Cardio-Ankle Vascular Index Predicts Post-Discharge Stroke in Patients with Heart Failure

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Aim: We aimed to evaluate the significance of the cardio-ankle vascular index (CAVI) to predict stroke in patients with heart failure (HF).

Methods: This was a prospective observational study, which recruited clinical data from a total of 557 patients who had been hospitalized for HF and undergone CAVI. According to the receiver operating characteristic curve analysis, the accurate cut-off value of CAVI in predicting post-discharge stroke was 9.64. We divided the patients into two groups: the high-CAVI group (HF patients with CAVI ≥ 9.64, n=111, 19.9%) and the low-CAVI group (HF patients with CAVI < 9.64, n=446, 80.1%). We compared the patients’ characteristics and post-discharge prognosis. The primary endpoint was stroke.

Results: The high-CAVI group was older (73.0 vs. 65.5 years old, \( P<0.001 \)). Male sex (73.9% vs. 61.4%, \( P=0.015 \)), coronary artery disease (47.7% vs. 36.1%, \( P=0.024 \)), and diabetes mellitus (54.1% vs. 37.4%, \( P=0.001 \)) were more prevalent in the high-CAVI group. In contrast, there was no difference in left ventricular ejection fraction, and prevalence of hypertension and dyslipidemia. The Kaplan-Meier analysis demonstrated that post-discharge stroke rate was higher in the high-CAVI group than in the low-CAVI group (log-rank \( P=0.005 \)). In multivariate Cox proportional hazard analysis, high CAVI was found to be an independent predictor of stroke, with an adjusted hazard ratio of 3.599, compared to low CAVI.

Conclusion: CAVI independently predicts stroke in patients with HF.

The trial registration number: UMIN000029132

Key words: Cardio-ankle vascular index, Arterial stiffness, Atherosclerosis, Heart failure, Stroke

Introduction

Atherosclerosis is one of the crucial pathophysiologicals of cardiovascular diseases (CVDs), including coronary artery disease, stroke, and heart failure (HF)¹,². To date, pulse wave velocity (PWV) has been the gold standard to measure arterial stiffness³,⁴. However, PWV is essentially affected by blood pressure (BP) at the time of measurement⁵. To overcome this limitation, Shirai et al. have developed a novel index called the cardio-ankle vascular index (CAVI) which, independently of BP, non-invasively represents the stiffness of the aorta, femoral artery, and tibial artery⁶. The formula of the index is as follows: \( \text{CAVI} = a \times \left[ \frac{2 \rho}{\Delta P} \times \ln \left( \frac{\text{systolic BP}}{\text{diastolic BP}} \right) \times \text{PWV}^2 \right] + b \), where \( \rho \) is blood density, \( \Delta P \) is pulse pressure, and \( a \) and \( b \) are coefficients⁶. CAVI also estimates atherosclerosis in the coronary and carotid arteries more closely than PWV⁷,⁸.

CAVI is useful not only for the evaluation of arterial stiffness, but also for prognosis prediction in patients who are at high risk of CVDs⁹-¹². However,
We divided patients into two groups based on this cut-off value: the high-CAVI group (patients with CAVI ≥ 9.64, n=111, 19.9%) and the low-CAVI group (those with CAVI < 9.64, n=446, 80.1%). We compared patient characteristics and post-discharge prognosis between the two groups. The primary endpoint of this study was post-discharge stroke, and we evaluated CAVI as a predictor for this endpoint.

Patient characteristics included demographic data at discharge, laboratory and echocardiographic data, and results of CAVI measurement. Laboratory and echocardiographic data were obtained within one week prior to discharge in a stable condition. Estimated glomerular filtration rate (eGFR) was assessed using a three-variable Japanese equation (19). The definitions of comorbidities and follow-up methods were in accordance with our previous studies (16, 17, 20).

This study complied with the Declaration of Helsinki and the statement of STROBE (Strengthening the Reporting of Observational studies in Epidemiology) (21, 22). The study protocol was approved by the ethical committee of Fukushima Medical University. All patients gave written informed consent to participate in this study.

