書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版年	ページ
坂田泰彦、下川宏明	心不全患者の治療と予後に違いはあるか？.	瀧原圭子	Heart View. Vol 19. 特集:女性の循環器疾患を考える:	メジカルビュー社	2015	178-184
坂田泰彦、下川宏明	心不全の実態と未来予想図	猪又孝元	臨床雑誌内科：2025年を見すえた心不全診療ロードマップ(Vol. 113)	南江堂	2014	419-424
横山　美帆、代田　浩之	ACS後のOMTとして外来心臓リハビリテーションをどう生かすか?	後藤葉一	Heart View	メジカルビュー社	2014	508-512

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, Takahashi J, Shimokawa H, on behalf of the CHART-2 Investigators.	Gender differences in clinical characteristics, treatment and long-term outcome in patients with stage C/D heart failure in Japan. Report from the CHART-2 study	Circ J	78	428-435	2014
Miura M, Sakata Y, Miyata S, Nochioka K, Takada T, Tadaki S, Ushigome R,	Prevalence, predictors and prognosis of patients with heart failure requiring nursing care.	Circ J	78	2276 - 2283	2014

Yamauchi T, Kenjiro S, Onose T, Tsuji K, Abe R, Takahashi J, Shimokawa H					
Miura M, Sakata Y, Miyata S, Nochioka K, Takada T, Tadaki S, Ushigome R, Yamauchi T, Takahashi J, Shimokawa H	Prognostic impact of subclinical microalbuminuria in patients with chronic heart failure.	Circ J	78	2890-2898	2014
Satake H, Fukuda K, Sakata Y, Miyata S, Nakano M, Kondo M, Hasebe Y, Segawa M, Shimokawa H	Current status of primary prevention of sudden cardiac death with implantable cardioverter defibrillator in patients with chronic heart failure – a report from the CHART-2 Study.	Circ J	79	381-390	2015
Nochioka K, Sakata Y, Miyata S, Miura M, Takada T, Tadaki S, Ushigome R, Yamauchi T, Takahashi J, Shimokawa H	Prognostic impact of statin use in patients with heart failure and preserved ejection fraction	Circ J	79	574-582	2015

Onose T, Nochioka K, Sakata Y, Miura M, Tadaki S, Ushigome R, Yamauchi T, Sato K, Tsuji K, Abe R, Miyata S, Takahashi J, Shimokawa H	Predictors and prognostic impact of post-traumatic stress disorder after the great East Japan earthquake in patients with cardiovascular disease	Circ J	79	664-667	2015
Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, Yamauchi T, Sato K, Onose T, Tsuji K, Abe R, Takahashi J, Shimokawa H	Improved Long-Term Prognosis of Dilated Cardiomyopathy With Implementation of Evidenced-Based Medication - Report From the CHART Studies	Circ J.		in press	2015
Sato K, Sakata Y, Miura M, Tadaki S, Ushigome R, Yamauchi T, Onose T, Tsuji K, Abe R, Nochioka K, Takahashi J, Miyata S, Shimokawa H	Comprehensive Risk Stratification of Japanese Patients With Aortic Stenosis - A Proposal of a New Risk Score from the CHART-2 Study.	Circ J		in press	2015

Miura M, Sakata Y, Miyata S, Nochioka K, Takada T, Tadaki S, Ushigome R, Yamauchi T, Kenjiro S, Onose T, Tsuji K, Abe R, Takahashi J, Shimokawa H	Different Prognostic Impacts of Diabetes Mellitus in Chronic Heart Failure between Patents with and Those without Ischemic Heart Disease -With a Special Reference to Nephropathy	Circ J		in press	2015
Sai E, Shimada K, Miyauchi K, Masaki Y, Kojima T, Miyazaki T, Kurata T, Ogita M, Tsuboi S, Yoshihara T, Miyazaki T, Ohsaka A, Daida H	Increased cystatin-C levels as a risk factor of cardiovascular events in patients with preserved estimated glomerular filtration rate after elective percutaneous coronary intervention with drug-eluting stents.	Heart Vessels		in press	2015
Konishi H, Miyauchi K, Kasai T, Tsuboi S, Ogita M, Naito R, Nishizaki Y, Okai I, Tamura H, Okazaki S, Isoda K, Daida H.	Long-term effect of β-blocker in ST-segment elevation myocardial infarction in patients with preserved left ventricular systolic function: a propensity analysis	Heart Vessels		in press	2015

Ogita M, Miyauchi K, Kasai T, Doi S, Wada H, Naito R, Konishi H, Tsuboi S, Dohi T, Tamura H, Okazaki S, Daida H	Impact of preprocedural high-sensitive C-reactive protein levels on long-term clinical outcomes of patients with stable coronary artery disease and chronic kidney disease who were treated with drug-eluting stents.	J Cardiol		in press	2015
Sai E, Shimada K, Yokoyama T, Sato S, Nishizaki Y, Miyazaki T, Hiki M, Tamura Y, Aoki S, Watada H, Kawamori R, Daida H.	Evaluation of myocardial triglyceride accumulation assessed by 1H-magnetic resonance spectroscopy in apparently healthy Japanese subjects	Internal Med	54	367-373	2015
Konishi H, Miyauchi K, Kasai T, Tsuboi S, Ogita M, Naito R, Sai E, Fukushima Y, Katoh Y, Okai I, Tamura H, Okazaki S, Daida H.	Impact of lipoprotein(a) as residual risk on long-term outcomes in patients after percutaneous coronary intervention.	Am J Cardiol	115	157-160	2015
Ogita M, Miyauchi K, Jiang M, Kasai T,	Circulating soluble LR11, a novel marker of smooth muscle cell proliferation, is enhanced after coronary stenting in response to	Atherosclerosis	237	374-378	2014

