The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 766-775. http://doi.org/10.5551/jat.58727

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

Yu Sato[1], Akiomi Yoshihisa[1, 2], Yasuhiro Ichijo[1], Koichiro Watanabe[1], Yu Hotsuki[1], Yusuke Kimishima[1], Tetsuro Yokokawa[1], Tomofumi Misaka[1, 2], Takamasa Sato[1], Takashi Kaneshiro[1], Masayoshi Oikawa[1], Atsushi Kobayashi[1] and Yasuchika Takeishi[1]

[1]Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan
[2]Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan

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 pathophysiologies 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 stiffness[3, 4]. However, PWV is essentially affected by blood pressure (BP) at the time of measurement[5]. 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 artery[6]. The formula of the index is as follows: $CAVI = a \times [(2\rho/\Delta P) \times \ln(\text{systolic BP} / \text{diastolic BP}) \times PWV^2] + b$, where ρ is blood density, ΔP is pulse pressure, and a and b are coefficients[6]. CAVI also estimates atherosclerosis in the coronary and carotid arteries more closely than PWV[7, 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 CVDs[9-12]. However,

Address for correspondence: Akiomi Yoshihisa, Department of Cardiovascular Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima, 960-1295, Japan E-mail: yoshihis@fmu.ac.jp

Received: June 19, 2020 Accepted for publication: August 19, 2020

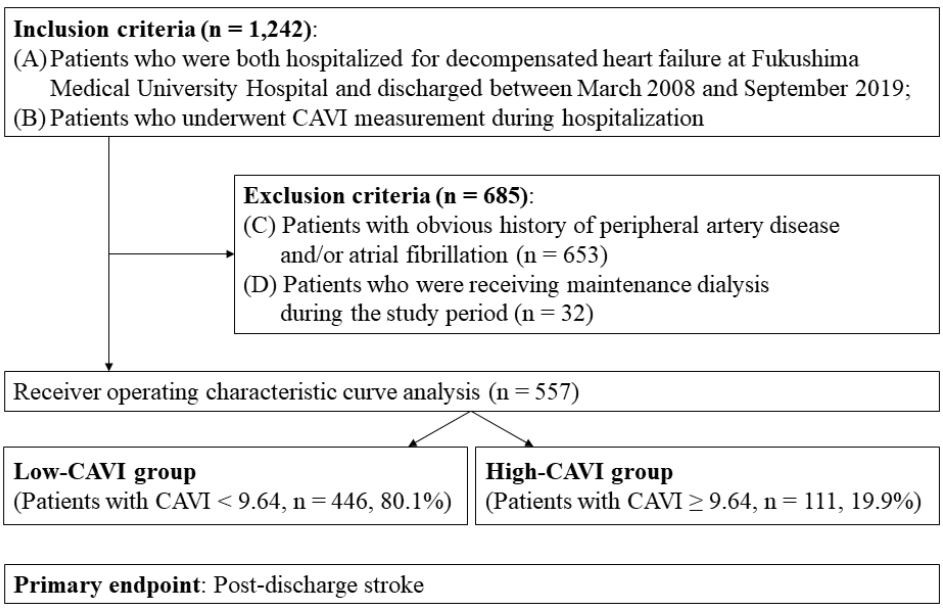

Fig. 1. Patient flowchart

CAVI, cardio-ankle vascular index.

the clinical implication of CAVI in patients with HF has not yet been fully examined, especially regarding prediction of stroke. Thus, the aim of the present study was to evaluate the predictive value of CAVI in terms of stroke in patients with HF.

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].

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.

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-

netic resonance imaging) or autopsy showed focal infarction or hemorrhage relevant to the symptoms[23-25].

