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ORIGINAL ARTICLE

The $CHADS_2$ score predicts ischemic stroke in chronic heart failure patients without atrial fibrillation: comparison to other stroke risk scores

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Abstract The $CHADS_2$ score is useful in stratifying the risk of ischemic stroke or transient ischemic attack (TIA) in patients with non-valvular atrial fibrillation (AF). However, it remains unclear whether the $CHADS_2$ score could predict stroke or TIA in chronic heart failure (CHF) patients without AF. Recently, the new stroke risk score was proposed from 2 contemporary heart failure trials. We evaluated the prognostic power of the $CHADS_2$ score for stroke or TIA in CHF patients without AF in comparison to the "stroke risk score". We retrospectively studied 127 CHF patients [left ventricular ejection fraction (LVEF) <40 %] without AF, who had been enrolled in our previous prospective cohort study. The primary endpoint was the incidence of stroke or TIA. The mean baseline $CHADS_2$ score was 2.1 ± 1.0. During the follow-up period of 8.4 ± 5.1 years, stroke or TIA occurred in 21 of 127 patients. At multivariate Cox analysis, $CHADS_2$ score (C-index 0.794), but not "stroke risk score" (C-index 0.625), was significantly and independently associated with stroke or TIA. The incidence of stroke or TIA appeared to increase in relation to the $CHADS_2$ score [low (=1), 0 per 100 person-years; intermediate (=2), 1.6 per 100 person-years; high (≥3), 4.7 per 100 person-years; $p = 0.04$]. $CHADS_2$ score could stratify the risk of ischemic stroke in CHF patients with the absence of AF, with greater prognostic power than the "stroke risk score".

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Keywords $CHADS_2$ score · Stroke · Chronic heart failure · Risk stratification

Introduction

In patients with chronic heart failure (CHF), the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system induces a hypercoagulable state, increased aggregation of thrombocytes, and reduced fibrinolysis [1, 2]. Moreover, CHF patients have endothelial dysfunction, malfunction of cerebral autoregulation and rheological alterations consistent with flow abnormality via low cardiac output and aberrant flow through dilated cardiac chambers [3–5]. Thus, CHF is associated with an increased risk of thrombus formation [6] and is accompanied by a two to threefold increased risk of stroke [7]. In the clinical setting, stroke in CHF patients is associated with poor outcomes and higher mortality [7]. Current guidelines recommend anticoagulation for CHF patients with concomitant atrial fibrillation (AF) but not for those in sinus rhythm [8]. It is clinically relevant to stratify the risk of stroke in CHF patients in sinus rhythm.

The $CHADS_2$ score and CHA_2DS_2-VASc score are proposed as a useful way to stratify the risk of ischemic stroke or transient ischemic attack (TIA) in patients with AF [9, 10]. These scores were reported to predict ischemic stroke in the absence of atrial fibrillation among patients with coronary heart disease [11]. However, it remains unclear whether the $CHADS_2$ score could predict ischemic stroke or TIA in CHF patients without AF. Recently, the new stroke risk score has been proposed to identify CHF patients without AF who were at high risk of ischemic stroke from 2 large and contemporary HF trials, the controlled rosuvastatin in multinational trial heart failure

(CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac-heart failure trial (GISSI-HF) [12]. This new "stroke risk score" included the following independent predictors of stroke: age, New York Heart Association (NYHA) functional class, diabetes mellitus with insulin, body mass index and prior stroke. The aim of the present study is to evaluate the prognostic power of the $CHADS_2$ score for ischemic stroke or TIA in CHF patients without AF in comparison to CHA_2DS_2-VASc score and the new "stroke risk score".