**Methods**

**Subjects and Protocol**

This was a prospective observational study. Fig. 1 shows a patient flowchart. Patients were included who (A) were both hospitalized for decompensated HF at Fukushima Medical University Hospital then discharged between March 2010 and September 2019; and (B) underwent CAVI measurement in a stable condition within one week prior to discharge. Decompensated HF was diagnosed on the basis of the current guidelines (2, 13, 14). A total of 1,242 patients met these criteria. Exclusion criteria included (C) Patients with obvious history of peripheral artery disease and/or atrial fibrillation (including all types: paroxysmal, persistent, long-standing persistent, and permanent atrial fibrillation (15)); and (D) those who were receiving maintenance dialysis during the study period. A total of 685 patients were excluded according to these criteria. The definition of peripheral artery disease and atrial fibrillation was in accordance with those used in previous studies (16-18). Finally, a total of 557 patients were analyzed. The receiver operating characteristic curve analysis revealed that the accurate cut-off value of CAVI in predicting post-discharge stroke was 9.64.

We divided patients into two groups based on this cut-off value: the high-CAVI group (patients with CAVI ≥ 9.64, n=111, 19.9%) and the low-CAVI group (those with CAVI < 9.64, n=446, 80.1%). We compared patient characteristics and post-discharge prognosis between the two groups. The primary endpoint of this study was post-discharge stroke, and we evaluated CAVI as a predictor for this endpoint. Patient characteristics included demographic data at discharge, laboratory and echocardiographic data, and results of CAVI measurement. Laboratory and echocardiographic data were obtained within one week prior to discharge in a stable condition. Estimated glomerular filtration rate (eGFR) was assessed using a three-variable Japanese equation (19). The definitions of comorbidities and follow-up methods were in accordance with our previous studies (16, 17, 20).

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**Definition of Stroke**

Stroke was defined by experienced neurologists in accordance with an established statement as an acute episode of focal dysfunction of the brain, retina, or spinal cord lasting longer than 24 hours, or of any duration if imaging (computed tomography or mag-
ngetic resonance imaging) or autopsy showed focal infarction or hemorrhage relevant to the symp-
toms23-25).

CAVI Measurement
CAVI was measured automatically using VaSera 
VS-1000 (Fukuda Denshi Co., Ltd., Tokyo, Japan) 
with the patient in the supine position20, 26). Cuffs 
were attached bilaterally to the upper arms and ankles. 
Electrocardiogram electrodes and a microphone were 
placed on both wrists and on the sternum, respectively. 
The average values of both sides of CAVI were 
entered into analyses. The measurement was per-
formed in a stable condition within one week prior to 
discharge.

Statistical Analysis
All continuous variables analyzed in this study 
were non-normally distributed according to the Shap-
iro-Wilk test, and were expressed as medians (25th, 
75th percentile). Categorical variables were presented 
as numbers (percent). Continuous and categorical 
variables were compared using the Mann-Whitney 
U test and the chi-square test, respectively. The receiver 
operating characteristic curve analysis for predicting 
post-discharge stroke was performed using EZR ver-
sion 1.40 (Saitama Medical Center, Jichi Medical 
University, Saitama, Japan)27). We compared the occur-
rence 1.40 (Saitama Medical Center, Jichi Medical 
University, Saitama, Japan)27). We compared the occur-
rence of post-discharge stroke using the Kaplan-Meier 
analysis with log-rank test. We assessed CAVI as a pre-
dictor for post-discharge stroke using the Cox propor-
tional hazard analysis. To adjust clinical confounding 
variables, we performed both the subgroup analysis and 
the multivariate Cox proportional hazard analysis. The univariate Cox proportional hazard analysis was sub-
divided by subgroups based on presence or absence of 
categorical factors and the median of continuous vari-
ables. Interaction $P$ values were obtained using multi-
variate model including CAVI, subgroup factors, and 
interactions between CAVI and subgroup factors. 
Multivariate Cox proportional hazard analysis was also 
performed. $P$ values < 0.05 were considered statisti-
cally significant in all analyses. All analyses, except for 
the receiver operating characteristic curve analysis, 
were conducted using IBM SPSS Statistics version 26 
(IBM, Armonk, NY, USA).