CAVI Measurement

CAVI was measured automatically using VaSera VS-1000 (Fukuda Denshi Co., Ltd., Tokyo, Japan) with the patient in the supine position[20, 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 performed 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 Shapiro-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 version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[27].We compared the occurrence of post-discharge stroke using the Kaplan-Meier analysis with log-rank test. We assessed CAVI as a predictor for post-discharge stroke using the Cox proportional hazard analysis. To adjust clinical confounding factors, we performed both the subgroup analysis and the multivariate Cox proportional hazard analysis. The univariate Cox proportional hazard analysis was subdivided by subgroups based on presence or absence of categorical factors and the median of continuous variables. Interaction *P* values were obtained using multivariate 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 statistically 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 prevalence 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/m^2, $P=0.008$) 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 statistical 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 m^2, $P<0.001$), and albumin (3.8 vs. 4.0 g/dL, $P<0.001$). As to echocardiographic findings including left ventricular ejection fraction, stroke volume, and inferior vena cava diameter, there were no statistical 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 according to the subgroup analysis **(Table 2)**. Furthermore, because of small event size and to avoid overfitting, we performed multivariate Cox proportional hazard analysis 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 differed between the groups, namely presence of coronary 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 fraction (Model 3). After adjustment for the above confounding factors, high CAVI was an independent predictor 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, $P=0.016$).

Table 1. Patient characteristics ($n=557$)

	Low-CAVI group ($n=446$)	High-CAVI group ($n=111$)	*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/m^2	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			0.055
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 m^2	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/m^2	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.

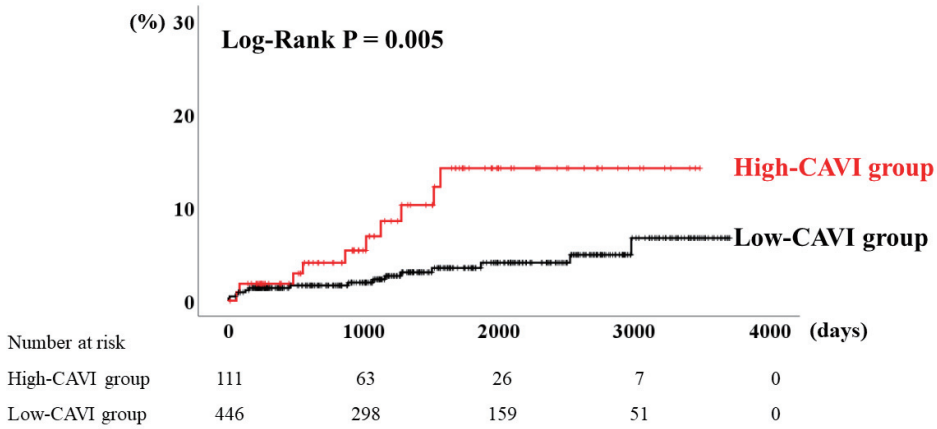

Fig. 2. Kaplan-Meier analysis for occurrence of post-discharge stroke
CAVI, cardio-ankle vascular index.

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[9]. 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[7]. Although both CAVI and PWV reflect arterial stiffness[6, 28], CAVI may be superior to PWV in patients with CVD including HF in terms of BP independency[29] because BP dramatically fluctuates in conjunctions with CVD itself and medication for CVD through the clinical course in those population[2, 13, 14, 30]. Atherosclerosis plays a key role in developing HF[2] 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[17, 31], but also muscle decline that is associated with atrial stiffness[32, 33]. BNP is a major marker of HF severity[2, 13, 14], and the authors have recently reported that BNP is a predictor of stroke in patients with HF[25]. Impaired renal function is one of the important comorbidities of HF[2, 13, 14, 34]. In addition, Kubozono *et al.* reported a negative correlation between eGFR and CAVI in the general population[35]. 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[2, 13, 14, 36-38]. Concordant with our results using cut-off value of CAVI of 9.64, a recent review of vascular function has proposed that CAVI ≥ 9.0 as an abnormal high range is a marker of vascular failure[39]. In addition, it has been reported that diabetic patients with CAVI ≥ 9.0 had more cardiovascular events[40], patients with metabolic syndrome and CAVI ≥ 10.0 had a higher incidence of cardiovascular events[41], and CAVI ≥ 9.0 was independently associated with rapid decline in eGFR in patients who were at high risk of CVDs[42].