Methods

We retrospectively studied 127 consecutive stable CHF outpatients with a radionuclide left ventricular ejection fraction (LVEF) <40 % and without a history of AF, who had been enrolled in our previous prospective cohort study from October 1995 to October 1998. CHF was diagnosed by clinical signs and symptoms according to the Framingham Heart Study criteria. These criteria require the presence of at least two major criteria or one major criterion in addition to two minor criteria [13] to confirm heart failure. To be included in the present study, all patients who had experienced at least one episode of decompensated heart failure were required to be stable for 3 months on conventional therapy. Patients were excluded from the present study if they had significant renal (serum creatinine level >3.0 mg/dl) or hepatic dysfunction (aspartate transaminase or alanine transaminase >three times of upper normal limits). The mean patient age was 64 ± 12 years. Of the 127 patients, 97 were men and 30 were women. CHF was due to ischemic heart disease in 76 patients and idiopathic dilated cardiomyopathy in 51. The average NYHA functional class was 2.0 ± 0.7, with 25 % of patients categorized as class I, 54 % of patients categorized as class II, and 20 % categorized as class III. The mean radionuclide LVEF was 30 ± 7 %. All patients gave a written informed consent for their participation in this study, which was approved by the Osaka General Medical Center's Review Committee.

At entry, we calculated the $CHADS_2$ score, CHA_2DS_2-VASc score and "stroke risk score" from baseline clinical characteristics. The $CHADS_2$ score is derived from the sum of point values of individual stroke risk factors [CHF, hypertension, age ≥75, diabetes mellitus (1 point each), and prior stroke or TIA (2 points)]. The CHA_2DS_2-VASc score is derived from the sum of point values of individual stroke risk factors [CHF, hypertension, age 65–75, diabetes mellitus, vascular disease and female sex (1 point each), and prior stroke or TIA and age 75 or older (2 points)]. Hypertension was defined by either self-report or systolic blood pressure ≥140 mmHg; blood pressure was measured in all participants in the sitting position after 5 min of rest. Diabetes mellitus was defined as self-reported diabetes, use of a diabetes medication, or hemoglobin A1c ≥6.5 %. Prior stroke and TIA were determined by self-report. Vascular disease included prior myocardial infarction, peripheral artery disease and aortic plaque in patients' history.

The "stroke risk score" was obtained by 5 individual stroke risk factors (age, NYHA class, diabetes mellitus on insulin, body mass index and prior stroke), which were significant predictors of stroke in Cox multivariate proportional hazard regression analysis among patients included in CORONA and GISSI-HF trials. The "stroke risk score" was calculated by multiplying age (per 10 years increase) by 3.31, BMI (per 5 kg/m^2 increase up to 30) by −3.01 and then adding 4.72 in the case of NYHA III or IV, 6.26 when patients had diabetes mellitus treated with insulin and 5.91 when patients had the prior stroke [12].

All patients underwent ECG-gated blood-pool scintigraphy with a conventional rotating gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. Patients were given 740 MBq of technetium-99 m-labeled human serum albumin (Nihon Medi-Physics, Nishinomiya, Japan). LVEF was calculated with a standard program [14]. In addition, all patients underwent echocardiography and 24-h ambulatory electrocardiographic monitoring, and a venous blood sampling. In echocardiography, left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and left atrial dimension were measured by standard techniques [15]. In 24-h ambulatory electrocardiographic monitoring, ventricular arrhythmias were classified according to the Lown's grade. Blood sampling for assessment of serum creatinine, sodium, albumin levels, and plasma noradrenaline concentration, was drawn from an intravenous cannula after the patients had rested for more than 30 min in the supine position. Estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula. Plasma norepinephrine concentration was determined in ethylenediaminetetraacetic acid-plasma by high-performance liquid chromatography [16] at Shionogi Biomedical Laboratories (Osaka, Japan). A duplicate determination in the laboratory showed a coefficient of variation of 0.4–5.5 %.

All study patients were followed in the heart failure unit of our hospital at least every 1 or 2 months. The primary endpoint of this study was the incidence of ischemic stroke or TIA, which was determined by the review of medical records performed by 2 independent and blinded physicians. If the 2 physicians agreed on the outcome classification, their classification was binding. In the event of a disagreement, a third blinded physician was consulted.

Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause, based on the WHO MONICA criteria [17]. All stroke outcomes were subtyped as hemorrhagic, ischemic,

or procedure-related, based on physician diagnosis, which was confirmed by computed tomography or magnetic resonance imaging. Stroke outcomes in this study were restricted to patients with non-procedure-related ischemic strokes. TIA outcomes were based on the clinical judgment of the physicians who were blinded to the medical records, guided by the definition of TIA as a focal neurologic deficit (in the absence of head trauma) lasting more than 30 s and no longer than 24 h, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 min and with subsequent complete resolution [11, 18].

