

# The CHA<sub>2</sub>DS<sub>2</sub>-VASc score as a predictor of high mortality in hospitalized heart failure patients

Akiomi Yoshihisa\*, Shunsuke Watanabe, Yuki Kanno, Mai Takiguchi, Akihiko Sato, Tetsuro Yokokawa, Shunsuke Miura, Takeshi Shimizu, Satoshi Abe, Takamasa Sato, Satoshi Suzuki, Masayoshi Oikawa, Nobuo Sakamoto, Takayoshi Yamaki, Koichi Sugimoto, Hiroyuki Kunii, Kazuhiko Nakazato, Hitoshi Suzuki, Shu-ichi Saitoh and Yasuchika Takeishi

Department of Cardiology and Hematology, Fukushima Medical University, Fukushima, Japan

## Abstract

**Aims** Atrial fibrillation (AF) is common in patients with heart failure (HF). CHA<sub>2</sub>DS<sub>2</sub>-VASc score was originally employed as a risk assessment tool for stroke in patients with AF; however, it has recently been used to predict not only stroke but also various cardiovascular diseases beyond the original AF field. We aimed to verify the CHA<sub>2</sub>DS<sub>2</sub>-VASc score as a risk assessment tool to predict mortality in patients with HF.

**Methods and Results** Consecutive 1011 patients admitted for treatment of HF were divided into three groups based on their CHA<sub>2</sub>DS<sub>2</sub>-VASc scores: score 1–3 group ( $n = 317$ ), score 4–6 group ( $n = 549$ ) and score 7–9 group ( $n = 145$ ). Of the 1011 HF patients, 387 (38.3%) had AF. We compared patient characteristics among the three groups and prospectively followed for all-cause mortality. Although left ventricular ejection fraction was similar among all three groups, all-cause mortality was higher in the score 4–6 group and score 7–9 group than in the score 1–3 group (37.9 and 29.3% vs. 15.1%, log-rank  $P < 0.001$ ). In the multivariable Cox proportional hazard analysis, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score 7–9 was an independent predictor of all-cause mortality (all HF patients: hazard ratio (HR) 1.822,  $P = 0.011$ ; HF patients with AF: HR 1.951,  $P = 0.031$ ; HF patients without AF: HR 2.215,  $P = 0.033$ ).

**Conclusions** The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was an independent predictor of all-cause mortality in HF patients with or without AF. This comprehensive risk assessment score may help identify HF patients who are at high risk for mortality in HF patient.

**Keywords** Heart failure; CHA<sub>2</sub>DS<sub>2</sub>-VASc score; Atrial fibrillation; Prognosis

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\*Correspondence to: Akiomi Yoshihisa, Department of Cardiology and Hematology, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan.

Tel: +81 24 547 1190; Fax: +81 24 548 1821. Email: yoshihis@fmu.ac.jp

## Introduction

Heart failure (HF) is a major cause of death among the elderly in many countries and has become a significant public health problem.<sup>1,2</sup> The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are risk assessment tools to predict stroke in patients with atrial fibrillation (AF)<sup>3</sup> and can be used to guide anticoagulation therapy,<sup>4,5</sup> in complement with or as a substitute of other risk scores for AF.<sup>6</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been proved to be more sensitive than the CHADS<sub>2</sub> score to predict cardio-embolic events in

AF patients.<sup>7</sup> In recent years, the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in predicting ischemic stroke, thromboembolism, and death has extended beyond the originally proposed AF field.<sup>8,9</sup> It has been reported that high CHA<sub>2</sub>DS<sub>2</sub>-VASc score are associated with mortality in patients with acute coronary syndrome,<sup>10</sup> irrespective of the presence or absence of AF. However, the impact of CHA<sub>2</sub>DS<sub>2</sub>-VASc score on mortality in HF patients remains unclear.

Therefore, the aims of the present study were to verify the value of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score as a risk assessment tool for

mortality in patients with HF, irrespective of the presence or absence of AF.