Tsuboi S, Naito R, Konishi H, Dohi T, Yokoyama T, Okazaki S, Shimada K, Bujo H, Daida H	vascular injury.				
Dai Y, Konishi H, Takagi A, Miyauchi K, Daida H.	Red cell distribution width predicts short- and long-term outcomes of acute congestive heart failure more effectively than hemoglobin.	Exp Ther Med	8	600-606	2014
Someya Y, Kawai S, Kohmura Y, Aoki K, Daida H.	Cardiorespiratory fitness and the incidence of type 2 diabetes: a cohort study of Japanese male athletes.	BMC Public Health.	14	493	2014
Saito M, Ueshima K, Saito M, Iwasaka T, Daida H. Kohzuki M, Makita S, Adachi H, Yokoi H, Omiya K, Mikouchi H, Yokoyama H, Goto Y	Japanese Cardiac Rehabilitation Survey Investigators. Safety of exercise-based cardiac rehabilitation and exercise testing for cardiac patients in Japan: a nationwide survey	Circ J	78	1646-1653	2014
Maruyama M, Daimon M, Kawata T, Kasai T, Ichikawa R, Miyazaki S,	Early hemodynamic performance of the trifecta bioprosthetic valve in patients with aortic valve disease	Circ J	78	1372-1378	2014

Ohmura H, Yamamoto T, Amano A, Daida H					
Masuda H, Miyazaki T, Shimada K, Tamura N, Matsudaira R, Yoshihara T, Ohsaka H, Sai E, Matsumori R, Fukao K, Hiki M, Kume A, Kiyanagi T, Takasaki Y, Daida H.	Disease duration and severity impacts on long-term cardiovascular events in Japanese patients with rheumatoid arthritis	J Cardiol	64	366-370	2014
Konishi H, Miyauchi K, Kasai T, Tsuboi S, Ogita M, Naito R, Katoh Y, Okai I, Tamura H, Okazaki S, Daida H	Long-term prognosis and clinical characteristics of young adults (≤40 years old) who underwent percutaneous coronary intervention	J Cardiol	64	171-174	2014
Miyazaki T, Hiki M, Shimada K, Kume A, Kiyanagi T, Sumiyoshi K, Daida H	High Molecular Weight Adiponectin Level is Associated with Atherogenic Lipoprotein Profiles in Healthy Japanese Males	J Atheroscler Thromb	21	672-679	2014

Miyazaki T, Shimada K, Hki M, Kume A, Kitamura Y, Oshida K, Yanagisawa N, Kiyanagi T, Matsumori R, Daida H	High hexacosanoic acid levels are associated with coronary artery disease	Atherosclerosis.	223	429-433	2014
Daida H, Teramoto T, Kitagawa Y, Matsushita Y, Sugihara M	The relationship between low-density lipoprotein cholesterol levels and the incidence of cardiovascular disease in high-risk patients treated with pravastatin: main results of the APPROACH-J study.	Int Heart J	55	39-47	2014
Naito R, Miyauchi K, Ogita M, Kasai T, Kawaguchi Y, Tsuboi S, Konishi H, Okazaki S, Kurata T, Daida H	Impact of admission glycemia and glycosylated hemoglobin A1c on long-term clinical outcomes of non-diabetic patients with acute coronary syndrome	J Cardiol	63	106-111	2014
Hosokawa K, Ando S, Tohyama T, Kiyokawa T, Tanaka Y, Otsubo H, Nakamura R, Kadokami T, Fukuyama T	Estimation of nocturnal cardiac output by automated analysis of circulation time derived from polysomnography	Int J Cardiol	181	14-16	2015

Ⅳ．研究成果の刊行物・別刷

Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

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

Received January 18, 2015; revised manuscript received March 13, 2015; accepted March 16, 2015; released online May 1, 2015 Time for primary review: 11 days

