Clinical Usefulness of the Cardio-Ankle Vascular Index as a Predictor of Primary Cardiovascular Events in Patients With Chronic Kidney Disease

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Abstract

Background: The cardio-ankle vascular index (CAVI) is a physiologic marker reflecting arterial function. There have been no prospective studies investigating the relationship between CAVI and cardiovascular events in patients with chronic kidney disease (CKD). The aim of this prospective study was to assess the clinical usefulness of CAVI as a predictor of primary cardiovascular events in patients with CKD.

Methods: The study enrolled 460 outpatients with CKD but no history of cardiovascular disease (152 men and 308 women; mean ± standard deviation age, 74 ± 12 years). Patients were assigned to one of three groups: low (L, CAVI < 9; n = 100), medium (M, CAVI 9 - 10; n = 199), or high (H, CAVI > 10; n = 161). The utility of the CAVI as a predictor of primary cardiovascular events was evaluated.

Results: During the follow-up period (median 60.1 months), major adverse cardiovascular events (MACE) occurred in 91 cases (L, 8 (8.0%); M, 31 (15.6%); H, 52 (32.3%); P < 0.001, log-rank test). On multivariate Cox regression analysis, the risk for a MACE was significantly higher in group H than in non-group H (hazard ratio, 2.04; 95% confidence interval, 1.31 - 3.02; P < 0.01). A CAVI cut-off of 9.7 yielded the largest area under the curve, 0.701 (95% confidence interval: 0.657 - 0.743, P < 0.001), indicating a sensitivity of 74.0% and a specificity of 59.6% for discriminating between those who did and did not experience a MACE during follow-up.

Conclusions: The results of this study showed that a high CAVI is a predictor of primary cardiovascular events in patients with CKD.

Keywords: Cardio-ankle vascular index; Chronic kidney disease; Primary cardiovascular events; Oxidative stress; Advanced glycation end products; Renin-angiotensin system inhibitor

Introduction

In recent years, the prevalence of chronic kidney disease (CKD) has increased because of both life-extending treatment and the increased incidence of life style-related disease such as hypertension, type 2 diabetes mellitus, and dyslipidemia [1, 2]. CKD is an important risk factor not only for end-stage renal disease but also for cardiovascular disease (CVD) [3, 4]. Complications of CVD in patients with CKD are associated with a poor prognosis [5, 6]. Therefore, for patients with CKD, it is crucial to be alert to risk factors for cardiovascular events and to consider treatment to prevent them.

Arterial dysfunction is an important risk factor for cardiovascular events. Among physiologic markers of arterial function, the cardio-ankle vascular index (CAVI) is a novel marker of atherosclerosis that reflects systemic arterial stiffness in vessels such as the aorta and the femoral and tibial arteries [7]. This stiffness parameter is reported to be independent of the blood pressure during measurement. In addition, CAVI is thought to reflect endothelial function [8, 9]. Several clinical studies have indicated the clinical significance of CAVI in relation to CKD [10-12]. However, there has been no prospective study of the relationship between CAVI and cardiovascular events in patients with CKD. Therefore, this study was designed to clarify the clinical usefulness of CAVI as a predictor of primary cardiovascular events in patients with CKD.

Materials and Methods

Participants

Between June 2011 and December 2013, 460 outpatients (152 men (33.0%) and 308 women (67.0%)) with CKD but no history of cardiovascular events were prospectively enrolled at the Hitsumoto Medical Clinic, Yamaguchi, Japan. Estimated glomerular filtration rate (eGFR) was calculated using the adjusted Modification of Diet in Renal Disease Study equation, as proposed by the working group of the Japanese Chronic Kidney Disease Initiative [13]. The definition of CKD for selection of participants was an eGFR from 15 to 59 mL/min/1.73m². The mean age (± standard deviation) was
74 ± 12 years. CAVI was measured as described below, after which the participants were assigned to one of three groups, those with a low (L, < 9; n = 100), medium (M, = 9 - 10; n = 199), or high (H, > 10; n = 161) CAVI. Cut-off levels of CAVI were determined by previous studies [14]. The study protocol was approved by Local Ethics Committee of Hit-sumoto Medical Clinic, and informed consent was obtained from all participants.

