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**Review**

# Protocol for Evaluating the Cardio-Ankle Vascular Index to Predict Cardiovascular Events in Japan: A Prospective Multicenter Cohort Study

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**Key Words**
Arterial stiffness · Protocol · Cardiovascular diseases · Risk factor

**Abstract**
***Introduction:*** The cardio-ankle vascular index (CAVI) was developed in Japan and is a blood pressure-independent index of arterial stiffness from the origin of the aorta to the ankle. In recent years, it has been studied by many researchers worldwide, and it is strongly anticipated that it will play a role as a predictive factor for arteriosclerotic diseases. The objective of this study was to examine the benefits of using CAVI as a predictor of cardiovascular events in high-risk patients. ***Methods and Design:*** This prospective multicenter study to evaluate the usefulness of the CAVI to predict cardiovascular events in Japan (CAVI-J) is a cohort study with central registration. Participants (n = 3,000) will be scheduled to enroll and data will be collected for up to 5 years from entry of participants into the study. To be eligible to participate in the CAVI-J study, individuals have to be aged between 40 and 74 years and have at least one of the following risk factors for arteriosclerosis: (1) type 2 diabetes mellitus; (2) high-risk hypertension; (3) metabolic syndrome; (4) chronic kidney disease (stage 3), or (5) history of coronary artery disease or noncardiogenic cerebral infarction. The primary endpoints of this study are cardiovascular death, nonfatal myocardial infarction, and stroke. The secondary endpoints are composite cardiovascular events including all cause

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death, angina pectoris with revascularization, new incidence of peripheral artery disease, abdominal aortic aneurysm, aortic dissection, heart failure requiring hospitalization, and deterioration in renal function. The cutoff for CAVI against the incidence of cardiovascular events will be determined.



## Introduction

Atherosclerosis is a major contributor to the development of cardiovascular diseases and thus a major cause of mortality and morbidity [1]. Reflecting the aging of society and adoption of westernized lifestyles, the number of patients with cardiovascular diseases is also increasing [2]. Risk factors for cardiovascular diseases include male sex, advanced age, hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking. Patients often have several risk factors [3]; these need to be carefully managed to prevent future cardiovascular events. The availability of a simple and noninvasive indicator for monitoring would be a powerful tool for managing atherosclerotic risk factors.

The cardio-ankle vascular index (CAVI) was developed in Japan and is a blood pressure-independent index of arterial stiffness from the origin of the aorta to the ankle [4]. In recent years, it has been studied by many researchers worldwide and it is strongly anticipated that it will play a role as a predictive factor for arteriosclerotic diseases. Published studies have shown that CAVI increases in the presence of cerebrovascular disease [5], dementia [6], cardiovascular disease [7–9], nephrosclerosis [10], vasculitis [11, 12], hypertension [13], hyperlipidemia [10], and lifestyle-related diseases including diabetes mellitus [14], smoking [15], sleep apnea syndrome [16], stress [17] and obesity [18], all of which are considered risk factors for arteriosclerosis. Recently, a single-center study reported a positive association between high CAVI values and incidence of cardiovascular diseases [19]. However, no long-term multicenter prospective studies of this association have yet been reported.

The objective of this 5-year prospective observational follow-up study is to examine the benefits of using CAVI as a predictor of cardiovascular events in high-risk patients.

## Methods

*Design*

This prospective multicenter study to evaluate the usefulness of the CAVI in Japan (CAVI-J) is a cohort study with central registration. Participants were scheduled to enroll in this study from May 2013 to December 2014. Data will be collected for up to 5 years from entry of participants into the study. The study was approved by the ethics committees of all hospitals involved. All participants provided written informed consent before enrollment. This study is conducted according to the principles expressed in the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01859897).