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

ISSN-1346-9843 doi:10.1253/circj.CJ-15-0062

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

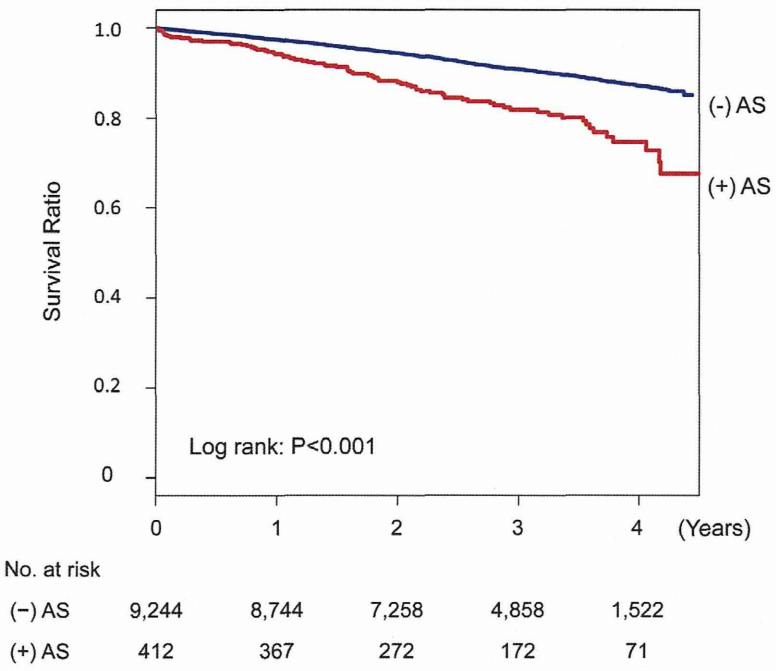

Figure 1. Kaplan-Meier survival curves for all-cause death in patients with and without aortic stenosis (AS).

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.

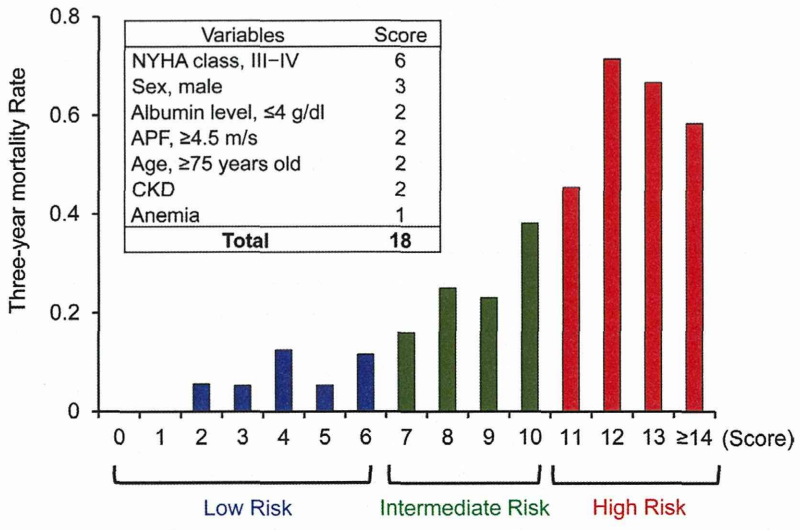

Figure 2. Scoring system and incidence of all-cause death. APF, aortic peak flow; CKD, chronic kidney disease; NYHA, New York Heart Association.

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

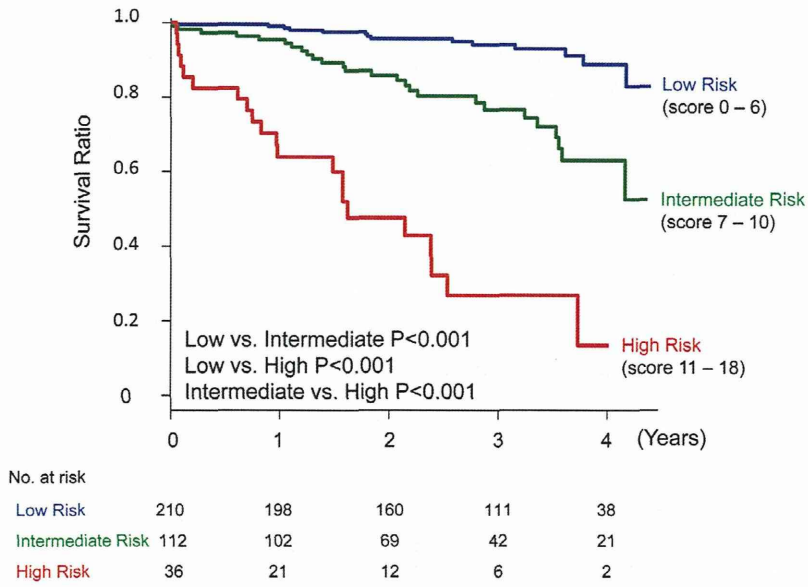

Figure 3. Kaplan-Meier survival curves for all-cause death in the 3 risk groups.