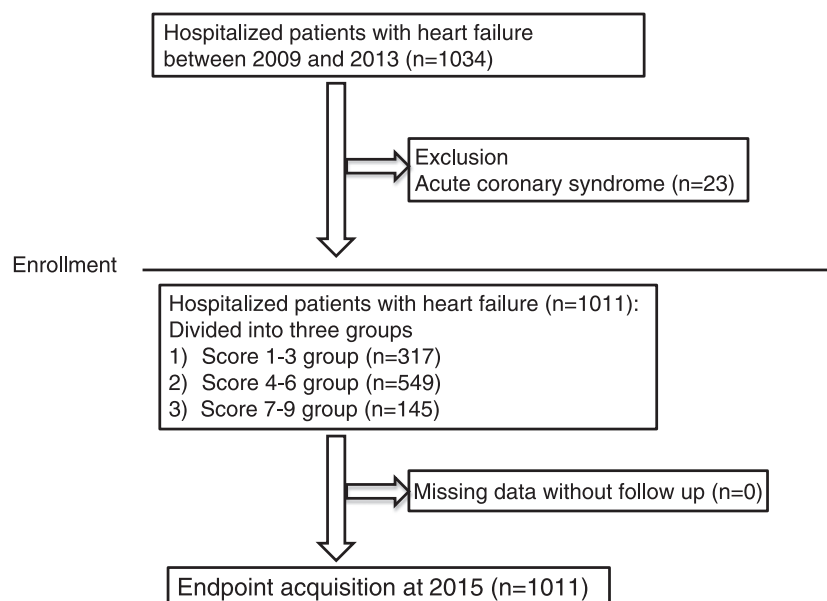
## Methods

### Subjects and study protocol

This was a prospective observational study that enrolled consecutive symptomatic HF patients hospitalized for treatment of decompensated HF at Fukushima Medical University between 2009 and 2013. Patients were defined based on the Framingham criteria<sup>11</sup> and New York Heart Association (NYHA) class  $\geq$  II at enrollment, and those with acute coronary syndrome were excluded (Figure 1). The patients were divided into three groups based on their CHA<sub>2</sub>DS<sub>2</sub>-VASc score during hospitalization (patients were given: 1 point for an age 65 to 74 years, female sex, HF, hypertension, diabetes mellitus, and vascular disease; and 2 points for an age 75 years or older, previous stroke/transient ischemic attack; and these were summed up as of 1–9 points): score 1–3 group ( $n=316$ ), score 4–6 group ( $n=549$ ) and score 7–9 group ( $n=145$ ).<sup>4</sup> We compared the clinical features and results from laboratory tests and echocardiography among the three groups. Hypertension was defined as recent use of antihypertensive drugs, or systolic blood pressure  $\geq$  140 mmHg, and/or diastolic blood pressure  $>$  90 mmHg. Diabetes was defined as recent use of insulin or antidiabetic drugs, a fasting blood glucose value of  $>$  126 mg/dL, and/or a hemoglobin A<sub>1c</sub> value of  $>$  6.5%. Dyslipidemia was defined

as recent use of cholesterol-lowering drugs, a triglyceride value of  $>$  150 mg/dL, a low-density lipoprotein cholesterol value of  $>$  140 mg/dL, and/or a high-density lipoprotein cholesterol value of  $<$  40 mg/dL. The estimated glomerular filtration rate (GFR) was measured by the Modification of Diet in Renal Disease formula.<sup>12</sup> Chronic kidney disease was defined as an estimated GFR  $<$  60 mL/min/1.73 m<sup>2</sup>.<sup>12</sup> Anemia was defined as hemoglobin of  $<$  12.0 g/dL in females and  $<$  13.0 g/dL in males.<sup>2</sup> AF was identified by an electrocardiogram performed during hospitalization and/or medical records including past history. Vascular disease includes coronary artery disease, cerebrovascular disease, and peripheral artery disease. The patients were followed up until March 2015 for all-cause mortality, which was the primary outcome of our study. We could follow up all of patients. Cardiac death was adjudicated by independent experienced cardiologists and included death due to worsened HF in accordance with the Framingham criteria,<sup>11</sup> ventricular fibrillation documented by electrocardiogram or other implantable devices and acute coronary syndrome. Non-cardiac death included death due to cancer, respiratory failure, renal failure, infection, sepsis, stroke, or digestive hemorrhage etc. Status and dates of death were obtained from the patients' medical records or their referring cardiologists. Survival time was calculated from the date of hospitalization until the date of death or last follow-up. Those administering the survey were blind to the analyses. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms to the principles outlined in