Measurement of CAVI

The CAVI was measured using a commercial device (Vasera; Fukuda Denshi, Tokyo, Japan) according to previously described methods [7]. Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs with the pressure maintained between 30 and 50 mm Hg to ensure that the cuff pressure had a minimal effect on the systemic hemodynamics. Blood and pulse pressures were determined simultaneously with the subjects lying supine, after they had first rested for 10 min in a quiet room. The CAVI recorded for the study was the mean of the left and right values. CAVI was calculated using the following formula: \( \text{CAVI} = \frac{a \times \ln \left( \frac{P_s}{P_d} \right)}{\rho \times (\Delta P)} + b \), where \( a \) and \( b \) are constants, \( \rho \) is blood density, \( \Delta P \) is \( P_s - P_d \), \( P_s \) is systolic blood pressure, \( P_d \) is diastolic blood pressure, and PWV is pulse wave velocity.

Evaluation of clinical parameters

Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Obesity was defined by the Japanese criteria of body mass index ≥ 25 kg/m². Current smoking was defined as smoking at least one cigarette per day during the previous 28 days. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥ 140 mg/dL, a high-density lipoprotein cholesterol level ≤ 40 mg/dL, a triglyceride level ≥ 150 mg/dL, or the use of antidylipeidemic medication. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dL or the use of antidiabetic medication. Skin autofluorescence (AF) reflects pentosidine, a major component of advanced glycation end products (AGEs) in tissues. It was measured using a commercial device (AGE Reader; DiagnOptics, Groningen, Netherlands), as previously described [15]. AF was defined as the average light intensity per nanometer between 300 nm and 420 nm. Skin AF levels were expressed in arbitrary units. The following blood or urine parameters were measured: serum lipid concentrations, plasma glucose concentrations, derivatives of reactive oxygen metabolites (d-ROMs), and urinary albumin concentrations. Blood samples were collected from the antecubital vein in the morning after 12 h of fasting, and urine samples were collected on the same day. Total cholesterol and triglyceride concentrations were measured using standard enzymatic methods. High- and low-density lipoprotein cholesterol concentrations were measured using selective inhibition and Friedewald’s formula, respectively [16]. Participants with a serum triglyceride concentration ≥ 400 mg/dL were excluded from the analysis, given the limitations of this method. Glucose concentrations were measured by the glucose oxidase method. As a marker of oxidative stress in vivo [17], the d-ROMs test was performed using a commercial kit (Diacon, Grosseto, Italy). Urinary albumin concentration was measured using a commercial kit (Siemens/Bayer DCA 2000+ Analyzer, Siemens Healthineers, Tokyo, Japan).

Follow-up

The study follow-up period ended in May 2018. The endpoint was a major adverse cardiovascular event (MACE), a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke and hospital admission for heart failure.

Statistical analysis

Data were analyzed using Stat View-J 5.0 (HULINKS, Tokyo, Japan) and MedCalc for Windows version 14.8.1 (MedCalc Software, Ostend, Belgium). Data are presented as mean ± standard deviation. One-way analysis of variance and the Kruskal-Wallis test were used for comparisons among the three groups. Post-hoc testing was performed using Fisher’s protected least significant differences or the Mann-Whitney U-test with the Bonferroni correction. Event-free survival rate curves were plotted using Kaplan-Meier analysis, and the differences between the curves were evaluated using the log-rank test. Multivariate analysis was performed using multivariate Cox regression analysis. Receiver operating characteristic (ROC) curves were constructed, and the Youden Index was used to determine the optimal cut-off for CAVI for predicting a MACE. P < 0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of the participants at study entry, and the dot graph of CAVI is shown in Figure 1. The mean CAVI for groups L, M, and H was 8.4 (range; 7.5 - 8.9), 9.5 (range: 9.0 - 10.0), and 10.9 (range: 10.1 - 13.7), respectively. The eGFR level was significantly lower in group H than in group M or group L. The following factors were significantly higher in group H than in group M or L: fasting blood glucose levels, skin AF, d-ROMs, and urinary albumin concentrations. Figure 2 shows the Kaplan-Meier curve for the incidence of MACE. The median follow-up was 60.1 months (range, 2 - 84 months). During follow-up, 91 participants experienced at least one MACE (L, 8 cases (8.0%)); M, 31 cases (15.6%)); H, 52 cases (32.3%). Group H had a significantly higher incidence of MACE compared with groups M and L (log-rank test, P < 0.001). Table 2 presents the clinical vari-
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### Table 1. Characteristics of Patients