Results
A total of 111 (19.9%) patients belonged to the 
high-CAVI group. Levels of CAVI were 10.4 (9.9, 
11.1) in the high-CAVI group and 7.9 (6.8, 8.7) in 
the low-CAVI group ($P<0.001$). Comparisons of 
patient characteristics between the two groups are 
shown in Table 1. The high-CAVI group was older 
(73.0 vs. 65.5 years old, $P<0.001$), had a higher prev-
ance of male sex (73.9% vs. 61.4%, $P=0.015$), and 
showed lower levels of body mass index (22.5 vs. 23.8 
kg/m², $P=0.008$) and higher levels of systolic BP 
(132.0 vs. 124.0 mmHg, $P=0.011$). In contrast, levels 
of diastolic BP and the prevalence of New York Heart 
Association functional class III or IV were equivalent 
between the two groups. With respect to past medical 
history, the prevalence of prior stroke was equivalent 
(18.0% vs. 13.5%, $P=0.220$), while coronary artery 
disease (47.7% vs. 36.1%, $P=0.024$) and diabetes 
mellitus (54.1% vs. 37.4%, $P=0.001$) were more 
prevalent in the high-CAVI group. There were no sta-
tistical differences in medication. The high-CAVI 
group showed higher levels of BNP (235.9 vs. 135.6 
pg/mL, $P=0.001$) and hemoglobin A1c (6.0% vs. 
5.7%, $P=0.028$), and lower levels of hemoglobin 
(12.5 vs. 13.3 g/dL, $P=0.006$), eGFR (54.3 vs. 63.4 
ml/kg/1.73 m², $P<0.001$), and albumin (3.8 vs. 4.0 
g/dL, $P<0.001$). As to echocardiographic findings 
including left ventricular ejection fraction, stroke vol-
ume, and inferior vena cava diameter, there were no sta-
tistical differences between the two groups.