Figure 1 Patient flow-chart.



the Declaration of Helsinki. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.<sup>13</sup>

## Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques. Echocardiographic parameters included left ventricular ejection fraction (LVEF), left atrial volume, the ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/E'), inferior vena cava diameter, peak systolic pulmonary artery pressure (SPAP) and right ventricular fractional area change.<sup>14</sup> The LVEF was calculated using Simpson's method. Mitral valve E/E' was calculated by transmitral Doppler flow and tissue Doppler imaging. Mitral valve E' was obtained from the average of septal and lateral annular velocities. SPAP was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient.<sup>14</sup> The right ventricular fractional area change, defined as (end diastolic area–end systolic area)/end diastolic area×100, is a measure of right ventricular systolic function.<sup>14</sup> All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

## Statistical analysis

Normally distributed data are presented as mean±SD and non-normally distributed data are presented as median (inter-quartile range). Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. We used the analysis of variance (ANOVA) followed by Tukey's post-hoc test. The Kaplan–Meier method was used for presenting the event-free rate, and the log-rank test was used for initial comparisons. Univariable and multivariable Cox proportional hazard analyses were used to analyze predictors of all-cause mortality to adjust confounding factors. Hazard ratio (HR) and 95% confidence interval (CI) are presented. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score to predict all-cause mortality in the Cox proportional hazards regression model was analysed by C-statistics. To prepare for potential confounding, we considered the following clinical factors, which are not included in the elements of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and are generally known to affect the risk of mortality in HF patients: the levels of systolic blood pressure, heart rate, NYHA class above III, presence of ischemic etiology, reduced LVEF (<50%), AF, chronic kidney disease, anemia, hyponatremia (<135 mEq/l), and usage of RAS-inhibitors,

β-blockers, diuretics, inotropic agents, anti-diabetic agents, and statins.

Furthermore, to assess the potential heterogeneity of associations between CHA<sub>2</sub>DS<sub>2</sub>-VASc score and all-cause mortality, we conducted subgroup analyses. Interactions between CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and clinically relevant variables, including systolic blood pressure (mean, 128 mmHg), heart rate (mean, 83 bpm), presence of NYHA class above III, reduced LVEF (LVEF < 50%), ischemic etiology, AF, chronic kidney disease, anemia, and hyponatremia, were estimated by a Cox proportional hazards regression model, and are shown in a Forest plot. A value of  $P < 0.05$  was considered statistically significant for all comparisons. These analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY, USA).

## Results

The clinical features of the present study's subjects are summarized in *Table 1*. The score 7–9 group had a higher prevalence of female gender, more co-morbidities, including hypertension, diabetes, chronic kidney disease, anemia, stroke and vascular disease, a higher age, and a higher systolic blood pressure than the score 1–3 and score 4–6 groups. Comparisons of laboratory data and parameters of echocardiography among the three groups are shown in *Table 2*. The score 7–9 group had lower levels of hemoglobin, estimated GFR, total protein, albumin, and higher levels of B-type natriuretic peptide, C-reactive protein, and glucose than the score 1–3 group. With regard to parameters of echocardiography, left and right ventricular systolic function did not differ among the three groups, and mitral valve E/E' was higher in the score 7–9 group than in the score 1–3 group.

During the follow-up period (median 801 days), there were 151 cardiac deaths, including 119 due to worsening HF and 32 with ventricular fibrillation, and 113 non-cardiac deaths (cancer,  $n = 29$ ; respiratory failure and/or pneumonia,  $n = 27$ ; infection/sepsis,  $n = 18$ ; stroke,  $n = 11$ ; renal failure/multiple organ failure,  $n = 9$ ; digestive hemorrhage,  $n = 6$ ; aneurysm,  $n = 4$ ; and other problems  $n = 9$ ). We estimated the C-statistic for CHA<sub>2</sub>DS<sub>2</sub>-VASc score (0.664, 95% CI: 0.625–0.702). The number of patients and mortality according to each CHA<sub>2</sub>DS<sub>2</sub>-VASc score is shown in the *Table S1*. As shown in *Figure 2*, all-cause mortality was significantly higher in the score 4–6 group and score 7–9 group than in the score 1–3 group ( $P < 0.001$ ). Furthermore, as shown in *Figures 3 and 4*, all-cause mortalities were significantly higher in the score 4–6 group and score 7–9 group than in the score 1–3 groups ( $P < 0.001$ ) in the HF patients, irrespective of the presence or absence of AF (*Figure 3A and B*), ischemic or non-ischemic etiology (*Figure 4A and B*), and reduced or preserved ejection fraction (EF) (*Figure 4C and D*). The Cox proportional hazard