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

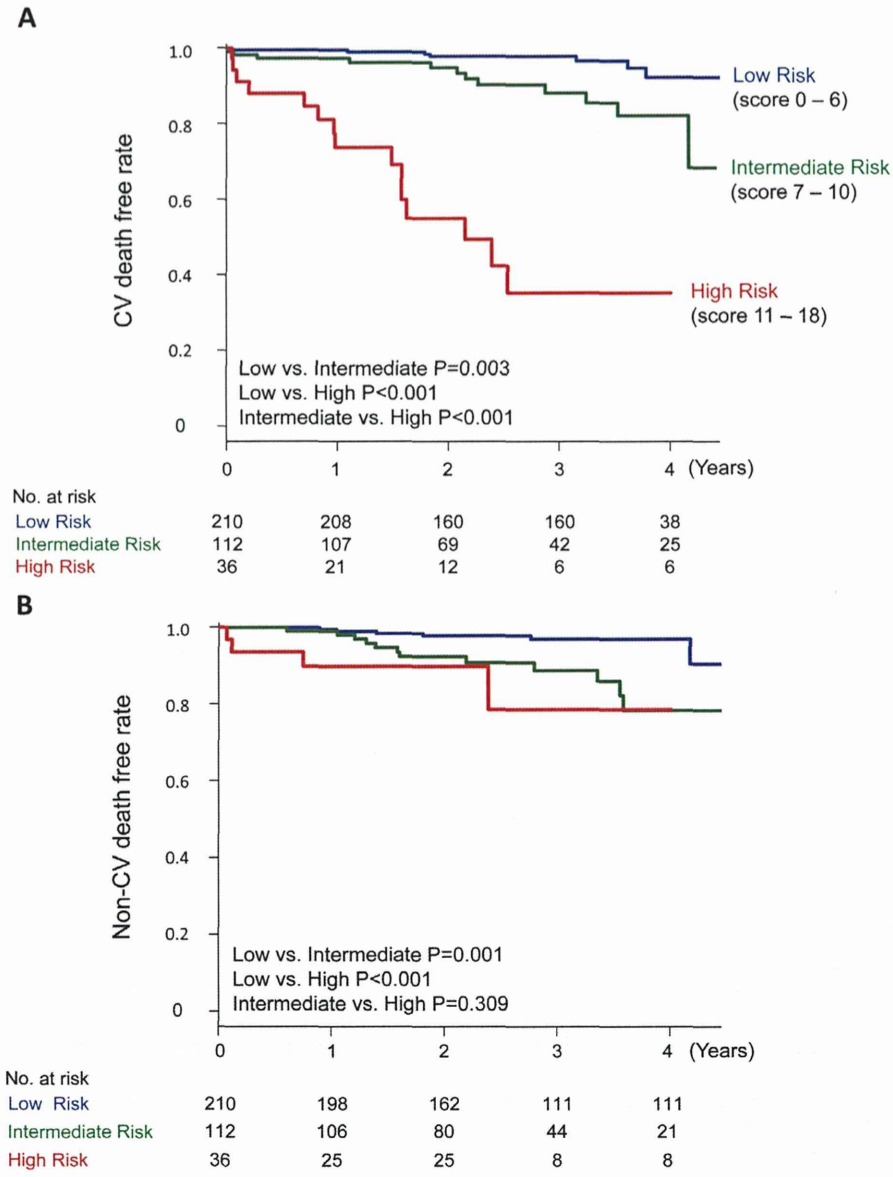

Figure 4. Kaplan-Meier survival curves for (**A**) cardiovascular (CV) and (**B**) non-CV death in the 3 risk groups.

chest pain was approximately 2, 3, and 5 years, respectively.[2] 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,[30–32] 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.[30] 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.[33] In general, aortic valve surgery has not been indicated if the patient is asymptomatic, has higher risk, or refuses it.[4] 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.[5,6,34] 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 cm^2 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.

Funding

This study was supported by Grants-in-Aid from the Research Grant from the Ministry of Health, Labor and Welfare (H.S.).

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

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: A population-based study. *Lancet* 2006; **368:** 1005–1011.
2. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968; **38**(Suppl 1)**:** 61–67.
3. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005; **111:** 3290–3295.
4. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 non-surgically managed patients with severe aortic stenosis. *Ann Thorac Surg* 2006; **82:** 2111–2115.
5. Sawa Y, Saito S, Kobayashi J, Niinami H, Kuratani T, Maeda K, et al. First clinical trial of a self-expandable transcatheter heart valve in Japan in patients with symptomatic severe aortic stenosis. *Circ J* 2014; **78:** 1083–1090.
6. Shibayama K, Watanabe H, Tabata M, Sasaki S, Takanashi S, Sumiyoshi T, et al. Impact of ejection fraction on long-term outcome after elective aortic valve replacement in octogenarians with aortic stenosis. *Circ J* 2012; **76:** 1761–1767.
7. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation* 2010; **121:** 1502–1509.
8. Henkel DM, Malouf JF, Connolly HA, Michelena HI, Scott CG, Pellikka PA, et al. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: Characteristics and outcomes. *J Am Coll Cardiol* 2012; **60:** 2325–2329.
9. Bonow RO, Carabello B, Chatterjee K, Otto CM, Shah PM, Shanewise JS, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1988 Guidelines for the Management of Patients With Valvular Heart Disease). *Circulation* 2006; **114:** 450–527.
10. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33:** 2451–2496.
11. Japanese Circulation Society. Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease (JCS2012). Available at: www.j-circ.or.jp/guideline/pdf/JCS2012_ookita_h.pdf (in Japanese) (accessed April 20, 2015).
12. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. *J Am Coll Cardiol* 2009; **54:** 1003–1011.
13. Garcia D, Pibarot P, Dumesnil JG, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: A new index based on the energy loss concept. *Circulation* 2000; **100:** 765–771.
14. Kume T, Okura H, Kawamoto T, Watanabe N, Hayashida A, Yoshida K, et al. Clinical implication of energy loss coefficient in patients with severe aortic stenosis diagnosed by Doppler echocardiography. *Circ J* 2008; **72:** 1265–1269.
15. Bahlmann E, Cramariuc D, Gerdts E, Gohlke-Baerwolf C, Nienaber CA, Eriksen E, et al. Impact of pressure recovery on echocardiographic assessment of asymptomatic aortic stenosis: A SEAS substudy. *JACC Cardiovasc Imaging* 2010; **3:** 555–562.
16. Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Stark ME, Shapiro BP, et al. Indices of von Willebrand factor as biomarkers of aortic stenosis severity (from the Biomarkers of Aortic Stenosis Severity [BASS] study). *Am J Cardiol* 2013; **111:** 374–381.
17. Ky B, French B, Levy WC, Sweitzer NK, Fang JC, Wu AH, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ Heart Fail* 2012; **5:** 183–190.
18. Weber M, Arnold R, Rau M, Brandt R, Berkovitsch A, Mitrovic V, et al. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. *Am J Cardiol* 2004; **94:** 740–745.
19. Qi W, Mathisen P, Kjekshus J, Simonsen S, Bjørnerheim R, Endresen K, et al. Natriuretic peptides in patients with aortic stenosis. *Am Heart J* 2001; **142:** 725–732.
20. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle heart failure model: Prediction of survival in heart failure. *Circulation* 2006; **113:** 1424–1433.
21. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: A risk score based on 39372 patients from 30 studies. *Eur Heart J* 2013; **34:** 1404–1413.
22. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; on behalf of the CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 study. *Circ J* 2011; **75:** 823–833.
23. Nochioka K, Sakata Y, Takahashi J, Miyata S, Miura M, Takada T, et al; on behalf of the CHART-2 Investigators. Prognostic impact of nutritional status in asymptomatic patients with cardiac diseases: A report from the CHART-2 Study. *Circ J* 2013; **77:** 2318–2326.
24. Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, et al. Gender differences in clinical characteristics, treatment and long-term outcome in patients with stage C/D heart failure in Japan: Report from the CHART-2 study. *Circ J* 2014; **78:** 2276–2283.
25. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **128:**