The pathological subtypes of stroke are ischemic stroke (cerebral, retinal, and spinal infarction) and hemorrhagic stroke (intracranial hemorrhage and subarachnoid hemorrhage)[24]. Ischemic and hemorrhagic stroke share a common pathology, but the proportion of pathological and etiological subtypes of stroke vary depending on the populations of different age, race, ethnicity, and country[24, 38]. Arteriosclerosis is one of the two main pathological features of cerebral small vessel disease[36]. Pathological changes in the cerebral small vessels (e.g. loss of smooth muscle cells, lumen restriction, vessel wall thickening, and microaneurysms) lead to both ischemic and hemorrhagic stroke[36]. 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

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 functional class	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	

(Cont. Table 2)

Factor	Subgroup	*n*	HR	95% CI	*P* value	Interaction *P* value
LDL cholesterol	≥ 108.0	206	6.303	1.410–28.187	0.016	0.956
	< 108.0	205	6.241	1.393–27.956	0.017	
HbA1c (JDS)	≥ 5.8	195	11.338	2.283–56.315	0.003	0.377
	< 5.8	194	4.219	0.944–18.867	0.060	
LVEF	≥ 52.2	209	1.699	0.360–8.014	0.503	0.209
	< 52.2	209	6.384	2.008–20.302	0.002	
Stroke volume	≥ 49.0	213	3.759	0.686–20.597	0.127	0.933
	< 49.0	208	3.082	1.146–8.287	0.026	
IVS thickness	≥ 10.6	255	4.342	1.709–11.028	0.002	0.595
	< 10.6	236	2.381	0.435–13.051	0.317	
PW thickness	≥ 10.6	251	6.115	2.206–16.952	0.001	0.155
	< 10.6	239	1.358	0.282–6.550	0.703	
LAVI	≥ 34.1	180	2.537	0.489–13.171	0.268	0.234
	< 34.1	180	7.746	1.726–34.776	0.008	
RV-FAC	≥ 41.8	118	5.079	0.401–64.306	0.210	0.892
	< 41.8	118	6.187	1.213–31.547	0.028	
TR-PG	≥ 23.0	188	2.272	0.565–9.134	0.248	0.377
	< 23.0	174	4.486	1.289–15.615	0.018	
IVC diameter	≥ 13.9	241	3.244	0.961–10.954	0.058	0.900
	< 13.9	237	4.125	1.383–12.301	0.011	

CAVI, cardio-ankle vascular index; HR, hazard ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; NYHA, New York Heart Association; 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.

Table 3. Multivariate Cox proportional hazard analysis for stroke (event *n*=25/557)

	HR	95% CI	*P* value
High CAVI (vs. low CAVI) unadjusted	3.015	1.351–6.727	0.007
High CAVI (vs. low CAVI) Model 1	2.784	1.168–6.634	0.021
High CAVI (vs. low CAVI) Model 2	2.719	1.134–6.518	0.025
High CAVI (vs. low CAVI) Model 3	3.599	1.269–10.212	0.016

HF, hazard ratio; CI, confidence interval; CAVI, cardio-ankle vascular index.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, coronary artery disease, and diabetes mellitus.
Model 3: adjusted for age, sex, New York Heart Association functional class 3 or 4, B-type natriuretic peptide, and left ventricular ejection fraction.

vessel diseases[43]. Atherosclerosis occurs not only in cerebral small vessels, but also in intracranial and extracranial large vessels, which account for 20% of ischemic stroke cases[44]. The relationship between carotid artery atherosclerosis and CAVI has been established in various patient populations[7, 8, 45-47]. In terms of assessment of intracranial atherosclerotic disease, one currently-used modality is high-resolution magnetic resolution resonance imaging, which can directly visualize the vessel wall permitting evaluation of not only luminal stenosis but also vessel wall pathology[48]. However, high-resolution magnetic resolution resonance imaging is limited by its cost and availability[44, 48]. 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[49]. 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 pre-

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 the representative of the general HF population. Since HF generally have several co-morbidities 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.

