
<tr>
<td>Severe MR</td>
<td>2.09</td>
<td>1.04–4.20</td>
</tr>
<tr>
<td>Severe AR</td>
<td>1.39</td>
<td>0.76–2.54</td>
</tr>
<tr>
<td><strong>Medical treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS-I</td>
<td>1.15</td>
<td>0.69–1.91</td>
</tr>
<tr>
<td>Statin</td>
<td>0.47</td>
<td>0.27–0.81</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>2.77</td>
<td>1.75–4.39</td>
</tr>
<tr>
<td>CCB</td>
<td>0.84</td>
<td>0.53–1.33</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.56</td>
<td>0.87–2.81</td>
</tr>
<tr>
<td>III–IV</td>
<td>5.94</td>
<td>3.08–11.45</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.
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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 AVPG ≥ 30 mmHg at the time of enrollment 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, 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. It is widely known that in 1968 Ross and Braunwald reported that the prognosis of AS patients from the onset of HF, syncope, and
Indeed, the present risk score correlated well with the 3-year mortality of AS patients.

Characteristics of Patients Treated Surgically
In the present study, 37 of 412 patients had surgical treatments during the follow-up. These patients were characterized by younger age and advanced AS severity but comparable NYHA class to those who did not receive the treatments, a consistent finding from previous study.

In general, aortic valve surgery has not been indicated if the patient is asymptomatic, has higher risk, or refuses it. However, recent advances in surgical and/or percutaneous interventions for AS have improved procedural success and outcomes in patients with higher age and/or at higher risk. Thus, the present risk score may help physicians estimate prognosis and make appropriate decisions for AS patients in their daily practice.

The present study provides important new information that the prognosis of AS patients has improved since that classical report.

Prognostic Factors and Development of the Risk Score
One of the novel findings of the present study is that in addition to the classical risk factors such as symptoms and AS severity, other comorbidities, including age, male sex, nutrition (as evidenced by serum albumin level), renal dysfunction and anemia, were significantly associated with the 3-year mortality of AS patients. This finding is reasonable because AS reflects one aspect of systemic degenerative processes in the elderly. From this viewpoint, the present risk score based on the HR of these comorbidities may be more useful than the previous risk scores that were based only on symptoms and echocardiographic parameters. Indeed, the present risk score correlated well with the 3-year mortality of AS patients.

Characteristics of Patients Treated Surgically
In the present study, 37 of 412 patients had surgical treatments during the follow-up. These patients were characterized by younger age and advanced AS severity but comparable NYHA class to those who did not receive the treatments, a consistent finding from previous study. In general, aortic valve surgery has not been indicated if the patient is asymptomatic, has higher risk, or refuses it. However, recent advances in surgical and/or percutaneous interventions for AS have improved procedural success and outcomes in patients with higher age and/or at higher risk. Thus, the present risk score may help physicians estimate prognosis and make appropriate decisions for AS patients in their daily practice.
Study Limitations

Several limitations should be mentioned for the present study. First, it was performed only in the Japanese population, so the present findings remain to be confirmed in other populations. Second, since we defined AS by peak-to-peak AVPG ≥30 mmHg, some patients with severe AS but small aortic valve area (AVA) and reduced peak-to-peak AVPG were excluded from the study population. In this regard, we carefully reviewed the database and found that 8 patients had AVA ≤1.5 cm² and AVPG <30 mmHg in the CHART-2 Study, of whom 1 patient died from HF and another one of cancer during the follow-up period. Thus, future studies are needed to stratify the risk of such AS patients with small AVA and reduced AVPG, because they may have different prognostic factors from the present study population. Third, since the echocardiographic evaluation was performed at each participating hospital, inter-hospital and inter-examiner variations could have been involved. Finally, the present study included patients who had surgical treatment, which might have affected the present results. However, even after excluding these patients, the results were consistent (Figure S1).

Conclusions

We were able to demonstrate that several comorbidities other than echocardiographic parameters and symptoms are associated with poor prognosis of AS patients without a prior history of surgical treatments registered in the CHART-2 Study. Furthermore, the present risk score based on the HR derived from the Cox proportional hazard model may be useful for the management of AS patients in real-world practice, although future validation studies are warranted.

Acknowledgments

We thank all the members of the Tohoku Heart Failure Society (as shown in the Appendix) and the staff of the Department of Evidence-based Cardiovascular Medicine for their contributions.

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Conflict of Interest

H.S. received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan) and Daiichi Sankyo Co, Ltd (Tokyo, Japan). The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo Co, Ltd (Tokyo, Japan), Bayer Yakuhin, Ltd (Osaka, Japan), Kyowa Hakko Kirin Co, Ltd (Tokyo, Japan), Kowa Pharmaceutical Co, Ltd (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co, Ltd (Osaka, Japan), and Nippon Boehringer Ingelheim Co, Ltd (Tokyo, Japan).

References


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**Appendix**

**The CHART-2 Study Investigators**

**Executive Committee**
Hiroaki Shimokawa (Chair), Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Mitsumasa Fukuchi, Kanichi Inoue, Atsushi Kato, Masafumi Sugii, Yasuo Ikeno, Tomoyuki Suzuki, Hiroko Hamada, Keiko Nagasawa, Sachiko Nagasawa, Sachie Kotaka, Wakiko Komatsu, Takeshi Yamauchi, Kenjiro Sato, Kanako Tsuji, Takeo Onose, Ruri Abe, Kotaro Nochioka, Masanobu Miura, Shigeto Oyama, Izumi Oikawa, Sanae Watanabe, Madoka Saga, Miki Washio, Chiharu Saga, Junko Suenaga, Yoko Yamada, Junko Kimura, Hiromi Tahara, Takeshi Ishizuka, Noriko Onoue, Nobuhiro Yamaguchi, Hiroshi Fujita (Sendai Medical Center); Atsushi Katoh, Shigeto Namiuchi, Tadashi Sugie, Kenjiro Otsuka, Yoshito Yamamoto, Sunao Toda, Yutaka Kitamukai (Sendai Tokushukai Hospital); Yasuharu Matsumoto (Shizugawa Public Hospital); Kanichi Inoue, Jiro Koyama, Tomoko Tomioka, Hiroki Shioiri, Yoshitaka Ito (Sendai Miyagi Medical Center); Hiroshi Kato, Chikako Takahashi, Akiko Kawana (Tohoku Rosai Hospital); Yasuhiko Sakata, Kenta Ito, Masaharu Nakayama, Koji Fukuda, Jun Takahashi, Satoshi Miyata, Kyouhiro Sugimura, Kimio Sato, Yasuharu Matsumoto, Makoto Nakano, Takashi Shiroto, Ryusui Tsunobuya, Kotaro Nochioka, Hiroki Yamamoto, Tatsuo Aoki, Kiyotaka Hao, Masakazu Murai, Shigeto Oyama, Shunsuke Tatebe, Saori Yamamoto, Hideaki Suzuki, Kensuke Nishimiyta, Nobuhiro Yatoa (Tohoku University Hospital).

**Fukushima Prefecture**

**Head Office and Coordinating Center**

**Supplementary Files**

**Supplementary File 1**

**Table S1.** Characteristics of AS patients treated with pharmacological and surgical treatments

**Figure S1.** Kaplan-Meier survival curves for all-cause death after excluding patients who had surgical treatment for aortic stenosis during the follow-up period.