During the post-discharge follow-up period 
(median 1415 days), 25 patients reached the primary 
endpoint (18 ischemic and 7 hemorrhagic stroke). 
The Kaplan-Meier analysis demonstrated that post-
discharge stroke rate was higher in the high-CAVI 
group than in the low-CAVI group (Fig. 2, log-rank 
$P=0.005$). The unadjusted Cox proportional hazard 
analysis revealed that high CAVI (vs. low CAVI) was 
a predictor of post-discharge stroke (Table 2, hazard 
ratio [HR] 3.015, 95% confidence interval [CI] 
1.351–6.727, $P=0.007$). In addition, there were no 
interactions between CAVI and all subgroups accord-
ing to the subgroup analysis (Table 2). Furthermore, 
because of small event size and to avoid overfitting, we 
performed multivariate Cox proportional hazard anal-
ysis under consideration of confounding factors as 
much as possible. The predictive value of CAVI was 
adjusted for three models: age and sex (Model 1); 
Model 1 plus atherosclerotic risk factors which dif-
ferrered between the groups, namely presence of coro-
nary artery disease and diabetes mellitus (Model 2); 
and Model 1 plus severity of HF, namely New York 
Heart Association functional class III or IV, B-type 
natriuretic peptide, and left ventricular ejection frac-
tion (Model 3). After adjustment for the above con-
 founding factors, high CAVI was an independent pre-
dictor of post-discharge stroke (Table 3; Model 1, HR 
2.784, 95% CI 1.168–6.634, $P=0.021$; Model 2, HR 
2.719, 95% CI 1.134–6.518, $P=0.025$; Model 3, HR 
3.599, 95% CI 1.269–10.212, $P=0.016$).
|                         | Low-CAVI group  | High-CAVI group | $P$ value |
|-------------------------|-----------------|-----------------|-----------|
| **Demographic data**    |                 |                 |           |
| Age, years old          | 65.5 (55.0, 75.0) | 73.0 (67.0, 80.0) | $<0.001$  |
| Male sex, n (%)         | 274 (61.4)      | 82 (73.9)       | 0.015     |
| BMI, kg/m²              | 23.8 (21.2, 26.7) | 22.5 (20.5, 25.5) | 0.008     |
| Systolic BP, mmHg       | 124.0 (110.0, 141.0) | 132.0 (114.5, 149.5) | 0.011     |
| Diastolic BP, mmHg      | 70.0 (60.0, 82.0) | 71.0 (61.5, 86.0) | 0.186     |
| NYHA functional class 3 or 4, n (%) | 16 (3.6) | 3 (2.7) | 0.456 |
| **Etiology of HF**      |                 |                 |           |
| Ischemic                | 121 (27.1)      | 41 (36.9)       |           |
| Valvular                | 142 (31.8)      | 22 (19.8)       |           |
| Cardiomyopathy          | 108 (24.2)      | 30 (27.0)       |           |
| Others                  | 75 (16.8)       | 18 (16.2)       |           |
| **Past medical history**|                 |                 |           |
| Prior stroke, n (%)     | 60 (13.5)       | 20 (18.0)       | 0.220     |
| CAD, n (%)              | 161 (36.1)      | 53 (47.7)       | 0.024     |
| Hypertension, n (%)     | 313 (70.2)      | 85 (76.6)       | 0.182     |
| Diabetes mellitus, n (%)| 167 (37.4)      | 60 (54.1)       | 0.001     |
| Dyslipidemia, n (%)     | 336 (75.3)      | 84 (75.7)       | 0.941     |
| COPD, n (%)             | 110 (26.4)      | 31 (30.4)       | 0.414     |
| Smoking, n (%)          | 248 (56.4)      | 66 (60.6)       | 0.429     |
| **Medication**          |                 |                 |           |
| RAS inhibitors, n (%)   | 321 (72.0)      | 82 (73.9)       | 0.689     |
| Beta blockers, n (%)    | 324 (72.6)      | 88 (79.3)       | 0.154     |
| Loop diuretics, n (%)   | 248 (55.6)      | 72 (64.9)       | 0.077     |
| CCBs, n (%)             | 162 (36.3)      | 45 (40.5)       | 0.411     |
| Anticoagulants, n (%)   | 198 (44.4)      | 39 (35.1)       | 0.077     |
| Antiplatelet agents, n (%) | 265 (59.4) | 75 (67.6) | 0.115 |
| **Laboratory data**     |                 |                 |           |
| BNP pg/mL               | 135.6 (47.9, 446.7) | 235.9 (99.6, 605.3) | 0.001     |
| Hemoglobin, g/dL        | 13.3 (12.1, 14.8) | 12.5 (11.3, 13.9) | 0.006     |
| eGFR, ml/kg/1.73 m²     | 63.4 (50.8, 75.8) | 54.3 (40.2, 64.6) | $<0.001$  |
| Sodium, mEq/L           | 140.0 (138.0, 142.0) | 140.0 (138.0, 142.0) | 0.378     |
| Albumin, g/dL           | 4.0 (3.7, 4.4)  | 3.8 (3.3, 4.2)  | $<0.001$  |
| LDL cholesterol, mg/dL  | 108.0 (89.0, 129.0) | 106.5 (88.0, 136.0) | 0.725     |
| HbA1c (JDS), %          | 5.7 (5.4, 6.3)  | 6.0 (5.4, 6.7)  | 0.028     |
| **Echocardiographic data**|                 |                 |           |
| LVEF, %                 | 53.5 (39.5, 64.4) | 48.9 (39.6, 57.0) | 0.055     |
| Stroke volume, mL       | 50.0 (38.3, 66.6) | 46.7 (36.7, 57.5) | 0.112     |
| IVS thickness, mm       | 10.7 (9.0, 12.3) | 10.6 (9.1, 12.0) | 0.853     |
| PW thickness, mm        | 10.6 (9.2, 12.0) | 10.7 (9.4, 12.1) | 0.611     |
| LAVI, mL/m²             | 34.0 (24.1, 49.6) | 35.6 (26.2, 51.1) | 0.363     |
| RV-FAC, %               | 41.7 (32.4, 47.8) | 42.0 (36.6, 47.7) | 0.584     |
| TR-PG, mm               | 23.0 (17.8, 33.1) | 23.1 (18.0, 32.0) | 0.630     |
| IVC diameter, mm        | 13.9 (11.5, 17.0) | 13.2 (10.8, 16.6) | 0.316     |