The Student's *t* test was used to compare differences in continuous variables, and the data were presented as mean ± standard deviation, if the data was normally distributed. If the data was not normally distributed, Mann–Whitney U test was used and the data were presented as median (interquartile range). The Fisher's exact test was used to compare differences in categorical variables. One-way analysis of variance followed by a post hoc Scheffé test was applied to find differences among low, intermediate, and high $CHADS_2$ score groups. Cumulative rates of events were calculated using the Kaplan–Meier method. Comparison of event-free survival rates between groups was assessed with a 2-sided log-rank test. Receiver-operating characteristic (ROC) curves and areas under the curve (AUC) analysis was performed to further explore the discriminatory ability of $CHADS_2$ score, CHA_2DS_2-VASc score and "stroke risk score" for ischemic stroke or TIA. Cox proportional hazards regression models were used to identify patients at risk of ischemic stroke or TIA and to calculate the multivariate-adjusted hazard ratios (HRs) and 95 % confidence interval (CI) of the parameters. The C-index was used to measure how well the model discriminated between patients with high and low risk of ischemic stroke or TIA. A value of 0.5 for C-index indicates no discrimination and a value equal to 1 indicates perfect discrimination. All data were statistically analyzed using StatView version 5 (SAS Institute, Cary, North Carolina), except for ROC analysis and the measurement of C-index, which was analyzed using EZR version 1.03 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19]. A p value <0.05 was considered statistically significant.

Results

At the baseline, there were 38, 51, 30, 2, 5, and 1 patients with a $CHADS_2$ score of 1, 2, 3, 4, 5, and 6, respectively. The mean value of $CHADS_2$ score and CHA_2DS_2-VASc score were 2.1 ± 1.0 and 3.7 ± 1.4, respectively. The mean "stroke risk score" was 4.8 (1.8–10.9). During a follow-up period of 8.4 ± 5.1 years (range 0–18), ischemic stroke or TIA was observed in 21 of 127 CHF patients (stroke in 17 and TIA in 4 patients), which was confirmed by computed tomography or magnetic resonance imaging in 86 % (18/21) of cases.

Baseline characteristics in CHF patients with and without ischemic stroke or TIA are shown in Table 1. Patients with ischemic stroke or TIA had a significantly higher incidence of hypertension and diabetes mellitus, a greater $CHADS_2$ score, CHA_2DS_2-VASc score and a higher medication rate with anticoagulation therapy than those without stroke or TIA, while there were no significant differences in baseline characteristics such as sex, age, NYHA class, "stroke risk score", LVEF, anti-platelet or anti-heart failure drug therapy, or estimated glomerular filtration rate between them.

When we demonstrated the discriminatory ability for ischemic stroke or TIA, $CHADS_2$ score had the highest AUC [0.805 (95 % CI 0.719–0.892)]. $CHADS_2$ score was statistically superior to "stroke risk score" [AUC 0.598 (95 % CI 0.465–0.731), $p = 0.003$] and tended to be superior to CHA_2DS_2-VASc score [AUC 0.739 (95 % CI 0.616–0.863), $p = 0.098$] (Fig. 1).

Univariate Cox proportional hazard analysis showed that the $CHADS_2$ score, CHA_2DS_2-VASc score, "stroke risk score", age ≥75 years, prior stroke or TIA, diabetes mellitus and hypertension were significantly associated with stroke or TIA, while there were no significant association between stroke or TIA and the other components of 3 risk scores such as gender, age ≥65 years, vascular disease, NYHA class (III or IV) and BMI. Adjusted in the model with anticoagulation therapy, $CHADS_2$ score (C-index 0.794, 95 % CI 0.663–0.925) and CHA_2DS_2-VASc score (C-index 0.740, 95 % CI 0.605–0.875), but not "stroke risk score" (C-index 0.625, 95 % CI 0.488–0.762), were still significantly associated with ischemic stroke or TIA (Table 2).