**Table 1** Comparisons of clinical features among CHA<sub>2</sub>DS<sub>2</sub>-VAsC score class (n = 1011)

	Score 1–3 (n = 317)	Score 4–6 (n = 549)	Score 7–9 (n = 145)	P-value
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score	2.4 ± 0.7	4.8 ± 0.8 **	7.3 ± 0.5 ** ††	< 0.001
Age (years)	54.3 ± 12.6	72.0 ± 12.1 **	78.3 ± 6.6 ** ††	< 0.001
Male gender (n, %)	224 (70.7)	329 (59.9)	58 (40.0)	< 0.001
Body mass index (kg/cm <sup>2</sup> )	23.1 ± 4.0	22.7 ± 4.2	23.3 ± 3.7	0.224
Systolic BP (mmHg)	122.4 ± 30.8	128.8 ± 33.0 *	139.2 ± 37.5 ** ††	< 0.001
Diastolic BP (mmHg)	73.9 ± 21.9	72.5 ± 20.9	72.6 ± 22.7	0.642
Heart rate (bpm)	86.7 ± 27.7	81.1 ± 24.4 **	85.3 ± 26.8	0.006
NYHA class III/IV	43 (13.6)	119 (21.7)	37 (25.5)	0.002
Ischemic etiology (n, %)	25 (7.9)	165 (30.1)	63 (44.8)	< 0.001
Reduced LVEF (n, %)	174 (54.9)	312 (56.8)	77 (53.1)	0.682
Co-morbidity				
Hypertension (n, %)	175 (55.2)	447 (81.4)	140 (96.6)	< 0.001
Diabetes (n, %)	63 (19.9)	260 (47.4)	96 (66.2)	< 0.001
Dyslipidemia (n, %)	234 (73.8)	434 (79.1)	115 (79.3)	0.175
Atrial fibrillation (n, %)	96 (30.3)	230 (41.9)	61 (42.1)	0.002
CKD (n, %)	136 (42.9)	362 (65.9)	108 (74.5)	< 0.001
Anemia (n, %)	124 (39.1)	347 (63.2)	123 (84.8)	< 0.001
Stroke/TIA (n, %)	5 (1.6)	101 (18.4)	115 (79.3)	< 0.001
Vascular disease (n, %)	48 (15.1)	278 (50.6)	110 (75.9)	< 0.001
Medications				
RAS inhibitors (n, %)	226 (71.3)	426 (77.6)	118 (81.4)	0.031
β-blockers (n, %)	253 (79.8)	416 (75.8)	107 (73.8)	0.263
Calcium channel blockers (n, %)	64 (20.2)	191 (34.8)	75 (51.7)	< 0.001
Diuretics (n, %)	187 (59.0)	382 (69.6)	105 (72.4)	0.002
Inotropic agents (n, %)	38 (12.0)	78 (14.2)	14 (9.7)	0.296
Anti-diabetic agents (n, %)	26 (8.2)	165 (30.1)	62 (42.8)	< 0.001
Statins (n, %)	82 (25.9)	231 (42.1)	68 (46.9)	< 0.001
Antiplatelets (n, %)	106 (33.4)	281 (51.2)	112 (77.2)	< 0.001
Anti-coagulations (n, %)	195 (61.5)	311 (56.6)	74 (51.0)	0.094

CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin-aldosterone system; TIA, transient ischemic attack.

\**P* < 0.05 and \*\**P* < 0.01 vs. low score group, †*P* < 0.05 and ††*P* < 0.01 vs. moderate score group.

model was used to examine the prognostic value of the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score in HF patients (Table 3).

In the multivariable analysis, the higher CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was an independent predictor of all-cause mortality in HF patients irrespective of the presence or absence of AF, after adjusting for other confounding factors. Interaction analyses rendered similar results to subgroup analyses, with the additional benefit of being able to statistically test for differences in associations between CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and all-cause mortality between subgroups.

