The CHA$_2$DS$_2$-VASc score as a predictor of high mortality in hospitalized heart failure patients

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Abstract

Aims Atrial fibrillation (AF) is common in patients with heart failure (HF). CHA$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-VASc score; Atrial fibrillation; Prognosis

Introduction

Heart failure (HF) is a major cause of death among the elderly in many countries and has become a significant public health problem. The CHADS$_2$ and CHA$_2$DS$_2$-VASc scores are risk assessment tools to predict stroke in patients with atrial fibrillation (AF) and can be used to guide anticoagulation therapy, in complement with or as a substitute of other risk scores for AF. The CHA$_2$DS$_2$-VASc score has been proved to be more sensitive than the CHADS$_2$ score to predict cardio-embolic events in AF patients. In recent years, the use of the CHA$_2$DS$_2$-VASc score in predicting ischemic stroke, thromboembolism, and death has extended beyond the originally proposed AF field. It has been reported that high CHA$_2$DS$_2$-VASc score are associated with mortality in patients with acute coronary syndrome, irrespective of the presence or absence of AF. However, the impact of CHA$_2$DS$_2$-VASc score on mortality in HF patients remains unclear.

Therefore, the aims of the present study were to verify the value of the CHA$_2$DS$_2$-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\(^{11}\) 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\(_2\)DS\(_2\)-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 \((n=145)\).\(^4\) 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\(_1c\) 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.\(^{12}\) Chronic kidney disease was defined as an estimated GFR \(< 60 \text{ mL/min/1.73 m}^2\).\(^2\) Anemia was defined as hemoglobin of \(< 12.0\) g/dL in females and \(< 13.0\) g/dL in males.\(^2\) 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,\(^{11}\) 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.

Hospitalized patients with heart failure between 2009 and 2013 \((n=1034)\)

Exclusion
Acute coronary syndrome \((n=23)\)

Enrollment

Hospitalized patients with heart failure \((n=1011)\): Divided into three groups
1) Score 1-3 group \((n=317)\)
2) Score 4-6 group \((n=549)\)
3) Score 7-9 group \((n=145)\)

Missing data without follow up \((n=0)\)

Endpoint acquisition at 2015 \((n=1011)\)
the Declaration of Helsinki. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.13

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 transmitial 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.14 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.14 The right ventricular fractional area change, defined as (end diastolic area-end systolic area)/end diastolic area x 100, is a measure of right ventricular systolic function.14 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 among the three groups. Interactions between CHA2DS2-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 CHA2DS2-VASc score (0.664, 95% CI: 0.625–0.702). The number of patients and mortality according to each CHA2DS2-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
CHA2DS2-VASc score and prespeci-
subgroups after adjustment for interactions between the
between the CHA2DS2-VASc score and all-cause mortality in

In the multivariable analysis, the higher CHA2DS2-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 CHA2DS2-VASc score and all-cause mortality between subgroups.

In Figure 5, a Forest plot illustrates the association between the CHA2DS2-VASc score and all-cause mortality in subgroups after adjustment for interactions between the CHA2DS2-VASc score and prespecified clinically important variables. There was no interaction CHA2DS2-VASc score and other important variables to affect all-cause mortality.

Discussion

We emphasized that CHA2DS2-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. 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. Although the CHADS2 and CHA2DS2-VASc score series are predictors of stroke in AF patients, their predictivity has recently extended beyond their original field as follows: (1) ischemic stroke in patients with coronary artery disease without AF, (2) mortality, recurrences of stroke, and major cardiovascular events in stroke patients without AF, (3) mortality in stroke survivors with or without AF, (4) hospitalization for cardiovascular causes in AF patients, and (5) HF hospitalization and cardiac death in HF patients who underwent cardiac resynchronization therapy. In addition, it has been recently reported that CHA2DS2-VASc score was associated with not only thromboembolic complications but also mortality in patients with HF. The absolute risk of thromboembolic complications in HF patients at high CHA2DS2-VASc scores is higher in those without AF than in those with AF, concordant with our data. Unlike the previous data, we focused on the impact of CHA2DS2-VASc scores on mortality under some clinically important background including NYHA class, LVEF, etiology of HF, and presence of chronic kidney disease, anemia, hyponatremia, and...
several medications. In our data, the predictivity of the CHA2DS2-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 CHA2DS2-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, which is associated with increased mortality and morbidity.24,25 It is also reported that HF patients have higher mortality after stroke.26 One possible explanation for this phenomenon might be a stroke-induced amplification of cardiac failure due to autonomic dysregulation and aspiration resulting in pneumonia.26,27 HF patients with ischemic etiology have higher mortality.1,2 A few studies have revealed that HF patients with peripheral artery disease had poor prognosis.28,29 On the other hand, female is associated with a decreased mortality.1,2

In addition, the CHADS 2 risk factors may directly contribute to left atrial remodeling, a process characterized by dilatation and mechanical dysfunction of the left atrium.30 The CHADS2 and CHA2DS2-VASc scores are associated with left atrial dysfunction, even in patients without baseline AF.31 In AF patients, the CHADS2 score is related to systemic inflammation and left atrial thrombus formation.32

### Study strengths and limitations

Our study has several strengths, and differs from previous studies.10,22 For instance, the present study is the first to show the association of high CHA2DS2-VASc score with high...
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 CHA2DS2-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 co-morbidities among the three groups might not have been completely adjusted, and the present results should be

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.
Table 3  Cox Proportional Hazard Model of All-Cause Mortality in heart failure: impact of CHA2DS2-VASc score

| CHA2DS2-VASc score | HR  | 95% CI      | P-value |
|-------------------|-----|-------------|---------|
| Total (n = 1011, death 264) |     |             |         |
| 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 |
| CHA2DS2-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) |     |             |         |
| CHA2DS2-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  |
| CHA2DS2-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) |     |             |         |
| CHA2DS2-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 |
| CHA2DS2-VASc score adjusted model **: |     |             |         |
| Score 1–3         | Ref |             |         |
| Score 4–6         | 2.151 | 1.040–4.327 | 0.037  |
| Score 7–9         | 2.215 | 1.024–4.787 | 0.033  |

HF, heart 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 CHA2DS2-VASc scores and all-cause mortality in subgroups after adjustment for interactions between the CHA2DS2-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$_2$DS$_2$-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$_2$DS$_2$-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$_2$DS$_2$-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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