According to CHADS2 score, the study patients were classified into three groups: low $CHADS_2$ score (=1), intermediate $CHADS_2$ score (=2), and high $CHADS_2$ score (≥3) groups. Baseline characteristics in CHF patients with low, intermediate, and high $CHADS_2$ scores are shown in Table 3. There were no significant differences in baseline characteristics such as age, NYHA class, LVEF, anticoagulation or anti-platelet therapies or anti-heart failure drug therapy among the three groups, except for hypertension, diabetes mellitus, prior stroke, systolic blood pressure and renal function. The estimated glomerular filtration rate was significantly lower in the high $CHADS_2$ score group than in the other 2 groups.

Ischemic stroke or TIA was observed in none of the 38 patients in the low $CHADS_2$ score group, 7 of 51 (1.6 per 100 person-years) in the intermediate $CHADS_2$ score group, and 14 of 38 (4.7 per 100 person-years) in the high $CHADS_2$ score group. The higher the $CHADS_2$ scores,

Table 1 Baseline clinical and study characteristics in chronic heart failure patients with and without ischemic stroke or transient ischemic attack

	With stroke or TIA ($n = 21$)	Without stroke or TIA ($n = 106$)	p value
Age (years)	66 ± 10	64 ± 12	0.4111
Gender (male, %)	76	76	0.9825
NYHA class	1.8 ± 0.8	2.0 ± 0.7	0.1581
Ischemic origin (%)	71	58	0.2578
Hypertension (%)	76	29	<0.0001
Diabetes mellitus (%)	71	33	0.0009
Diabetes mellitus on insulin (%)	5	2	0.4320
BMI (kg/m^2)	22.7	23.3	0.4391
Prior stroke (%)	24	6	0.0066
Current smoker (%)	24	24	0.9825
Heart rate (bpm)	71 ± 9	75 ± 12	0.1543
Systolic BP (mmHg)	133 ± 15	128 ± 18	0.2809
$CHADS_2$ score	3.2 ± 1.2	1.9 ± 0.9	<0.0001
CHA_2DS_2-VASc score	4.9 ± 1.7	3.5 ± 1.2	<0.0001
"Stroke risk score"	7.8 (4.8–12.8)	4.8 (1.6–10.5)	0.1555
Medications (%)			
ACEI/ARB	95	80	0.0946
Beta-blocker	76	72	0.7222
Statins	43	40	0.7842
Anti-coagulation therapy	62	39	0.0497
Anti-platelet therapy	29	35	0.5788
Antiarrhythmic drug (Ib/III)	24	26	0.7359
LV ejection fraction (%)	30 ± 8	30 ± 7	0.7174
LVDd (mm)	61 ± 6	63 ± 7	0.1867
LAD (mm)	40 ± 6	41 ± 7	0.6284
Lown's grade	3.7 ± 1.4	3.3 ± 1.4	0.3104
Laboratory			
sCr (mg/dL)	0.898 ± 0.228	0.872 ± 0.257	0.6696
eGFR (ml/min/1.73 m^2)	64 ± 23	67 ± 19	0.6460
Sodium (mEq/L)	139 ± 3	139 ± 3	0.5666
Albumin (mg/dl)	3.9 ± 0.3	4.0 ± 0.4	0.3364
Noradrenaline (pg/ml)	429 ± 273	429 ± 232	0.9929

Data is presented as the mean value SD or percentage of patients, except for stroke risk score (median value with interquartile range)

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *LAD* left atrial dimension, *LVDd* left ventricular end-diastolic dimension, *NYHA* New York Heart Association, *sCr* serum creatinine

the more stroke or TIA occurred (high vs intermediate, $p = 0.01$; intermediate vs low, $p = 0.01$) (Fig. 2). Compared to patients with an intermediate $CHADS_2$ score, those with high $CHADS_2$ scores had a significantly higher risk of stroke or TIA (adjusted HR, 3.2; 95 % CI 1.3–7.9).

Although no study patients had the diagnosis of AF at entry, 22 of 127 CHF patients (17 %) developed new non-valvular AF documented by electrocardiography during the follow-up period; 6 of 38 patients (16 %) in the low $CHADS_2$ score group, 10 of 51 (20 %) in the intermediate $CHADS_2$ score group, and 6 of 38 (16 %) in the high $CHADS_2$ score group. We continuously followed all study patients despite the development of AF. Even if we stopped following these 22 patients at the time of AF development, at multivariate analysis, $CHADS_2$ score, but not CHA_2DS_2-VASc score or "stroke risk score", was significantly and independently associated with ischemic stroke or TIA ($p = 0.006$, C-index 0.776, 95 % CI 0.635–0.917).