In Figure 5, a Forest plot illustrates the association between the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and all-cause mortality in subgroups after adjustment for interactions between the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and prespecified clinically important variables. There was no interaction CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and other important variables to affect all-cause mortality.

## Discussion

We emphasized that CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was useful in predicting mortality in HF patients, irrespective of the presence or absence of AF, ischemic or non-ischemic etiology, and reduced or preserved EF.

In HF patients, AF is a frequent co-morbidity and its prevalence is related to the severity of the clinical status of patients.<sup>15</sup> HF and AF share common risk-factors, and the occurrence of either of them may induce the onset of a vicious circle which, in turn, facilitates the manifestation of the other.<sup>16</sup> Although the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VAsC score series are predictors of stroke in AF patients,<sup>3</sup> their predictivity has recently extended beyond their original field as follows: (1) ischemic stroke in patients with coronary artery disease without AF,<sup>17</sup> (2) mortality, recurrences of stroke, and major cardiovascular events in stroke patients without AF,<sup>18</sup> (3) mortality in stroke survivors with or without AF,<sup>19</sup> (4) hospitalization for cardiovascular causes in AF patients,<sup>20</sup> and (5) HF hospitalization and cardiac death in HF patients who underwent cardiac resynchronization therapy.<sup>21</sup> In addition, it has been recently reported that CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was associated with not only thromboembolic complications but also mortality in patients with HF.<sup>22</sup> The absolute risk of thromboembolic complications in HF patients at high CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores is higher in those without AF than in those with AF,<sup>22</sup> concordant with our data. Unlike the previous data,<sup>22</sup> we focused on the impact of CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores on mortality under some clinically important backgrounds including NYHA class, LVEF, etiology of HF, and presence of chronic kidney disease, anemia, hyponatremia, and

**Table 2** Laboratory data and echocardiographic data

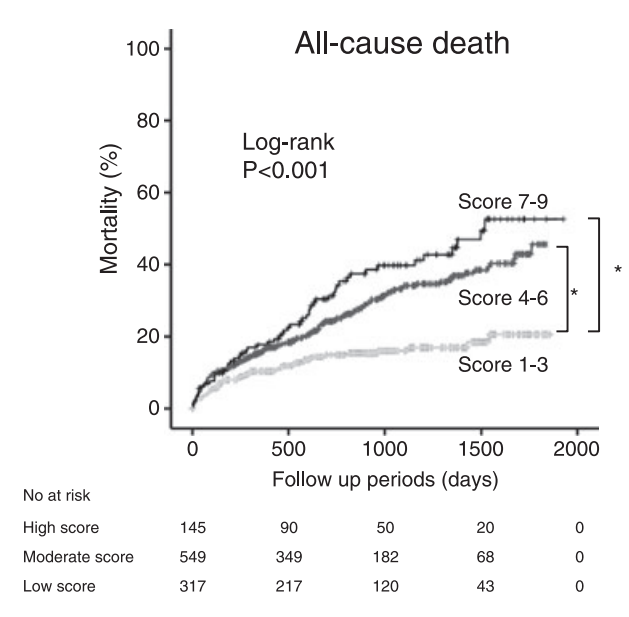
	Score 1–3 (n = 317)	Score 4–6 (n = 549)	Score 7–9 (n = 145)	P-value
<b>Laboratory data</b>				
Hemoglobin (g/dL)	13.4 ± 2.2	12.1 ± 2.4 **	11.2 ± 1.8 ** ††	<0.001
BNP (pg/mL) §	248.5 (549)	384.4 (590)	541.4 (879) **	0.006
eGFR (mL/min/1.73 cm <sup>2</sup> )	64.3 ± 24.4	52.7 ± 23.8 **	40.0 ± 22.3 ** ††	<0.001
C-reactive protein (mg/dL)	0.23 (1)	0.28 (1)	0.60 (3) ** ††	0.004
Total protein (g/dL)	7.0 ± 0.9	6.9 ± 0.8	6.8 ± 0.7 *	0.017
Albumin (g/dL)	3.8 ± 0.6	3.6 ± 0.6 **	3.4 ± 0.5 **	<0.001
Sodium (mEq/L)	139.4 ± 3.1	138.4 ± 4.5 **	138.5 ± 3.8	0.002
Glucose (mg/dL)	111.5 ± 30.4	137.8 ± 64.7 **	144.3 ± 68.0 **	<0.001
HemoglobinA1c (%)	5.5 ± 0.6	5.9 ± 1.1	6.0 ± 1.2	0.061
Total cholesterol (mg/dL)	182.7 ± 43.0	175.8 ± 42.5	176.6 ± 39.2	0.268
HDL (mg/dL)	49.4 ± 20.0	48.8 ± 19.2	47.7 ± 17.1	0.830
LDL (mg/dL)	110.7 ± 36.8	102.0 ± 38.0 *	102.7 ± 31.0	0.022
Triglyceride (mg/dL)	125.4 ± 81.4	112.9 ± 74.8	120.0 ± 43.9	0.122
<b>Echocardiography</b>				
LVEF (%)	47.6 ± 17.4	48.3 ± 16.2	48.5 ± 13.2	0.834
Left atrial volume (mL)	78.7 ± 52.8	87.1 ± 66.4	85.9 ± 50.2	0.248
Mitral valve E/E'	14.6 ± 9.2	16.0 ± 8.4	17.7 ± 7.6 *	0.011
Inferior vena cava diameter (mm)	15.2 ± 4.9	15.3 ± 5.3	15.8 ± 6.9	0.708
SPAP (mmHg)	30.9 ± 17.5	30.8 ± 14.9	30.7 ± 15.6	0.996
RV-FAC (%)	42.0 ± 17.3	41.6 ± 13.1	45.5 ± 18.0	0.258