e240–e327, doi:10.1161/CIR.0b013e31829e8776.
26. World Health Organization. Nutritional anemias: Report of a WHO scientific group. *WHO Tech Rep Ser* 1968; **405:** 3–37.
27. Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. *Am Heart J* 1980; **99:** 419–424.
28. Bouma B, van den Brink RB, van der Meulen JH, Verheul HM, Cheriex EC, Hamer HM, et al. To operate or not on elderly patients with aortic stenosis: The decision and its consequences. *Heart* 1999; **82:** 143–148.
29. Perera S, Wijesinghe N, Ly E, Devlin G, Pasupati S. Outcomes of patients with untreated severe aortic stenosis in real-world practice. *NZ Med J* 2011; **124:** 40–48.
30. Monin JL, Lancellotti P, Monchi M, Lim P, Weiss E, Piérard L, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. *Circulation* 2009; **120:** 69–75.
31. Pellika PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990; **15:** 1012–1017.
32. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; **343:** 611–617.
33. Ohno M, Hashimoto Y, Suzuki M, Matsumura A, Isobe M. Current state of symptomatic aortic valve stenosis in the Japanese elderly. *Circ J* 2011; **75:** 2474–2481.
34. Brown ML, Pellikka PA, Schaff HV, Scott CG, Mullany CJ, Orszulak TA, et al. The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. *J Thorac Cardiovasc Surg* 2008; **135:** 308–315.

Appendix

The CHART-2 Study Investigators

Executive Committee

Hiroaki Shimokawa (Chair), Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Mitsumasa Fukuchi, Kanichi Inoue, Atsushi Kato, Masafumi Sugi, Masatoshi Ohe, Tsuyoshi Shinozaki, Satoru Horiguchi, Hiroshi Kato.

Steering Committee

Kanichi Inoue, Tetsuya Hiramoto, Masahiko Ogata, Atsushi Kato, Shoichi Sato, Masafumi Sugi.

Collaborating Hospitals and Active Investigators by Prefecture

Aomori Prefecture

Shigeto Oyama (Towada City Hospital).

Iwate Prefecture

Eiji Nozaki, Akihiro Nakamura, Tohru Takahashi, Hideaki Endo, Shigefumi Fukui, Sota Nakajima (Iwate Prefectural Central Hospital); Makoto Nakagawa, Tetsuji Nozaki, Takuya Yagi (Iwate Prefectural Isawa Hospital).

Akita Prefecture

Satoru Horiguchi, Etsuko Fushimi, Yoshinao Sugai, Satoru Takeda, Kouhei Fukahori, Kentaro Aizawa (Hiraka General Hospital).

Yamagata Prefecture

Masatoshi Ohe, Takurou Tashima, Katsuhiko Sakurai, Tadashi Kobayashi (Kojirakawa Shiseido Hospital); Toshikazu Goto, Motoyuki Matsui, Yoshiaki Tamada, Tomoyasu Yahagi, Akio Fukui, Katsuaki Takahashi, Yoku Kikuchi (Yamagata Prefectural Central Hospital).