|                        | Overall    | Group L    | Group M    | Group H    | P value |
|------------------------|------------|------------|------------|------------|---------|
| n (male/female)        | 460 (152/308) | 100 (25/75) | 199 (63/136) | 161 (64/97)*** | < 0.05  |
| Age (yrs)              | 74 ± 12    | 71 ± 10    | 73 ± 11    | 75 ± 13**   | < 0.05  |
| Risk factors           |            |            |            |            |         |
| CAVI                   | 9.7 ± 1.1  | 8.4 ± 0.5  | 9.5 ± 0.2* | 10.9 ± 0.8** | < 0.001 |
| Obesity, n (%)         | 136 (30)   | 27 (27)    | 56 (28)    | 53 (33)     | 0.503   |
| Current smoker, n (%)  | 79 (17)    | 12 (12)    | 33 (17)    | 34 (21)     | 0.159   |
| Hypertension, n (%)    | 323 (70)   | 65 (65)    | 135 (68)   | 123 (76)    | 0.09    |
| SBP (mm Hg)            | 142 ± 16   | 138 ± 17   | 141 ± 16   | 144 ± 13**  | < 0.05  |
| DBP (mm Hg)            | 87 ± 11    | 85 ± 11    | 88 ± 11*** | 89 ± 11**   | < 0.05  |
| Dyslipidemia, n (%)    | 320 (70)   | 77 (77)    | 133 (67)   | 110 (68)    | 0.181   |
| Diabetes mellitus, n (%)| 155 (34)  | 24 (24)    | 65 (33)    | 66 (41)**   | < 0.05  |
| Laboratory findings    |            |            |            |            |         |
| eGFR (mL/min/1.73m²)   | 47 ± 9     | 50 ± 8     | 47 ± 9**   | 45 ± 10*#** | < 0.001 |
| Total cholesterol (mg/dL) | 216 ± 37 | 217 ± 35 | 214 ± 39 | 218 ± 37 | 0.626 |
| LDL cholesterol (mg/dL) | 129 ± 35  | 130 ± 30  | 126 ± 35  | 133 ± 36  | 0.246  |
| Triglyceride (mg/dL)   | 138 ± 63   | 148 ± 72   | 139 ± 62   | 130 ± 57   | 0.073  |
| HDL cholesterol (mg/dL) | 59 ± 15   | 58 ± 14    | 60 ± 15    | 59 ± 15    | 0.462  |
| FBG (mg/dL)            | 110 ± 22   | 107 ± 20   | 108 ± 20   | 116 ± 25**## | < 0.001 |
| Skin AF (AU)           | 2.7 ± 0.5  | 2.5 ± 0.5  | 2.7 ± 0.5*** | 2.9 ± 0.5** | < 0.001 |
| d-ROMs test (U.Carr)   | 328 ± 86   | 307 ± 88   | 324 ± 82   | 346 ± 88#### | < 0.001 |
| U-Alb (mg/g Cr)        | 1.5 ± 0.6  | 1.4 ± 0.5  | 1.5 ± 0.6  | 1.6 ± 0.6#### | < 0.01  |
| Medication             |            |            |            |            |         |
| RAS inhibitor, n (%)   | 164 (36)   | 36 (36)    | 63 (32)    | 65 (40)     | 0.229  |
| Statin, n (%)          | 158 (34)   | 32 (32)    | 75 (38)    | 51 (32)     | 0.421  |
| Anti-diabetic drugs, n (%) | 116 (25) | 20 (20)    | 53 (27)    | 43 (27)     | 0.399  |

Continuous values are mean ± SD. CAVI: cardio-ankle vascular index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBG: fasting blood glucose; AF: autofluorescence; d-ROMs: derivatives of reactive oxygen metabolites; U-Alb: urinary albumin; RAS: renin-angiotensin system. *P < 0.001 vs. Group L; **P < 0.01 vs. Group L; ***P < 0.05 vs. Group L; #P < 0.05 vs. Group M; ##P < 0.01 vs. Group M; ###P < 0.05 vs. Group M.

Discriminable at study entry of all the participants, comparing those who experienced MACEs with those who did not. Age, current smoking status, prevalence of hypertension, systolic blood pressure, prevalence of diabetes mellitus, fasting blood glucose concentrations, skin AF, d-ROMs, and urinary albumin concentration were considerably higher in participants who had a MACE than in those who did not. The eGFR levels and use of renin-angiotensin system (RAS) inhibitors or statins were considerably lower. Table 3 presents the results of the multivariate Cox regression analysis for the MACE. A total of 11 variables were significant factors for MACE on univariate analysis or in a check of multicollinearity among the variables. Of these 11, six variables (CAVI, a CAVI >10, diabetes mellitus, age, skin AF, d-ROMs, and RAS-inhibitor use) had a significant hazard ratio for MACE. Figure 3 shows the ROC curve analysis for the incidence of MACE based on CAVI. A cut-off value of 9.7 yielded the largest area under the curve, 0.701 (95% confidence interval: 0.657 - 0.743, P < 0.001). This indicated a sensitivity of 74.0% and specificity of 59.6% to discriminate between those who did and did not have a MACE during follow-up.