When we divided all study patients into 2 groups according to the presence of anti-coagulation therapy at baseline, ischemic stroke or TIA was observed in 8 of 73 patients without anti-coagulation therapy and 13 of 54 with that. In patients with anti-coagulation therapy, $CHADS_2$ score, CHA_2DS_2-VASc score, diabetes mellitus, and hypertension

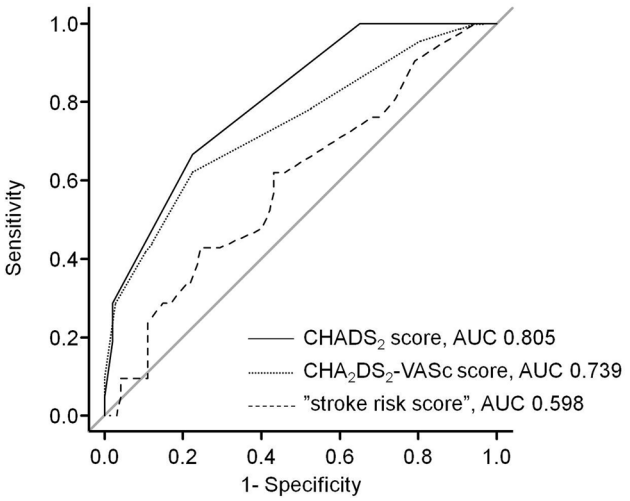

Fig. 1 Receiver operating characteristics (ROC) curves for $CHADS_2$ score, CHA_2DS_2-VASc score and "stroke risk score" in discriminating ischemic stroke or TIA, *TIA* transient ischemic attack

Table 2 Cox proportional hazard analysis for the identification of patients at risk of ischemic stroke or transient ischemic attack

	p value	HR (95 % CI)
$CHADS_2$ score	<0.0001	2.200 (1.637–2.958)
CHA_2DS_2-VASc score	<0.0001	1.786 (1.358–2.350)
"Stroke risk score"	0.0458	1.079 (1.001–1.163)
Age ≥75	0.0389	3.049 (1.058–8.783)
Prior stroke	0.0050	4.335 (1.558–12.063)
Diabetes mellitus	0.0033	4.187 (1.609–10.896)
Hypertension	0.0020	4.903 (1.791–13.424)
Anti-coagulation therapy	0.0855	2.170 (0.897–5.249)
Vascular disease	0.5448	–
Age ≥65	0.4952	–
Age (numerical)	0.1652	–
Gender (female)	0.9228	–
NYHA class (III and IV)	0.8070	–
BMI	0.2485	–
Ischemic origin	0.3328	–
Models with anti-coagulation therapy		
$CHADS_2$ score	<0.0001	2.231 (1.526–3.262)
Anti-coagulation therapy	0.1067	–
CHA_2DS_2-VASc score	<0.0001	1.836 (1.393–2.420)
Anti-coagulation therapy	0.1925	–
"Stroke risk score"	0.0776	1.071 (0.993–1.155)
Anti-coagulation therapy	0.1337	–

BMI body mass index, *NYHA* New York Heart Association

were significantly associated with stroke or TIA while the stroke risk score showed no significant association with stroke or TIA. In patients without anti-coagulation therapy, only $CHADS_2$ score was also significantly associated with stroke or TIA ($p = 0.009$, C-index 0.806, 95 % CI 0.769–0.843).

Discussion

This study revealed that the $CHADS_2$ score could also be useful in stratifying the risk for ischemic stroke or TIA in CHF patients without AF, and that the prognostic power of the prediction for ischemic stroke of $CHADS_2$ score was greater than "stroke risk score".

Some factors could cause the superiority of $CHADS_2$ score to the "stroke risk score". First, this study had lower proportion of CHF patients with severe symptom (NYHA III or IV) and with diabetes mellitus treated with insulin than patients enrolled in CORONA and GISSI-HF, and so we could not reflect exactly the stroke risk in these patients. Secondly, patients had the lower medication rate of anti-platelet therapy and higher medication rate of anticoagulant therapy in this study than those enrolled in CORONA and GISSI-HF. It might result in the difference in the mechanism of stroke, atherothrombotic or cardioembolic, and might affect stroke risk in study patients. Finally, this study had quite long period of follow-up. Patients in this study might acquire increased stroke risk during the longer follow-up period, even when their stroke risk had been regarded as low at the entry.