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Mitral valve E/E', ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; RV-FAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure.

\* $P < 0.05$  and \*\* $P < 0.01$  vs. low score group, † $P < 0.05$  and †† $P < 0.01$  vs. moderate score group.

§Data are presented as median (interquartile range).

**Figure 2** Kaplan–Meier analysis for all-cause mortality in the score 1–3 group, the score 4–6 group, and the score 7–9 group in HF patients. \*  $P < 0.05$ .



several medications. In our data, the predictivity of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for mortality was consistent under consideration of other important confounders and several situations, such as those the presence or absence of AF, ischemic or non-ischemic etiology, reduced or preserved EF.

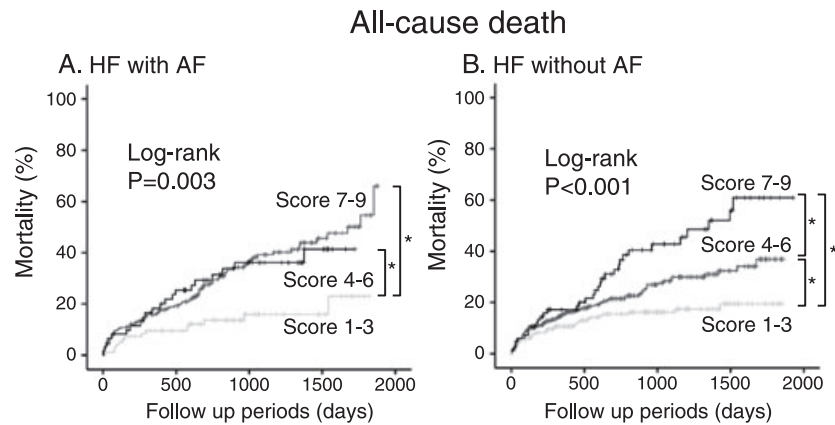
Although the CHA<sub>2</sub>DS<sub>2</sub>-VASc components indeed may increase the risk of mortality, not all the individual components have been identified as mortality risk factors in the HF population. It is suggested that 8–41% of HF patients have diabetes mellitus,<sup>23</sup> which is associated with increased mortality and morbidity.<sup>24,25</sup> It is also reported that HF patients have higher mortality after stroke.<sup>26</sup> One possible explanation for this phenomenon might be a stroke-induced amplification of cardiac failure due to autonomic dysregulation and aspiration resulting in pneumonia.<sup>26,27</sup> HF patients with ischemic etiology have higher mortality.<sup>1,2</sup> A few studies have revealed that HF patients with peripheral artery disease had poor prognosis.<sup>28,29</sup> On the other hand, female is associated with a decreased mortality.<sup>1,2</sup>