*Subjects*

The inclusion criteria are shown in table 1. To be eligible to participate in the CAVI-J study, individuals had to be aged between 40 and 74 years and have at least one of the following risk factors for arteriosclerosis: (1) type 2 diabetes mellitus; (2) high-risk hypertension; (3) metabolic syndrome; (4) chronic kidney disease (stage 3), or (5) history of coronary artery disease or noncardiogenic cerebral infarction. Diabetes mellitus was defined according to the American Diabetes Association [20]. High-risk hypertension was defined as a complication of diabetes mellitus or chronic kidney disease, or organ damage or multiple risk factors according to the guidelines of the Japanese Society for Hypertension 2009 [21]. Metabolic syndrome was defined according to Japanese guidelines [22]. Chronic kidney disease (stage 3) was defined as including patients with estimated glomerular filtration rates from 30 to 60 ml/

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**Table 1.** Inclusion criteria (patients between 40 and 74 years of age who have at least one of the following)

| | |
|---|---|
| 1 | Type 2 diabetes mellitus[a] |
| 2 | Metabolic syndrome[b] |
| 3 | Hypertension in the highest-risk category[c] |
| 4 | Chronic kidney disease (stage 3)[d] |
| 5 | History of coronary artery disease or noncardiogenic cerebral infarction |

[a] Definition of the American Diabetes Association [20]. [b] Guidelines of the Japanese Society for Hypertension 2009 [21]. [c] Japanese Guideline for metabolic syndrome [22]. [d] Position statement from Kidney Disease: Improving Global Outcomes (KDIGO) [23].

**Table 2.** Exclusion criteria

| | |
|---|---|
| 1 | Under 40 years of age or over 75 years of age |
| 2 | Ankle-brachial index ≤0.9 |
| 3 | Chronic atrial fibrillation |
| 4 | Heart failure (NYHA class III or IV) or left ventricular dysfunction (EF below 40%) |
| 5 | Medical history of cancer and/or treatment for cancer within the last 5 years |
| 6 | Estimated glomerular filtration rate <30 ml/min/1.73 $m^2$ (according to the Modification of Diet in Renal Disease equation) or receiving dialysis due to renal failure |
| 7 | Treatment with systemic steroids or immunosuppressants |
| 8 | Liver cirrhosis |
| 9 | Determined as unsuitable for this study by a physician |

min/1.73 $m^2$ in accordance with the position statement in Kidney Disease: Improving Global Outcomes (KDIGO) [23]. Coronary artery disease included angina pectoris, myocardial infarction, and unstable angina. The diagnosis of unstable angina required a history of prolonged ischemic chest pain (>15 min in duration) accompanied by transient ischemic ST segment and T-wave abnormalities in an electrocardiographic tracing but not accompanied by the development of Q-wave abnormalities or serum enzyme changes characteristic of myocardial necrosis. Myocardial infarction was defined according to the expert consensus document [24].

The exclusion criteria are shown in table 2. Patients with an ankle-brachial index of not more than 0.9 and those with chronic atrial fibrillation were excluded because their CAVI measurements may not have been accurate.

*Sample Size*

The relative risk of cerebrovascular events in patients with a CAVI >10 has been estimated to be 1.73 compared with patients with a CAVI ≤10; thus, the study enrolled 2.5 times as many patients with a CAVI ≤10 as patients with a CAVI >10 [19], in whom the risk of cerebrovascular events is anticipated to be 4.6% in 5 years [25]. From these data, the risks of cerebrovascular events in patients with a CAVI ≤10 and in those with a CAVI >10 were anticipated to be 0.038 and 0.066 in 5 years, respectively. To detect this risk difference, the required sample size was calculated by Freedman's method to be 810 for those with a CAVI ≤10 and 2,024 for those with a CAVI >10, with a two-sided α of 5%, 80% power and 20% dropout rate [26]. On the basis of these assumptions, a sample size of 3,000 was chosen for this study.

*Endpoints*

Primary and secondary endpoints are shown in table 3. The primary endpoints of this study are the only hard endpoints. Stroke included ischemic stroke and hemorrhagic stroke. The secondary endpoints are composite cardiovascular events. Each event will be evaluated, determined, and classified by the Event Committee according to predetermined detailed definitions.