CAVI, cardio-ankle vascular index; BMI, body mass index; BP, blood pressure; NYHA, New York Heart Association; HF, heart failure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin system; CCB, calcium-channel blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; JDS, Japan Diabetes Society; LVEF, left ventricular ejection fraction; IVS, interventricular septum; PW, posterior wall; LAVI, left atrial volume index; RV-FAC, right ventricular fractional area change; TR-PG, tricuspid regurgitation pressure gradient; IVC, inferior vena cava.
have recently reported that BNP is a predictor of stroke in patients with HF. Impaired renal function is one of the important comorbidities of HF. In addition, Kubozono et al. reported a negative correlation between eGFR and CAVI in the general population. The main features of patients in the high-CAVI group, such as aging, coronary artery disease, diabetes mellitus, and impaired renal function, are associated not only with HF, but also with stroke. Concordant with our results using cut-off value of CAVI of 9.64, a recent review of vascular function has proposed that CAVI $\geq 9.0$ as an abnormal high range is a marker of vascular failure. In addition, it has been reported that diabetic patients with CAVI $\geq 9.0$ had more cardiovascular events, patients with metabolic syndrome and CAVI $\geq 10.0$ had a higher incidence of cardiovascular events, and CAVI $\geq 9.0$ was independently associated with rapid decline in eGFR in patients who were at high risk of CVDs.

The pathological subtypes of stroke are ischemic stroke (cerebral, retinal, and spinal infarction) and hemorrhagic stroke (intracranial hemorrhage and subarachnoid hemorrhage). Arteriosclerosis is one of the two main pathological features of cerebral small vessel disease. Choi et al. recruited the data of individuals who had undergone general health examinations, and found that participants with the highest quartile of CAVI were significantly associated with cerebral small vessel disease.

**Discussion**

To the best of our knowledge, this study was the first to investigate the association between CAVI and post-discharge stroke in hospitalized patients with HF. The main findings of this study were that: (A) patients with high CAVI (≥ 9.64) had several indicators for severity of HF, including higher age, lower body mass index, coronary artery disease, diabetes mellitus, elevated levels of BNP, lower levels of hemoglobin, impaired renal function, and malnutrition; and (B) high CAVI was an independent predictor of stroke in patients with HF.

The main differences between the two groups in this single-center observational study were consistent with the results of the nationwide multicenter registry of patients who were at risk of CVD: CAVI levels were higher in men than in women, and increased according to age. Atherosclerosis-related diseases were more prevalent in the High-CAVI group. Izuhara et al. reported that CAVI, not PWV, was associated with carotid artery atherosclerosis and multi-vessel coronary artery stenosis in patients with suspected coronary disease. Although both CAVI and PWV reflect arterial stiffness, CAVI may be superior to PWV in patients with CVD including HF in terms of BP independence because BP dramatically fluctuates in conjunctions with CVD itself and medication for CVD through the clinical course in those population. Atherosclerosis plays a key role in developing HF and the high-CAVI group were complicated with severe HF. The lower body mass index in the high-CAVI group suggested not only elevated inflammation and right heart pressure, but also muscle decline that is associated with atrial stiffness. BNP is a major marker of HF severity, and the authors have recently reported that BNP is a predictor of stroke in patients with HF. Impaired renal function is one of the important comorbidities of HF. In addition, Kubozono et al. reported a negative correlation between eGFR and CAVI in the general population. The main features of patients in the high-CAVI group, such as aging, coronary artery disease, diabetes mellitus, and impaired renal function, are associated not only with HF, but also with stroke. Concordant with our results using cut-off value of CAVI of 9.64, a recent review of vascular function has proposed that CAVI $\geq 9.0$ as an abnormal high range is a marker of vascular failure. In addition, it has been reported that diabetic patients with CAVI $\geq 9.0$ had more cardiovascular events, patients with metabolic syndrome and CAVI $\geq 10.0$ had a higher incidence of cardiovascular events, and CAVI $\geq 9.0$ was independently associated with rapid decline in eGFR in patients who were at high risk of CVDs.