In addition, the CHADS<sub>2</sub> risk factors may directly contribute to left atrial remodeling, a process characterized by dilatation and mechanical dysfunction of the left atrium.<sup>30</sup> The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are associated with left atrial dysfunction, even in patients without baseline AF.<sup>31</sup> In AF patients, the CHADS<sub>2</sub> score is related to systemic inflammation and left atrial thrombus formation.<sup>32</sup>

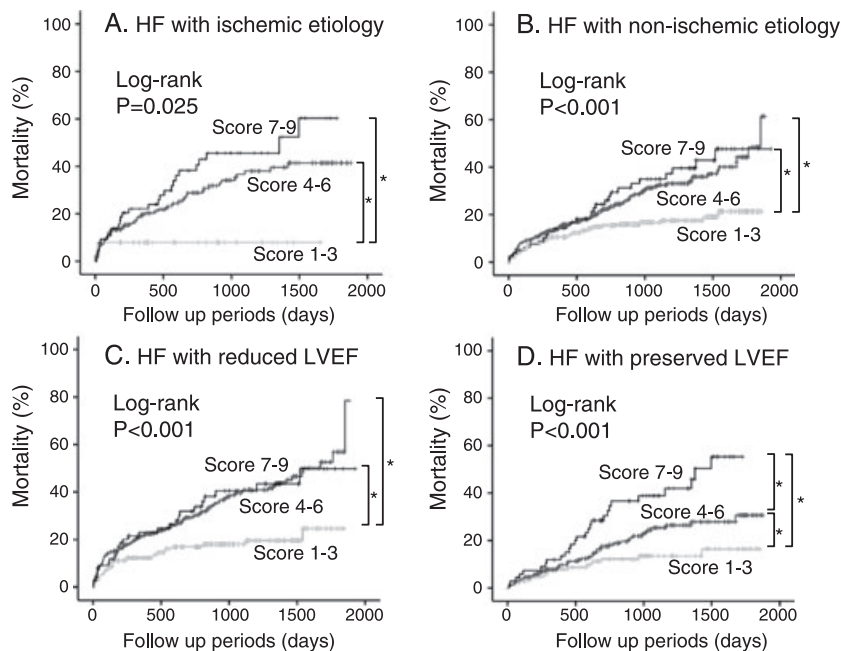
## Study strengths and limitations

Our study has several strengths, and differs from previous studies.<sup>10,22</sup> For instance, the present study is the first to show the association of high CHA<sub>2</sub>DS<sub>2</sub>-VASc score with high

**Figure 3** Kaplan–Meier analysis for all-cause mortality in the score 1–3 group, the score 4–6 group, and the score 7–9 group in heart failure (HF) patients with Atrial fibrillation (AF) (A) and without AF (B). \*  $P < 0.05$ .



**Figure 4** Kaplan–Meier analysis for all-cause mortality in the score 1–3 group, the score 4–6 group, and the score 7–9 group in heart failure (HF) patients with ischemic etiology (A), non-ischemic etiology (B), reduced left ventricular ejection fraction (LVEF) (C), and preserved LVEF (D). \*  $P < 0.05$ .



all-cause mortality in HF patients, under consideration of several confounders and background, using multivariable analyses and subgroup analyses. In addition, HF diagnosis was made and detailed causes of death were determined by our experienced cardiologists. Furthermore, there were no patients who dropped out.

There are several limitations to the present study. Conducted as a prospective observational study in a single

institution with relatively small number of subjects, it is possible that the present study is somewhat underpowered to accurately estimate the association between CHA<sub>2</sub>DS<sub>2</sub>-VASc score and mortality in HF. Although we assessed using the multivariable Cox proportional hazard regression analyses and subgroup analyses, the effects of differences in comorbidities among the three groups might not have been completely adjusted, and the present results should be

**Table 3** Cox Proportional Hazard Model of All-Cause Mortality in heart failure: impact of CHA<sub>2</sub>DS<sub>2</sub>-VAsC score