Acknowledgements

The authors thank Ms. Kumiko Watanabe, Ms. Yumi Yoshihisa, and Ms. Tomiko Miura for their technical assistance.

Notice of Grant Support

This study was supported in part by a grant-in-aid for Scientific Research (No. 20K07828) from the Japan Society for the Promotion of Science.

COI

Akiomi Yoshihisa and Tomofumi Misaka belong to the Department of Advanced Cardiac Therapeutics at Fukushima Medical University, which is supported by Fukuda-denshi Co, Ltd. This company is not associated with the contents of this study.

References

1) Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Munoz D, Smith SC, Jr., Virani SS, Williams KA, Sr., Yeboah J and Ziaeian B: 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol, 2019; 74: e177-e232
2) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F and American Heart Association Task Force on Practice G: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2013; 62: e147-239
3) Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T, Artery S, European Society of Hypertension Working Group on Vascular S, Function and European Network for Noninvasive Investigation of Large A: Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens, 2012; 30: 445-448
4) Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I and Group ESCSD: 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J, 2018; 39: 3021-3104
5) Shirai K, Suzuki K, Tsuda S, Shimizu K, Takata M, Yamamoto T, Maruyama M and Takahashi K: Comparison of Cardio-Ankle Vascular Index (CAVI) and CAVI0 in Large Healthy and Hypertensive Populations. J Atheroscler Thromb, 2019; 26: 603-615
6) Shirai K, Utino J, Otsuka K and Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2006; 13: 101-107
7) Izuhara M, Shioji K, Kadota S, Baba O, Takeuchi Y, Uegaito T, Mutsuo S and Matsuda M: Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary arteriosclerosis. Circ J, 2008; 72: 1762-1767
8) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiratsuka A and Matsuzaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res, 2008; 31: 1347-1355
9) Kario K, Kabutoya T, Fujiwara T, Negishi K, Nishizawa M, Yamamoto M, Yamagiwa K, Kawashima A, Yoshida T, Nakazato J, Matsui Y, Sekizuka H, Abe H, Abe Y, Fujita Y, Sato K, Narita K, Tsuchiya N, Kubota Y, Hashizume T and Hoshide S: Rationale, design, and baseline characteristics of the Cardiovascular Prognostic COUPLING Study in Japan (the COUPLING Registry). J Clin Hypertens (Greenwich), 2020;