Several mechanisms might explain the relationship between a high $CHADS_2$ score and stroke in CHF patients without AF. Even in the absence of AF, CHF patients develop a hypercoagulable state and endothelial dysfunction [3–5]. Other components of the $CHADS_2$ score such as hypertension, diabetes mellitus and prior stroke have an association with hypercoagulability and endothelial dysfunction [20–22]. Therefore, CHF patients with a high $CHADS_2$ score have activated thrombus formation.

The components of the $CHADS_2$ score such as CHF, hypertension and diabetes mellitus could contribute to left atrial remodeling, characterized by dilation and mechanical dysfunction of the left atrium [23, 24]. A dilated left atrium could result in blood stasis, and thus an increased risk of thromboembolism [25, 26], independent of cardiac rhythm, although there was no significant difference in left atrial dimension among low, intermediate high $CHADS_2$ scores in the present study.

The use of antithrombotic treatments remains an important question in the care of patients with CHF. In the present study, the event rate in non-AF CHF parents with high $CHADS_2$ scores (3–6) was comparable to the rate in AF patients with moderate-to-high $CHADS_2$ scores (2–3), a population known to derive benefit from stroke prevention therapies such as anticoagulation. Studies that have examined the role of anticoagulation therapy for reducing

Table 3 Baseline clinical and study characteristics in chronic heart failure patients with low, intermediate and high $CHADS_2$ score

$CHADS_2$ score	Low (score = 1) ($n = 38$)	Intermediate (score = 2) ($n = 51$)	High (score = 3–6) ($n = 38$)	*p* value
Age (years)	61 ± 12	65 ± 12	66 ± 10	0.3407
Gender (male, %)	90	75	66	0.0492
NYHA class	1.9 ± 0.7	2.1 ± 0.7	1.8 ± 0.6	0.1275
Ischemic origin (%)	62	57	63	0.8059
Hypertension (%)	0	31	82	<0.0001
Diabetes mellitus (%)	0	43	74	<0.0001
Diabetes mellitus on insulin (%)	0	4	3	0.4825
BMI (kg/m^2)	23.2	23.1	23.4	0.9842
Prior stroke (%)	0	0	29	<0.0001
Current smoker (%)	32	22	18	0.3667
Heart rate (bpm)	77 ± 13	74 ± 10	72 ± 11	0.2921
Systolic BP (mmHg)	120 ± 14	132 ± 17	135 ± 19	0.0010
Medications (%)				
ACEI/ARB	84	78	87	0.5723
Beta-blocker	73	67	82	0.2955
Statins	33	42	41	0.7940
Anti-coagulation therapy	53	41	34	0.2619
Anti-platelet therapy	37	29	37	0.6885
Antiarrhythmic drug(Ib/III)	21	33	21	0.3092
LV ejection fraction (%)	30 ± 7	30 ± 7	29 ± 8	0.1512
LVDd (mm)	63 ± 6	62 ± 7	62 ± 8	0.8032
LAD(mm)	39 ± 6	41 ± 6	42 ± 8	0.2325
Lown's grade	3.3 ± 1.4	3.4 ± 1.5	3.5 ± 1.4	0.6301
Laboratory				
sCr(mg/dL)	0.852 ± 0.283	0.841 ± 0.213	0.949 ± 0.259	0.0443
eGFR(ml/min/1.73 m^2)	72 ± 19	68 ± 20	58 ± 17	0.0046
Sodium (mEq/L)	138 ± 3	139 ± 3	140 ± 3	0.2745
Albumin (g/dl)	4.0 ± 0.4	4.1 ± 0.3	3.9 ± 0.3	0.4113
Noradrenaline (pg/ml)	448 ± 255	432 ± 225	408 ± 246	0.6744

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *LAD* left atrial dimension, *LVDd* left ventricular end-diastolic dimension, *NYHA* New York Heart Association, *sCr* serum creatinine