Figure 1. The dot graph of CAVI. CAVI: cardio-ankle vascular index.
Table 2. Clinical Parameters at Registration of Patients With and Without Major Adverse Cardiovascular Events

| Parameter                      | MACE (-)     | MACE (+)     | P value |
|-------------------------------|--------------|--------------|---------|
| n (male/female)               | 363 (121/242) | 97 (31/66)   | 0.798   |
| Age (yrs)                     | 72 ± 11      | 79 ± 11      | < 0.001 |
| Obesity, n (%)                | 110 (30)     | 26 (27)      | 0.503   |
| Current smoker, n (%)         | 55 (15)      | 24 (25)      | < 0.05  |
| Hypertension, n (%)           | 241 (66)     | 82 (85)      | < 0.001 |
| SBP (mm Hg)                   | 140 ± 15     | 147 ± 16     | < 0.001 |
| DBP (mm Hg)                   | 87 ± 11      | 89 ± 11      | 0.093   |
| Dyslipidemia, n (%)           | 257 (71)     | 63 (65)      | 0.267   |
| Diabetes mellitus, n (%)      | 104 (29)     | 51 (53)      | < 0.001 |
| eGFR (mL/min/1.73m²)          | 48 ± 8       | 43 ± 11      | < 0.001 |
| Total cholesterol (mg/dL)     | 216 ± 38     | 217 ± 36     | 0.852   |
| LDL cholesterol (mg/dL)       | 129 ± 35     | 130 ± 35     | 0.893   |
| Triglyceride (mg/dL)          | 138 ± 63     | 139 ± 62     | 0.927   |
| HDL cholesterol (mg/dL)       | 59 ± 15      | 59 ± 14      | 0.939   |
| FBG (mg/dL)                   | 109 ± 20     | 116 ± 27     | < 0.01  |
| Skin AF (AU)                  | 2.6 ± 0.5    | 3.0 ± 0.5    | < 0.001 |
| d-ROMs test (U. Carr)         | 319 ± 84     | 360 ± 89     | < 0.001 |
| U-Alb (mg/g Cr)               | 1.5 ± 0.5    | 1.7 ± 0.7    | < 0.001 |
| RAS inhibitor, n (%)          | 143 (39)     | 21 (21)      | < 0.01  |
| Statin, n (%)                 | 135 (37)     | 23 (24)      | < 0.05  |
| Anti-diabetic drug, n (%)     | 94 (26)      | 22 (23)      | 0.518   |

Continuous values are mean ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBG: fasting blood glucose; AF: autofluorescence; d-ROMs: derivatives of reactive oxygen metabolites; U-Alb: urinary albumin; RAS: renin-angiotensin system.

Table 3. Multivariate Cox Regression Analysis for Major Adverse Cardiovascular Events

| Parameter                      | HR     | 95% CI          | P value |
|-------------------------------|--------|-----------------|---------|
| Diabetes mellitus             | 2.50   | 1.38 - 4.60     | < 0.01  |
| Group H (vs non-Group H)      | 2.04   | 1.31 - 3.02     | < 0.01  |
| Age (≥ 75yrs)                 | 1.81   | 1.03 - 3.22     | < 0.05  |
| Skin AF (≥ 3.0AU)             | 1.64   | 1.09 - 2.63     | < 0.05  |
| d-ROMs test (≥ 330 U. Carr)   | 1.61   | 1.01 - 2.79     | < 0.05  |
| RAS inhibitor                 | 0.58   | 0.23 - 0.99     | < 0.05  |
| Current smoker                | 1.58   | 0.93 - 2.69     | 0.089   |
| Albuminuria                   | 1.39   | 0.92 - 2.11     | 0.137   |
| Statin                        | 0.70   | 0.42 - 1.15     | 0.178   |
| eGFR (< 30mL/min/1.73m²)      | 1.40   | 0.79 - 2.53     | 0.255   |
| Hypertension                  | 1.26   | 0.73 - 2.16     | 0.399   |

HR: hazard ratio; CI: confidence interval; AF: autofluorescence; d-ROMs: derivatives of reactive oxygen metabolites; RAS: renin-angiotensin system; eGFR: estimated glomerular filtration rate.