Miyagi Prefecture

Akihiko Sugimura, Junko Ohashi (Sendai Red Cross Hospital); Hiroyuki Kanno, Junji Kaneko (Katta General Hospital); Shu Suzuki, Kikuyo Takahashi (KKR Tohoku Kosai Hospital); Kenjiro Akai (Kurihara Central Hospital); Dai Katayose (Miyagi Rifu Ekisaikai Hospital); Sachio Onodera, Tetsuya Hiramoto, Seiji Komatsu, Masanobu Chida, Kaoru Iwabuchi, Masaharu Takeuchi, Hirokazu Yahagi, Nozomu Takahashi (Osaki Citizen Hospital); Keiji Otsuka, Yoshito Koseki, Masaki Morita (Saito Hospital); Tsuyoshi Shinozaki, Takeshi Ishizuka, Noriko Onoue, Nobuhiro Yamaguchi, Hiroshi Fujita (Sendai Medical Center); Atsushi Katoh, Shigeto Namiuchi, Tadashi Sugie, Kenya Saji, Toru Takii, (Sendai Open Hospital); Mitsumasa Fukuchi, Masahiko Ogata, Toshinori Tanikawa, Osamu Kitamukai (Sendai Tokushukai Hospital); Yasuharu Matsumoto (Shizugawa Public Hospital); Kanichi Inoue, Jiro Koyama, Tomoko Tomioka, Hiroki Shioiri, Yoshitaka Ito (South Miyagi Medical Center); Hiroshi Kato, Chikako Takahashi, Akiko Kawana (Tohoku Rosai Hospital); Yasuhiko Sakata, Kenta Ito, Masaharu Nakayama, Koji Fukuda, Jun Takahashi, Satoshi Miyata, Koichiro Sugimura, Kimio Sato, Yasuharu Matsumoto, Makoto Nakano, Takashi Shiroto, Ryuji Tsuburaya, Kotaro Nochioka, Hiroaki Yamamoto, Tatsuo Aoki, Kiyotaka Hao, Masanobu Miura, Masaki Kondo, Shunsuke Tatebe, Saori Yamamoto, Hideaki Suzuki, Kensuke Nishimiya, Nobuhiro Yaoita (Tohoku University Hospital).

Fukushima Prefecture

Masafumi Sugi, Yoshito Yamamoto, Sunao Toda, Yutaka Minatoya, Yusuke Takagi, Yuhi Hasebe, Taro Nihei (Iwaki Kyouritsu Hospital); Koji Fukuda (Watanabe Hospital).

Head Office and Coordinating Center

Yasuhiko Sakata, Yoshihiro Fukumoto, Jun Takahashi, Satoshi Miyata, Kotaro Nochioka, Masanobu Miura, Soichiro Tadaki, Ryoichi Ushigome, Takeshi Yamauchi, Kenjiro Sato, Kanako Tsuji, Takeo Onose, Ruri Abe, Chiharu Saga, Junko Suenaga, Yoko Yamada, Junko Kimura, Hiromi Ogino, Izumi Oikawa, Sanae Watanabe, Madoka Saga, Miki Washio, Keiko Nagasawa, Sachiko Nagasawa, Sachie Kotaka, Wakiko Komatsu, Reiko Hashimoto, Yasuko Ikeno, Tomoyuki Suzuki, Hiroko Hamada.

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.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0062

Advance Publication by-J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Improved Long-Term Prognosis of Dilated Cardiomyopathy With Implementation of Evidenced-Based Medication

– Report From the CHART Studies –

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

Background: Recent trends in the clinical characteristics, management and prognosis of dilated cardiomyopathy (DCM) remain to be examined in Japan.

Methods and Results: We compared 306 and 710 DCM patients in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 (2000–2005, n=1,278) and the CHART-2 (2006–present, n=10,219) Studies, respectively. Between the 2 groups of DCM patients, there were no significant differences in baseline characteristics. The prevalence of hypertension, dyslipidemia and diabetes mellitus were all significantly increased from the CHART-1 to the CHART-2 Study. The use of β-blockers and aldosterone antagonists was significantly increased, while that of loop diuretics and digitalis was significantly decreased in the CHART-2 Study. The 3-year mortality rate was significantly improved from 14% in the CHART-1 to 9% in the CHART-2 Study (adjusted HR, 0.60; 95% CI: 0.49–0.81; P=0.001). In particular, 3-year incidence of cardiovascular death was significantly decreased (adjusted HR, 0.26; 95% CI: 0.14–0.50, P<0.001), while that of HF admission was not (adjusted HR, 0.90; 95% CI: 0.59–1.37, P=0.632). The prognostic improvement was noted in patients with BNP <220 pg/ml, LVEF>40%, β-blocker use and aldosterone antagonist use.

Conclusions: Long-term prognosis of DCM patients has been improved, along with the implementation of evidence-based medication in Japan.

Key Words: Beta-blocker; Dilated cardiomyopathy; Lifestyle disease; Prognosis

Idiopathic dilated cardiomyopathy (DCM) is a disorder of the heart muscle in which the heart chambers are progressively enlarged or dilated.[1–3] The nationwide survey by the Japanese Ministry of Health, Labour and Welfare reported that the number of DCM patients in Japan was estimated to be 17,700 with a prevalence of 140/million in 1999.[4] Fuster et al reported that mortality in idiopathic DCM patients was 77% over 11 years between 1960 and 1973, while most of the deaths occurred during the first 2 years after diagnosis.[1] Recently, Merlo et al reported that an evidence-based therapeutic approach has improved the long-term prognosis of idiopathic DCM in the last 3 decades.[5] In Japan, it was reported that 5-year survival rate in idiopathic DCM improved from 62% in the 1980s to 90% in the 1990s.[6]