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Table 2. Cox proportional hazard analysis and the subgroup analysis for predicting stroke (25 events/n=557): the impact of high CAVI (vs. low CAVI)

| Factor                  | Subgroup | n     | HR   | 95% CI    | P value | Interaction P value |
|-------------------------|----------|-------|------|-----------|---------|---------------------|
| Total                   | -        | 557   | 3.015| 1.351–6.727 | 0.007   | -                   |
| Age                     | ≥ 68.0   | 281   | 2.148| 0.737–6.260 | 0.161   | 0.327               |
|                         | < 68.0   | 276   | 4.631| 1.355–15.828| 0.015   |                      |
| Sex                     | Male     | 356   | 2.430| 0.863–6.842 | 0.093   | 0.381               |
|                         | Female   | 201   | 5.679| 1.518–21.253| 0.010   |                      |
| BMI                     | ≥ 23.4   | 273   | 3.757| 1.224–11.534| 0.021   | 0.573               |
|                         | < 23.4   | 270   | 2.076| 0.495–8.698 | 0.318   |                      |
| Systolic BP             | ≥ 126.0  | 281   | 2.769| 1.030–7.441 | 0.044   | 0.936               |
|                         | < 126.0  | 276   | 2.839| 0.709–11.370| 0.141   |                      |
| Diastolic BP            | ≥ 71.0   | 281   | 2.710| 0.884–8.309 | 0.081   | 0.766               |
|                         | < 71.0   | 276   | 3.199| 1.015–10.082| 0.047   |                      |
| NYHA                    | 1 or 2   | 538   | 2.925| 1.263–6.775 | 0.012   | 0.617               |
|                         | 3 or 4   | 19    | 3.266| 0.188–56.776| 0.417   |                      |
| Prior stroke            | Yes      | 80    | 2.962| 0.770–11.389| 0.114   | 0.781               |
|                         | No       | 477   | 2.927| 1.041–8.233 | 0.042   |                      |
| CAD                     | Yes      | 214   | 1.154| 0.306–4.350 | 0.833   | 0.066               |
|                         | No       | 343   | 6.318| 2.202–18.124| 0.001   |                      |
| Hypertension            | Yes      | 398   | 3.093| 1.301–7.357 | 0.011   | 0.751               |
|                         | No       | 159   | 1.887| 0.196–18.180| 0.583   |                      |
| Diabetes mellitus       | Yes      | 227   | 3.428| 1.101–10.667| 0.033   | 0.819               |
|                         | No       | 330   | 2.525| 0.777–8.204 | 0.123   |                      |
| Dyslipidemia            | Yes      | 420   | 2.044| 0.775–5.390 | 0.148   | 0.112               |
|                         | No       | 137   | 10.350| 1.876–57.108| 0.007   |                      |
| COPD                    | Yes      | 141   | 2.735| 0.611–12.244| 0.188   | 0.874               |
|                         | No       | 378   | 2.391| 0.815–7.015 | 0.112   |                      |
| Smoking                 | Yes      | 314   | 4.721| 1.440–15.476| 0.010   | 0.213               |
|                         | No       | 235   | 1.722| 0.463–6.412 | 0.418   |                      |
| RAS inhibitors          | Yes      | 403   | 3.689| 1.497–9.088 | 0.005   | 0.356               |
|                         | No       | 154   | 1.276| 0.145–11.258| 0.826   |                      |
| Beta blockers           | Yes      | 412   | 3.876| 1.570–9.569 | 0.003   | 0.338               |
|                         | No       | 145   | 1.065| 0.124–9.115 | 0.954   |                      |
| Loop diuretics          | Yes      | 320   | 2.955| 1.165–7.492 | 0.022   | 0.774               |
|                         | No       | 237   | 2.458| 0.473–12.770| 0.285   |                      |
| CCBs                    | Yes      | 207   | 2.517| 0.957–6.617 | 0.061   | 0.808               |
|                         | No       | 350   | 3.248| 0.765–13.790| 0.110   |                      |
| Anticoagulants          | Yes      | 237   | 3.976| 1.109–14.247| 0.034   | 0.632               |
|                         | No       | 320   | 2.449| 0.871–6.887 | 0.089   |                      |