Figure 2. Kaplan-Meier curve for the incidence of major adverse cardiovascular events. The Kaplan-Meier curve confirmed that group H had a significantly higher incidence of major adverse cardiovascular events compared with groups M and L (log-rank test, P < 0.001). *P < 0.01 vs. group L, **P = 0.112 vs. group L, ***P < 0.001 vs. group M.
markers of kidney function such as eGFR or albuminuria is reported to be an important risk factor for cardiovascular events [4]. However, multivariate analysis in this study indicated that these renal function variables were not independently predictive of a MACE, even though they were significantly associated with such events on univariate analysis. However, eGFR and albuminuria were significantly associated with CAVI. Previous studies also indicated that an increase in the CAVI is closely associated with a decreased eGFR or increased albuminuria [10, 27]. Thus, these results can be interpreted that increase of CAVI in the background of decrease in eGFR or albuminuria of CKD patients acts crucial role in the incidence of CVD.

It is no doubt a fact that oxidative stress is an important factor in the pathogenesis of CVD. Various oxidative stress markers have been reported to be associated clinically with CVD, and several clinical studies have indicated the clinical usefulness of measuring d-ROMs as a risk factor for cardiovascular events [28-30]. The results of the present study also found that elevated d-ROM levels were a predictor of primary cardiovascular events in patients with CKD. This study found that higher d-ROM levels were associated with a high CAVI. Previous studies have reported that anti-oxidant medications result in a reduced CAVI [25, 31, 32]. Thus, findings of the present study again are consistent with the notion that oxidative stress increases cardiovascular events in patients with CKD, and this may be reflected in an elevated CAVI. This raises the possibility of reducing CAVI with anti-oxidant medication and, therefore, the incidence of primary cardiovascular events.

Recent basic and clinical studies have emphasized the important role played by AGEs in various diseases, such as the complications of diabetes, CKD, and CVD [33]. In addition, researchers have reported that increased skin AF is a cardiovascular risk factor [34-37]. The results of this study also indicate that a high skin AF is an independent predictor of primary cardiovascular events in patients with CKD. In addition, a high skin AF level had a significant positive correlation with CAVI, suggesting that accumulation of AGEs in arterial vessel walls contributes to arterial dysfunction in patients with CKD.

Genevieve et al examined the relationship between skin AF and hemoglobin A1c (HbA1c) levels, which reflect the preceding 1- to 2-month glucose levels [38]. They measured HbA1c levels every 6 months and found that the skin AF level was significantly related to the preceding five and 10 mean HbA1c levels. Isami et al reported that lifestyle habits such as physical activity, nonsmoking, adequate sleep, low mental stress level, eating breakfast, and abstaining from sugary foods were each independently associated with lower skin AF levels [39]. Thus, long-term glucose control and good lifestyle habits are important to maintain lower skin AF levels and a lower CAVI.

It is well known that the RAS system is an important factor in the pathogenesis of both CKD and CVD. In fact, RAS inhibitors are clinically shown to suppress the progression of CKD and the incidence of CVD events [40, 41]. In addition, administration of RAS inhibitors has been shown to reduce the incidence of cardiovascular events in patients with CKD [42, 43]. The results of this study also indicate that the use of RAS inhibitors was independently associated with fewer MACEs in patients with CKD. Several studies have in fact reported that...
RAS inhibition is effective in improving the CAVI [32, 44, 45]. Among patients of the present study, RAS inhibitors were used in 40% of patients in group H. Therefore, greater use of RAS inhibitors is required to improve arterial function in patients with a high CAVI, with the expectation that it will help reduce primary cardiovascular events in patients with CKD.

**Limitations**

This study had several limitations. First, it was conducted at a single center with a relatively small sample, so the findings cannot be generalized to all populations. Second, CAVI was measured only once at study entry. A further investigation of serial changes in CAVI in relation to primary cardiovascular events is needed. Finally, further studies of patients with a high CAVI are warranted to confirm whether interventions, such as lifestyle modification or medications, reduce the incidence of primary cardiovascular events in patients with CKD along with improvement in CAVI.

**Conclusions**

This study demonstrated that CAVI is a predictor of primary cardiovascular events in patients with CKD. Further studies of patients with a high CAVI are warranted to confirm whether interventions, such as lifestyle modification or medications, reduce the incidence of primary cardiovascular events in patients with CKD along with improvement in the CAVI.

**Conflict of Interest**

Author has no conflict of interest.

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