**Table 3.** Endpoints

| | |
|---|---|
| *Primary endpoints* | |
| 1 | Cardiovascular death |
| 2 | Nonfatal myocardial infarction |
| 3 | Stroke |
| *Secondary endpoints* | |
| 1 | All cause death |
| 2 | Angina pectoris with revascularization |
| 3 | New incidence of peripheral arterial disease (arteriosclerosis obliterans) |
| 4 | Aortic aneurysm |
| 5 | Aortic dissection |
| 6 | Heart failure with hospitalization |
| 7 | Deterioration in renal function (dialysis or renal transplantation) |

*Variables*

Baseline information on age, sex, height, weight, abdominal circumference, and drinking and smoking status will be recorded. Laboratory data, including total cholesterol, high-density lipoprotein cholesterol, triglyceride, serum creatinine, uremic acid, hemoglobin $A_{1c}$, and proteinuria, will be collected after fasting when appropriate. Medications for diabetes mellitus, hypertension, dyslipidemia, osteoporosis and antiplatelet and anticoagulation therapy will be recorded.

*Physical Activity*

Moderate physical activity (≥150 min per week), vigorous physical activity (≥75 min per week) or no physical activity (<75 min per week) will be recorded [27].

*CAVI Measurements*

CAVI was measured using a CAVI device (Vasera; Fukuda Denshi, Tokyo, Japan). Electrocardiogram electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were applied to the upper arms and ankles bilaterally with the patient lying in supine position and the head held in the midline position. The examinations were performed after resting for 10 min. The pressure of all cuffs was kept low at 50 mm Hg to minimize the effect of cuff pressure on hemodynamics. Blood pressure was then measured. Pulse wave velocity was to be obtained by dividing vascular length by the time (T) taken for the pulse wave to travel from the aortic valve to the ankle. However, in practice T was difficult to obtain because the time the blood left the aortic valve was difficult to identify from the sound of the valve opening. Thus, because the time between the sound of the aortic valve closing and the notch of the brachial pulse wave is theoretically equal to the time between the sound of the aortic valve opening and the rise of the brachial pulse wave, T was obtained by adding the time between the sound of the aortic valve closing and the notch of the brachial pulse wave and the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave. CAVI was determined using the following formula: $CAVI = a\{(2\rho / \Delta P) \times \ln (Ps / Pd) PWV^2\} + b$, where a and b are constants, ρ is blood density, ΔP is Ps – Pd, Ps is systolic blood pressure, Pd is diastolic blood pressure, and PWV is pulse wave velocity.

*Statistical Analysis*

The cutoff for CAVI against the incidence of cardiovascular events will be determined by ROC analysis. After dividing the participants into low and high CAVI groups, the comparability of the two groups at baseline will be evaluated using the $\chi^2$ or Fisher's exact test for qualitative variables, and t test or Mann-Whitney test for continuous variables. The effect of CAVI on each endpoint will be analyzed using the proportional hazards model. Statistical analysis will be performed according to the intention-to-treat principle.

## Discussion

The Framingham risk score has conventionally been widely accepted as a risk score for cardiovascular events and used in clinical practice [28]. This CAVI-J study is expected to ascertain whether CAVI is able to predict cardiovascular events. In addition, the CAVI-J study will clarify whether CAVI is superior to the Framingham risk score. Furthermore, whether the 'Framingham-CAVI score', which is a combination of the Framingham risk score and CAVI, is superior to conventional risk scores will be determined. CAVI was developed in Japan and is considered a stable index with the advantages of requiring only a simple measurement method and having less interexaminer and interfacility variations in measured values than conventional arteriosclerosis indices. We expect that the clinical usefulness of CAVI measurement in general practice will be established by the CAVI-J study.

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## Disclosure Statement

All authors have no conflicts of interest.

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# Erratum

In the article by Miyoshi T. et al., entitled “Protocol for Evaluating the Cardio-Ankle Vascular Index to Predict Cardiovascular Events in Japan: A Prospective Multicenter Cohort Study” [Pulse 2016;4(suppl 1):11–16, DOI: 10.1159/000448464], the last author’s name was misspelt and should read H. Orimo.