10) Matsushita K, Ding N, Kim ED, Budoff M, Chirinos JA, Fernhall B, Hamburg NM, Kario K, Miyoshi T, Tanaka H and Townsend R: Cardio-ankle vascular index and cardiovascular disease: Systematic review and meta-analysis of prospective and cross-sectional studies. J Clin Hypertens (Greenwich), 2019; 21: 16-24
11) Gohbara M, Iwahashi N, Sano Y, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Umemura S and Kimura K: Clinical Impact of the Cardio-Ankle Vascular Index for Predicting Cardiovascular Events After Acute Coronary Syndrome. Circ J, 2016; 80: 1420-1426
12) Kirigaya J, Iwahashi N, Tahakashi H, Minamimoto Y, Gohbara M, Abe T, Akiyama E, Okada K, Matsuzawa Y, Maejima N, Hibi K, Kosuge M, Ebina T, Tamura K and Kimura K: Impact of Cardio-Ankle Vascular Index on Long-Term Outcome in Patients with Acute Coronary Syndrome. J Atheroscler Thromb, 2020; 27; 657-668
13) Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P and Group ESCSD: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2016; 37: 2129-2200
14) Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, Kitakaze M, Kinugawa K, Kihara Y, Goto Y, Komuro I, Saiki Y, Saito Y, Sakata Y, Sato N, Sawa Y, Shiose A, Shimizu W, Shimokawa H, Seino Y, Node K, Higo T, Hirayama A, Makaya M, Masuyama T, Murohara T, Momomura SI, Yano M, Yamazaki K, Yamamoto K, Yoshikawa T, Yoshimura M, Akiyama M, Anzai T, Ishihara S, Inomata T, Imamura T, Iwasaki YK, Ohtani T, Onishi K, Kasai T, Kato M, Kawai M, Kinugasa Y, Kinugawa S, Kuratani T, Kobayashi S, Sakata Y, Tanaka A, Toda K, Noda T, Nochioka K, Hatano M, Hidaka T, Fujino T, Makita S, Yamaguchi O, Ikeda U, Kimura T, Kohsaka S, Kosuge M, Yamagishi M, Yamashina A, Japanese Circulation S and the Japanese Heart Failure Society Joint Working G: JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version. Circ J, 2019; 83: 2084-2184
15) Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P and Group ESCSD: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J, 2016; 37: 2893-2962
16) Nakamura Y, Kunii H, Yoshihisa A, Takiguchi M, Shimizu T, Yamauchi H, Iwaya S, Owada T, Abe S, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Impact of peripheral artery disease on prognosis in hospitalized heart failure patients. Circ J, 2015; 79: 785-793
17) Sato Y, Yoshihisa A, Kimishima Y, Yokokawa T, Abe S, Shimizu T, Misaka T, Yamada S, Sato T, Kaneshiro T, Oikawa M, Kobayashi A, Yamaki T, Kunii H and Takeishi Y: Prognostic factors in heart failure patients with cardiac cachexia. J Geriatr Cardiol, 2020; 17: 26-34
18) Yoshihisa A, Sato Y, Sato T, Suzuki S, Oikawa M and Takeishi Y: Better clinical outcome with direct oral anticoagulants in hospitalized heart failure patients with atrial fibrillation. BMC Cardiovasc Disord, 2018; 18: 11
19) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A and Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
20) Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. J Cardiol, 2014; 64: 256-264
21) Rickham PP: Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki. Br Med J, 1964; 2: 177
22) von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP and Initiative S: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ, 2007; 335: 806-808
23) Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV, American Heart Association Stroke Council CoCS, Anesthesia, Council on Cardiovascular R, Intervention, Council on C, Stroke N, Council on E, Prevention, Council on Peripheral Vascular D, Council on Nutrition PA and Metabolism: An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2013; 44: 2064-2089
24) Hankey GJ: Stroke. Lancet, 2017; 389: 641-654
25) Hotsuki Y, Sato Y, Yoshihisa A, Watanabe K, Kimishima Y, Kiko T, Yokokawa T, Abe S, Misaka T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K and Takeishi Y: B-type natriuretic peptide is associated with post-discharge stroke in hospitalized patients with heart failure. ESC Heart Fail, 2020;
26) Tomita Y, Kasai T, Ishiwata S, Daida H and Narui K: Aortic Knob Width as a Novel Indicator of Atherosclerosis and Obstructive Sleep Apnea. J Atheroscler Thromb, 2020; 27: 501-508
27) Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant, 2013; 48: 452-458
28) Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T and American Heart Association Council on H: Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Associa-