From 2000 to 2005, we conducted a multicenter prospective cohort of chronic heart failure (CHF) patients, named the Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1, n=1,278).[7,8] The CHART-1 Study found that the prognosis of CHF patients in Japan was equally poor compared with those in Western countries.[7,8] In 2006, we started the CHART-2 Study to elucidate the characteristics and prognosis of CHF patients in stages B–D.[8,9] In the CHART Studies, we reported that the use of renin angiotensin system inhibitors (RASI) and β-blockers for CHF patients was significantly increased, whereas that of loop diuretics and digitalis had decreased in the past years.[8,9] Recent trends in the clinical characteristics, management and prognosis of DCM patients in Japan, however, remain to be examined. In the present

Received August 24, 2014; revised manuscript received January 29, 2015; accepted February 16, 2015; released online April 2, 2015 Time for primary review: 36 days

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

The Guest Editor for this article was Hiroshi Ito, 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

ISSN-1346-9843 doi:10.1253/circj.CJ-14-0939

study, we thus examined the recent trends in baseline characteristics, treatment and long-term prognosis of DCM patients, by comparing the CHF database between the CHART-1 and CHART-2 Studies.

Methods

Study Design and Subjects

In the present study, a total of 1,016 DCM patients were enrolled from the database of the CHART-1 and the CHART-2 Studies (306 and 710 patients from the CHART-1 and CHART-2 Studies, respectively).[7–9] Both Studies are multicenter, prospective, hospital-based observational cohort studies of Japanese CHF patients. The CHART-1 Study was conducted between February 2000 and December 2005 and a total of 1,278 patients with CHF from the 26 hospitals (Tohoku University hospital and 25 affiliated hospitals) were enrolled.[7,8] The purpose of the CHART-1 Study was to elucidate the clinical characteristics, treatment and prognosis in Japanese CHF patients.[7,8] All patients had a structural disorder of the heart and were treated with standard therapy for CHF, including diuretics, digitalis, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and β-blocker. In 2006, we started the CHART-2 Study and successfully enrolled 10,219 consecutive patients, including 5,483 cardiovascular patients at high risk for development of HF (coronary artery disease or stage B)[10] and 4,736 patients with symptomatic CHF (stages C/D)[10] in the 24 hospitals (Tohoku University hospital and 23 affiliated hospitals). Tohoku University Hospital and 14 hospitals participated in both the CHART-1 and CHART-2 Studies, accounting for 74.0% and 75.8% of the total subjects enrolled, respectively. No patients enrolled in the CHART-1 Study were included in the CHART-2 Study. Diagnosis of CHF was based on the Framingham criteria,[11] while CHF stage was classified according to the ACCF/AHA HF Guidelines.[10]

The CHART-1 Study was approved by the committee of Tohoku University Hospital. The CHART-2 Study was approved by the human research committee of Tohoku University School of Medicine (conforming to the ethics guidelines of the 1975 Declaration of Helsinki), and also by the local ethics committee in each participating hospital and registered at Clinical Trials.gov (NCT00418041). Written informed consent was provided by all patients before enrollment. Information on medical history and baseline demographics, including medication and echocardiographic data, were collected at the time of enrollment by clinical research coordinators.

Definition of DCM

DCM was diagnosed by the attending physicians and/or the investigators at each hospital, based on the definition of DCM in the guidelines of the Japanese Circulation Society.[9] Briefly, DCM was diagnosed when a patient had global systolic dysfunction with dilated left ventricle (LV) after exclusion of known cardiac diseases, including ischemic cardiomyopathy, hypertensive heart disease, dilated phase of hypertrophic cardiomyopathy, cardiac sarcoidosis, myocarditis, amyloidosis, arrhythmogenic right ventricular cardiomyopathy, beriberi heart, alcoholic cardiomyopathy, non-compaction of ventricular myocardium, cardiomyopathy caused by muscular dystrophy, mitochondrial myopathy, chemical toxic cardiomyopathy, Fabry's disease, and postpartum cardiomyopathy.[9,12] Coronary angiography data were available in 98% of the patients enrolled from the CHART-2 study, in which absence of coronary artery stenosis was confirmed. No patients enrolled from the CHART-1 study had coronary angiography data in the database.[7,8]

Subjects

In the CHART-1 Study (n=1,278), 24 patients with missing data were excluded. Of these 1,254 patients, 306 patients (24.4%) were diagnosed as having DCM in the CHART-1 Study. In the CHART-2 Study (n=10,219), 5 patients with missing data were initially excluded. To make the selection bias minimal, we first selected patients from the CHART-2 Study according to the inclusion criteria of the CHART-1 Study. As a result, we selected 5,920 patients who met at least one of the following CHART-1 criteria: (1) LV ejection fraction (LVEF) <50%; (2) LV end-diastolic diameter (LVDd) ≥55 mm; or (3) at least one episode of congestive heart failure. From this population, 710 DCM patients (11.0%) were finally enrolled from the CHART-2 study. Finally, 306 and 710 DCM patients were enrolled from the CHART-1 and CHART-2 Studies, respectively.

Outcomes

The study endpoints were 3-year mortality, mode of death and 3-year hospitalization for worsening HF. Cardiovascular death was defined as death due to cardiovascular origins. Non-cardiovascular death was defined as death due to non-cardiovascular causes. For all patients, only the main mode of death was used. Hospitalization for worsening HF was defined as documentation of worsening HF requiring hospitalization. A patient admitted for worsening HF had to show signs and symptoms of HF and to require treatment with i.v. diuretics. Follow-up was made at least once a year by clinical research coordinators by means of review of medical records, surveys and telephone interviews.[8,9] All events were reviewed and assigned on consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association, by reviewing case reports, death certificates, medical records and hospital course summaries provided by the investigators.

