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ORIGINAL RESEARCH

Predictive Value of the Cardio-Ankle Vascular Index for Cardiovascular Events in Patients at Cardiovascular Risk

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BACKGROUND: Arterial stiffness is an important predictor of cardiovascular events; however, indexes for measuring arterial stiffness have not been widely incorporated into routine clinical practice. This study aimed to determine whether the cardio-ankle vascular index (CAVI), based on the blood pressure–independent stiffness parameter β and reflecting arterial stiffness from the origin of the ascending aorta, is a good predictor of cardiovascular events in patients with cardiovascular disease risk factors in a large prospective cohort.

METHODS AND RESULTS: This multicenter prospective cohort study, commencing in May 2013, with a 5-year follow-up period, included patients (aged 40–74 years) with cardiovascular disease risks. The primary outcome was the composite of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Among 2932 included patients, 2001 (68.3%) were men; the mean (SD) age at diagnosis was 63 (8) years. During the median follow-up of 4.9 years, 82 participants experienced primary outcomes. The CAVI predicted the primary outcome (hazard ratio, 1.38; 95% CI, 1.16–1.65; $P<0.001$). In terms of event subtypes, the CAVI was associated with cardiovascular death and stroke but not with myocardial infarction. When the CAVI was incorporated into a model with known cardiovascular disease risks for predicting cardiovascular events, the global χ^2 value increased from 33.8 to 45.2 ($P<0.001$), and the net reclassification index was 0.254 ($P=0.024$).

CONCLUSIONS: This large cohort study demonstrated that the CAVI predicted cardiovascular events.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01859897.

Key Words: arterial stiffness ■ blood pressure ■ cardiovascular events ■ pulse-wave velocity ■ risk factor

Arterial stiffness is an important predictor of future cardiovascular events.[1] Several indexes for measuring arterial stiffness, such as the carotid-femoral pulse-wave velocity (PWV) and the augmentation index, have been proposed[2–5]; however, these have not been widely incorporated into routine clinical practice. Among these indexes, the carotid-femoral PWV has been considered the reference standard. Previous studies have shown that a greater carotid-femoral PWV is associated with an increased risk of cardiovascular events in the general population and patients with hypertension or type 2 diabetes mellitus.[6–9]

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CLINICAL PERSPECTIVE

What Is new?

- This prospective cohort study demonstrated that the cardio-ankle vascular index, a marker of arterial stiffness based on the stiffness parameter β, predicted cardiovascular events in patients with cardiovascular disease risk factors.
- In terms of event subtypes, the cardio-ankle vascular index was associated with the risk of cardiovascular death, nonfatal stroke, all-cause mortality, and heart failure with hospitalization.

What Are the Clinical Implications?

- The cardio-ankle vascular index may be clinically useful for assessing the risk of cardiovascular events among patients with risk factors for cardiovascular disease.
- Our findings warrant the need for future studies to verify our results, compare the cardio-ankle vascular index with other arterial stiffness markers, and estimate the threshold for each cardiovascular event.

Nonstandard Abbreviations and Acronyms

CAVI	cardio-ankle vascular index
PWV	pulse-wave velocity

However, the use of carotid-femoral PWV has several limitations, such as a complex measurement procedure and a bias introduced by the determination distance.[10] Furthermore, because carotid-femoral PWV is a measure of the speed of the pulse wave, it is affected by blood pressure,[11,12] which is an important confounding factor for cardiovascular disease (CVD). Similarly, it remains unclear whether carotid-femoral PWV has a significant impact on decision making in medium- and high-risk individuals.

The cardio-ankle vascular index (CAVI) is a marker of arterial stiffness based on the stiffness parameter β, developed in Japan in 2004. It reflects arterial stiffness from the origin of the ascending aorta to the ankle.[13] The CAVI can be obtained automatically by wrapping pressure cuffs around the upper arms and lower legs and is less dependent on blood pressure.[14] Several studies have demonstrated that the CAVI is associated with target organ damage, such as the presence of coronary artery disease (CAD) and stroke.[15–18] In addition, studies have reported the association between a greater CAVI and a high incidence of cardiovascular events in patients with diabetes mellitus, obesity, and several CVD risk factors.[19–22] Nevertheless, these were single-center or relatively small-scale studies, and some studies failed to show a significant association between the CAVI and cardiovascular events in patients with metabolic syndrome or at high risk of developing CVD.[23,24] Therefore, a large multicenter prospective study is needed to elucidate the association between CAVI and cardiovascular events.

This study aimed to investigate (1) whether the CAVI is a good predictor of cardiovascular events in patients with CVD risk factors and (2) whether the CAVI offers incremental value for predicting future cardiovascular events in a large multicenter prospective cohort.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The CAVI-J (Prospective Multicenter Study to Evaluate Usefulness of Cardio-Ankle Vascular Index in Japan) was a multicenter, prospective, cohort study that evaluated the usefulness of the CAVI.[25] This study was approved by the ethics committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, as well as the ethics committees of each participating center. It was conducted in compliance with the Declaration of Helsinki. All participants provided written informed consent, and this trial was registered at ClinicalTrials.gov (NCT01859897).