| Antiplatelet agents     | Yes      | 340   | 2.403| 0.855–6.756 | 0.096   | 0.453               |
|                         | No       | 217   | 4.950| 1.376–17.812| 0.014   |                      |
| BNP                     | ≥ 158.9  | 245   | 2.556| 0.858–7.613 | 0.092   | 0.415               |
|                         | < 158.9  | 244   | 5.089| 1.137–22.773| 0.033   |                      |
| Hemoglobin              | ≥ 13.2   | 261   | 2.767| 0.692–11.070| 0.150   | 0.815               |
|                         | < 13.2   | 258   | 3.700| 1.315–10.407| 0.013   |                      |
| eGFR                    | ≥ 61.1   | 258   | 1.886| 0.216–16.512| 0.566   | 0.657               |
|                         | < 61.1   | 257   | 2.844| 1.066–7.582 | 0.037   |                      |
| Sodium                  | ≥ 140.0  | 312   | 2.323| 0.713–7.565 | 0.162   | 0.535               |
|                         | < 140.0  | 206   | 4.279| 1.305–14.033| 0.016   |                      |
| Albumin                 | ≥ 4.0    | 259   | 3.095| 0.567–16.908| 0.192   | 0.916               |
|                         | < 4.0    | 227   | 3.543| 1.350–9.295 | 0.010   |                      |
However, high-resolution magnetic resonance imaging is limited by its cost and availability. Considering this limitation, CAVI is less expensive, widely used, and able to be a first step screening. CAVI can also indicate the presence of silent brain infarction. The present study was the first to find that CAVI was an independent predictor for stroke in patients with HF. From our results, clinicians should check for and control atherosclerotic risk factors in patients with HF, especially in those with high values of CAVI, in order to both predict and prevent vessel diseases. Atherosclerosis occurs not only in cerebral small vessels, but also in intracranial and extracranial large vessels, which account for 20% of ischemic stroke cases. The relationship between carotid artery atherosclerosis and CAVI has been established in various patient populations. In terms of assessment of intracranial atherosclerotic disease, one currently-used modality is high-resolution magnetic resonance imaging, which can directly visualize the vessel wall permitting evaluation of not only luminal stenosis but also vessel wall pathology. However, high-resolution magnetic resolution resonance imaging is limited by its cost and availability. Considering this limitation, CAVI is less expensive, widely used, and able to be a first step screening. CAVI can also indicate the presence of silent brain infarction. The present study was the first to find that CAVI was an independent predictor for stroke in patients with HF. From our results, clinicians should check for and control atherosclerotic risk factors in patients with HF, especially in those with high values of CAVI, in order to both predict and prevent vessel diseases.
vent stroke.

**Study Limitations**

The present study has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients, the present results may not be representative of the general HF population. Since HF generally have several comorbidities such as atrial fibrillation or peripheral artery disease, measurement of CAVI in all HF patients may not be necessarily useful for predicting stroke. Second, although we performed both subgroup analysis and multivariate Cox proportional hazard analysis with several confounding factors as much as possible, we could not rule out residual confounding variables, and the differences in the backgrounds between the groups might not be completely adjusted. Third, asymptomatic stroke may have failed to have been detected. Fourth, changes in CAVI through the clinical course were not taken into consideration due to the study protocol. Fifth, the data of PWV and carotid artery ultrasonography were not available in the dataset.

**Conclusions**

High CAVI is an independent predictor of stroke in patients with HF.

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