tion. Hypertension, 2015; 66: 698-722
29) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O and Tei C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94
30) Sato Y, Yoshihisa A, Oikawa M, Nagai T, Yoshikawa T, Saito Y, Yamamoto K, Takeishi Y and Anzai T: Relation of Systolic Blood Pressure on the Following Day with Post-Discharge Mortality in Hospitalized Heart Failure Patients with Preserved Ejection Fraction. Int Heart J, 2019; 60: 876-885
31) Takiguchi M, Yoshihisa A, Miura S, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Suzuki H, Saitoh S and Takeishi Y: Impact of body mass index on mortality in heart failure patients. Eur J Clin Invest, 2014; 44: 1197-1205
32) Abbatecola AM, Chiodini P, Gallo C, Lakatta E, Sutton-Tyrrell K, Tylavsky FA, Goodpaster B, de Rekeneire N, Schwartz AV, Paolisso G, Harris T and Health ABCs: Pulse wave velocity is associated with muscle mass decline: Health ABC study. Age (Dordr), 2012; 34: 469-478
33) Kohara K, Okada Y, Ochi M, Ohara M, Nagai T, Tabara Y and Igase M: Muscle mass decline, arterial stiffness, white matter hyperintensity, and cognitive impairment: Japan Shimanami Health Promoting Program study. J Cachexia Sarcopenia Muscle, 2017; 8: 557-566
34) Miura S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Oikawa M, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Association of Hypocalcemia With Mortality in Hospitalized Patients With Heart Failure and Chronic Kidney Disease. J Card Fail, 2015; 21: 621-627
35) Kubozono T, Miyata M, Ueyama K, Nagaki A, Hamasaki S, Kusano K, Kubozono O and Tei C: Association between arterial stiffness and estimated glomerular filtration rate in the Japanese general population. J Atheroscler Thromb, 2009; 16: 840-845
36) Pantoni L: Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol, 2010; 9: 689-701
37) Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA, American Heart Association Stroke C, Council on C, Stroke N, Council on Clinical C, Council on Functional G, Translational B and Council on H: Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2014; 45: 3754-3832
38) Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D, American Heart Association Stroke C, Council on C, Stroke N and Council on Clinical C: Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 2015; 46: 2032-2060
39) Tanaka A, Tomiyama H, Maruhashi T, Matsuzawa Y, Miyoshi T, Kabutoya T, Kario K, Sugiyama S, Munakata M, Ito H, Ueda S, Vlachopoulos C, Higashi Y, Inoue T, Node K and Physiological Diagnosis Criteria for Vascular Failure C: Physiological Diagnostic Criteria for Vascular Failure. Hypertension, 2018; 72: 1060-1071
40) Chung SL, Yang CC, Chen CC, Hsu YC and Lei MH: Coronary Artery Calcium Score Compared with Cardio-Ankle Vascular Index in the Prediction of Cardiovascular Events in Asymptomatic Patients with Type 2 Diabetes. J Atheroscler Thromb, 2015; 22: 1255-1265
41) Sato Y, Nagayama D, Saiki A, Watanabe R, Watanabe Y, Imamura H, Yamaguchi T, Ban N, Kawana H, Nagumo A, Ohira M, Endo K, Kurosu T, Tomaru T, Shirai K and Tatsuno I: Cardio-Ankle Vascular Index is Independently Associated with Future Cardiovascular Events in Outpatients with Metabolic Disorders. J Atheroscler Thromb, 2016; 23: 596-605
42) Satirapoj B, Triwatana W and Supasyndh O: Arterial Stiffness Predicts Rapid Decline in Glomerular Filtration Rate Among Patients with High Cardiovascular Risks. J Atheroscler Thromb, 2020; 27: 611-619
43) Choi SY, Park HE, Seo H, Kim M, Cho SH and Oh BH: Arterial stiffness using cardio-ankle vascular index reflects cerebral small vessel disease in healthy young and middle aged subjects. J Atheroscler Thromb, 2013; 20: 178-185
44) Marulanda-Londono E and Chaturvedi S: Stroke due to large vessel atherosclerosis: Five new things. Neurol Clin Pract, 2016; 6: 252-258
45) Okura T, Watanabe S, Kurata M, Manabe S, Koresawa M, Irita J, Enomoto D, Miyoshi K, Fukuoka T and Higaki J: Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. Hypertens Res, 2007; 30: 335-340
46) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Matsuda T, Hiratsuka A and Matsuzaki M: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J, 2007; 71: 1710-1714
47) Ibata J, Sasaki H, Kakimoto T, Matsuno S, Nakatani M, Kobayashi M, Tatsumi K, Nakano Y, Wakasaki H, Furuta H, Nishi M and Nanjo K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract, 2008; 80: 265-270
48) Bodle JD, Feldmann E, Swartz RH, Rumboldt Z, Brown T and Turan TN: High-resolution magnetic resonance imaging: an emerging tool for evaluating intracranial arterial disease. Stroke, 2013; 44: 287-292
49) Saji N, Kimura K, Shimizu H and Kita Y: Silent brain infarct is independently associated with arterial stiffness indicated by cardio-ankle vascular index (CAVI). Hypertens Res, 2012; 35: 756-760