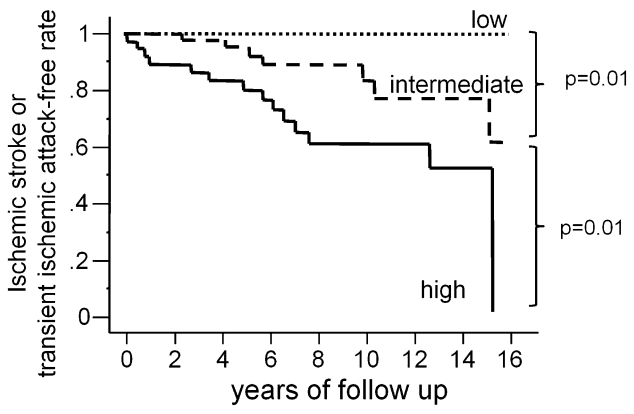

Fig. 2 Ischemic stroke- or TIA-free rate curves in CHF patients with low, intermediate, and high $CHADS_2$ scores, Low $CHADS_2$ score = 1, intermediate = 2, and high = 3–6, *CHF* chronic heart failure, *TIA* transient ischemic attack

thromboembolic risk have been inconclusive [27]. The multicenter, randomized double-blind and placebo-controlled Heart Failure Long-term Antithrombotic Study (HELAS) and the unblinded randomized Warfarin/Aspirin Study in Heart failure (WASH) did not find a benefit with antithrombotic therapy [28]. Although the clinical outcome studies [the prospective randomized warfarin and anti-platelet therapy in chronic heart failure (WATCH) study and the multicenter, double-blinded and randomized warfarin versus aspirin in patients with reduced cardiac ejection fraction (WARCEF) study] suggested that warfarin may reduce stroke risk compared with anti-platelet therapy [27, 29], the lack of a placebo group and lower-than-projected enrollment prevents definitive conclusions from being made [29]. Thus, current evidence does not support the routine use of anticoagulation for preventing

thromboembolic events in CHF patients who remain in sinus rhythm [29].

There are some limitations to our study. First, the small and empirically chosen population sample size is a major limitation. Second, medications such as anticoagulation therapy at baseline and during the follow-up period, might affect the incidence of ischemic stroke. At baseline, the rate of anticoagulation therapy tended to decrease as $CHADS_2$ score increased with no significant difference. The incidence of stroke or TIA was higher in patient with than without anticoagulation at baseline, although the statistical difference was not significant (24 vs 11 %, $p = 0.08$, adjusted HR 2.170 95 % CI 0.897–5.249). In the present study, anticoagulation therapy was performed more in CHF patients with than without ischemic origin (old myocardial infarction) [61 %(46/76) vs 16(8/51), $p < 0.0001$], possibly according to the usefulness of antithrombotic therapy in the secondary prevention of myocardial infarction [30]. So, the higher incidence of stroke or TIA in patients with anticoagulation therapy might be due to selection bias. During the follow-up period, an anticoagulation drug was newly administered in 13 of 73 patients without anticoagulation therapy at entry. There was no difference in the medication rate of anticoagulation at the last follow-up visit among low, intermediate, and high $CHADS_2$ score groups (63, 49, and 47 %, respectively). Third, we evaluated the presence of AF according to past history and electrocardiography at entry. However, we could not eliminate the possibility that CHF patients with paroxysmal AF could be misclassified into the sinus rhythm group if they have no symptoms such as palpitations and no evidence of AF on baseline electrocardiography [31]. Such silent AF might have an influence on the incidence of ischemic stroke in our study. Fourth, we could not investigate the mechanism of ischemic stroke, whether atherothrombotic or cardioembolic. Thus, we could not clarify which mechanism was mainly associated with a high stroke risk in CHF patients with high $CHADS_2$ scores. Identifying the mechanism of ischemic stroke may be useful in determining appropriate stroke prevention therapy in patients with CHF. Finally, we included only CHF patients with LVEF less than 40 %, and so our results could not be applied to CHF patients with preserved ejection fraction either.

In conclusion, we found that $CHADS_2$ score could stratify the risk of ischemic stroke in CHF patients with the absence of AF, with greater prognostic power than the "stroke risk score".

Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest to disclose concerning the paper.

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