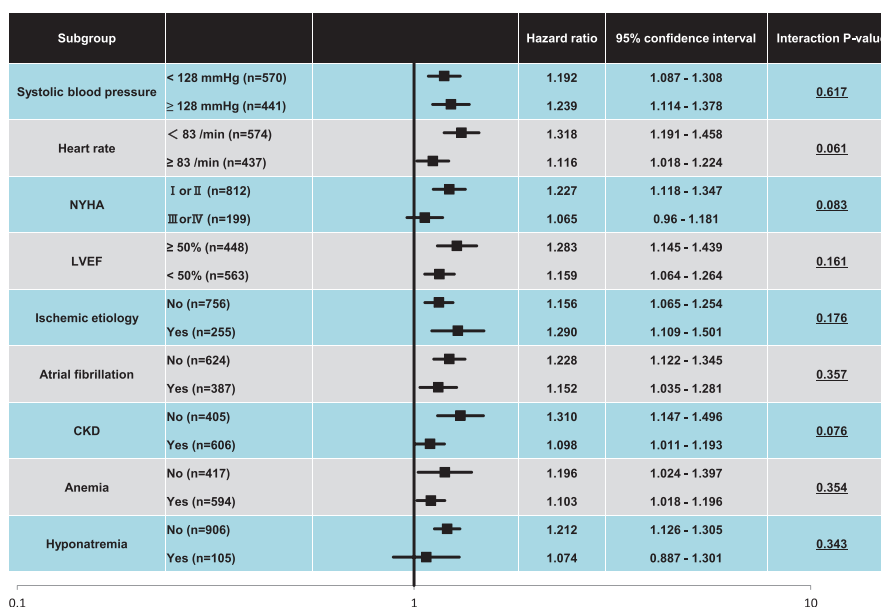
	HR	95% CI	P-value
Total (n = 1011, death 264)			
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score:			
Score 1–3	Ref		
Score 4–6	2.067	1.497–2.853	<0.001
Score 7–9	2.699	1.832–3.975	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score adjusted model *:			
Score 1–3	Ref		
Score 4–6	1.507	1.048–2.169	0.027
Score 7–9	1.822	1.145–2.898	0.011
HF with atrial fibrillation (n = 387, death 118)			
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score:			
Score 1–3	Ref		
Score 4–6	2.468	1.254–4.856	0.009
Score 7–9	2.596	1.473–4.577	0.001
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score adjusted model **:			
Score 1–3	Ref		
Score 4–6	1.740	1.002–3.691	0.038
Score 7–9	1.951	1.064–3.578	0.031
HF without atrial fibrillation (n = 624, death 146)			
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score:			
Score 1–3	Ref		
Score 4–6	1.714	1.146–2.565	0.009
Score 7–9	2.899	1.802–4.665	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VAsC score adjusted model **:			
Score 1–3	Ref		
Score 4–6	1.915	1.040–3.524	0.037
Score 7–9	2.215	1.024–4.787	0.033

HF, hear failure.

\*Adjusted Model: Adjusted for systolic blood pressure, heart rate, NYHA class over III, presence of ischemic etiology, reduced left ventricular ejection fraction, atrial fibrillation, chronic kidney disease, anemia, hyponatremia, and usage of RAS-inhibitors, β-blockers, calcium channel blockers, diuretics, inotropic agents, anti-diabetic agents, statins, antiplatelets, and anti-coagulations.

\*\*Adjusted Model: Adjusted for NYHA class over III, presence of ischemic etiology, reduced left ventricular ejection fraction, chronic kidney disease, anemia, hyponatremia, and usage of RAS-inhibitors, β-blockers, diuretics, inotropic agents, anti-diabetic agents, and statins.

**Figure 5** Forest plot of hazard ratios by patients’ subgroups. The subgroup analysis describes associations between CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores and all-cause mortality in subgroups after adjustment for interactions between the CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores and prespecified clinically important variables. CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



viewed as preliminary. Therefore, further studies with a larger population are needed.

## Conclusions

CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which is a simple and comprehensive risk assessment score, provides important information concerning prognosis in HF patients. In HF patients, irrespective of AF, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score would identify those at a higher risk of mortality.

## Conflicts of interest

None declared.

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## Supporting information

Supporting information may be found in the online version of this article.

**Table S1.** Comparisons of all-cause mortality among each CHA<sub>2</sub>DS<sub>2</sub>-VASc score (N = 1011).

**Figure S1.** Kaplan–Meier analysis for (A) Re-hospitalization and (B) Cardiac mortality in the score 1–3 group, the score 4–6 group, and the score 7–9 group in heart failure patients.



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