Statistical Analysis

Continuous variables are expressed as mean±SE or median (IQR), as appropriate. Discrete variables are expressed as n (%). Wilcoxon rank sum and Fisher's exact test were used to compare the characteristics between patients from the CHART-1 and CHART-2 Studies. Kaplan-Meier curves were plotted to evaluate the association between DCM and all-cause death, cardiovascular death or hospitalization for worsening HF. Comparison of the survival time between the 2 groups was performed using log-rank test. Multivariate Cox proportional hazards model was used to analyze the relationship between survival and prognostic indices. The covariates were selected as follows: first, the univariate Cox models were fitted for each of the CHART-1 and the CHART-2 patients separately, with candidate variables of sex, age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, heart rate, New York Heart Association (NYHA) class, LVEF, LVDd, diabetes mellitus, dyslipidemia, atrial fibrillation, ventricular tachycardia, brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), β-blocker, RASI, aldosterone antagonist, and Ca channel blocker. Then, after the multivariate Cox models were fitted for each of the CHART-1 and the CHART-2 samples individually, using all the covariates with $P<0.2$ in each univariate model, the optimal subset of covariates was selected by stepwise backward elimination in each model. Finally, all the variables selected in either or both models were used as the final set of variables for the final

Table 1. Baseline DCM Patient Characteristics

	Total (n=1,014)		
	CHART-1 (n=306)	CHART-2 (n=710)	P-value
Age (years)	61.7±0.8	62.9±0.5	0.205
Male sex	222 (72.5)	517 (72.8)	0.939
Blood pressure (mmHg)			
Systolic	122.8±1.3	120.5±0.7	0.126
Diastolic	73.3±0.8	72.5±0.5	0.463
Heart rate (beats/min)	73.1±1.0	73.0±0.6	0.934
BMI (kg/m²)	23.4±0.3	23.5±0.2	0.787
NYHA classification			<0.001
I	40 (13.1)	135 (19.0)	
II	206 (67.3)	499 (70.4)	
III	57 (18.6)	71 (10.0)	
IV	3 (1.0)	4 (0.6)	
Laboratory data			
Hb (g/dl)	13.7±0.1	13.8±0.1	0.873
Anemia	77 (26.7)	159 (22.6)	0.164
BUN (mg/dl)	20.6±1.0	19.1±0.3	0.065
Cre (mg/dl)	1.03±0.06	1.00±0.03	0.651
eGFR (ml·min^{-1}·1.73 m^{-2})	67.7±1.4	66.4±0.9	0.451
BNP (pg/ml)	101.0 (41.3–259.5)	103.6 (42.9–254.6)	0.969
Echocardiography			
LVEF (%)	42.6±0.7	44.9±0.5	0.014
LVEF ≤40%	129 (42.6)	272 (38.6)	0.262
LVDd (mm)	61.1±0.5	58.8±0.3	<0.001
LVDs (mm)	48.8±0.5	46.0±0.4	<0.001
Comorbidity			
Hypertension	116 (37.9)	473 (66.7)	<0.001
Dyslipidemia	39 (12.7)	490 (69.0)	<0.001
Diabetes mellitus	43 (14.1)	145 (20.4)	0.017
Atrial fibrillation	107 (35.0)	292 (41.3)	0.059
Ventricular tachycardia	61 (19.9)	105 (14.8)	0.052
Medicine			
RASI	245 (80.1)	605 (82.5)	0.052
ACEI	203 (66.3)	407 (57.3)	0.008
ARB	48 (15.7)	222 (31.3)	<0.001
β-blockers	147 (48.0)	567 (79.9)	<0.001
Loop diuretics	213 (74.7)	449 (63.2)	<0.001
Digitalis	164 (55.8)	254 (35.8)	<0.001
Aldosterone antagonists	58 (20.2)	262 (36.9)	<0.001
Ca channel blockers	43 (14.6)	98 (13.8)	0.765
ICD/CRT-D	2 (0.7)	34 (4.8)	0.001

Data given as mean±SE, median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body-mass index; BNP, brain natriuretic peptide; Ca, calcium; CRT-D, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RASI, renin angiotensin system inhibitor.

multivariate model. In the Cox models, we used the following covariates as binary variables: age (<70 and ≥70 years), LVEF (≤40 and >40%), BNP (<220 and ≥220 pg/ml), eGFR (≤50 and >50 ml·min^{-1}·1.73 m^{-2}) and BMI (<18.5 and ≥18.5 kg/m^2).[13] The split values of age, LVEF, BNP and eGFR were determined using classification and regression tree (CART) analysis.[14–17] We examined the associations between β-blocker or aldosterone blocker use and outcomes with inverse probability of treatment weighting (IPTW) using the propensity score.[18] In IPTW analysis, we used propensity score calculated with the following covariates: sex, systolic blood pressure, diastolic blood pressure, heart rate, LVDd, history of HF admission, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, calcium channel blocker, RASI, loop diuretics, aldosterone antagonist, age, BNP, and eGFR. Two-sided P<0.05 was considered to be statistically significant. Interactions between