The details of the inclusion and exclusion criteria are described in Data S1. The eligibility criteria included individuals aged between 40 and 74 years and those who had at least one of the following risk factors for CVD: type 2 diabetes mellitus,[26] hypertension (categorized as high risk, according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2009),[27] metabolic syndrome,[28] chronic kidney disease of stage 3,[29] or a history of CAD or cerebral infarction. In contrast, the exclusion criteria were as follows: aged <40 years or >75 years, ankle-brachial index ≤0.9, chronic atrial fibrillation, severe heart failure (New York Heart Association class greater than level III) or left ventricular dysfunction (left ventricular ejection fraction of <40%), medical history of cancer and/or treatment for cancer within the past 5 years, estimated glomerular filtration rate of <30 mL/min per 1.73 m^2 or receiving long-term dialysis, treatment with systemic steroids or immunosuppressants, or liver cirrhosis, and judgment of an attending physician that the individual was ineligible for inclusion in the study. Metabolic syndrome was diagnosed with the criteria of the Examination Committee for the Diagnosis of Metabolic Syndrome in Japan, 2005.[28] The definition

of metabolic syndrome was abdominal obesity with a waist circumference ≥85 cm for men and ≥90 cm for women and ≥2 of the following 3 risk factors: (1) high blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg or treatment for previously diagnosed hypertension), (2) hyperglycemia (fasting glucose level ≥110 mg/dL or treatment for previously diagnosed type 2 diabetes mellitus), and (3) dyslipidemia (triglyceride levels ≥150 mg/dL and/or high-density lipoprotein [HDL] cholesterol <40 mg/dL or treatment for previously diagnosed dyslipidemia).

In total, 3026 patients were enrolled between May 2013 and December 2014. The participants were followed up prospectively for 5 years from the date of determining the CAVI. Participants' status was checked from medical records in their corresponding hospitals or clinics and by mail or telephone for any participants who had moved during the follow-up. Participants were managed by their attending physicians, who were encouraged to treat CVD risk factors, including hypertension, dyslipidemia, and diabetes mellitus, to achieve the best available standard of care in accordance with the relevant guidelines.

Primary Exposure

The primary exposure was the baseline CAVI, measured with a VaSera device (Fukuda Denshi, Tokyo, Japan). The CAVI was determined using the following formula: CAVI=a {(2ρ/ΔP)×ln (Ps/Pd) PWV^2}+b, where a and b are constants applied according to the value derived from the equation: (2ρ/ΔP)×ln (Ps/Pd) PWV^2 (a and b: 0.850 and 0.695, 0.658 and 2.103, and 0.432 and 4.441, respectively),[30] ρ is blood density (the fixed value of 1.05 is used), ΔP is Ps–Pd, Ps is systolic blood pressure, Pd is diastolic blood pressure, and PWV is the pulse-wave velocity. The details of the measurement have been described previously.[13] ECG electrodes were placed on both wrists, a microphone was placed on the sternum to detect heart sounds, and cuffs were applied to the upper arms and ankles, bilaterally, with the patient in the supine position. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure of 30 to 50 mm Hg was used to minimize the effect of cuff pressure on hemodynamics. Thereafter, blood pressure was measured from the cuff on the upper arm. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to propagate from the aortic valve to the ankle; it was measured using cuffs at the upper arms and ankles. Intraobserver and interobserver variability have been reported to be <3.8% and 2.4%, respectively.[13,17,31–33] To ensure the quality of the measurement, 2 conditions were established. First, qualified hospitals or clinics, based on the past performance of the CAVI measurement, could participate in this study. Second, all raw data of CAVI were sent for evaluation at the central office. Subsequently, remeasurement was required in case of inappropriate data.

Outcomes

The primary outcome was the composite cardiovascular events of cardiovascular death, myocardial infarction, and stroke. Stroke included ischemic stroke and hemorrhagic stroke. In contrast, secondary outcomes were all-cause death, stable angina pectoris with revascularization, the new incidence of peripheral arterial disease, aortic aneurysm, aortic dissection, heart failure with hospitalization, and deterioration in renal function. The details of definitions are provided in Data S1. All events were reported annually by each institution to the Clinical Endpoint Review Committee. The committee, consisting of members blinded to information about the patients, assessed the appropriateness of the clinical judgment of all events according to prespecified criteria.

Covariates

A self-administered questionnaire on smoking habits and physical activity was checked by trained interviewers. These variables were classified as being either habitual or not. The use of medications was similarly checked. Blood pressure was measured twice using an automated sphygmomanometer with participants in the sitting position after a 5-minute rest. The mean of the 2 measurements was used for the present analysis. Serum total and HDL cholesterol concentrations were determined enzymatically. Obesity was defined as a body mass index >30.0 kg/m^2, and all clinical examinations and blood tests were conducted on the same day.

Statistical Analysis

The sample size was calculated as follows: 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,[34] in whom the risk of cerebrovascular events is anticipated to be 4.6% in 5 years.[35] From these data, the risks of cerebrovascular events in patients with a CAVI ≤10 and those with a CAVI >10 were anticipated to be 0.038 and 0.066 in 5 years, respectively. To detect this difference in risk, the required sample size was calculated, using the Freedman method, to be 810 for those with a CAVI ≤10 and 2024 for those with a CAVI >10, with a 5% 2-sided α value, 80% power, and 20% dropout rate. On the basis of these assumptions, a sample size of 3000 was chosen for this study.

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as mean (SD). Baseline characteristics were compared according to the CAVI quintile (quintile 1, ≤7.55; quintile 2, 7.60–8.20; quintile 3, 8.25–8.80; quintile 4, 8.85–9.45; and quintile 5, ≥9.50). The linear trends in the mean values and the frequencies of risk factors across the CAVI levels were tested using linear regression analysis and logistic regression analysis, respectively. Cumulative event rates were estimated by the Kaplan-Meier method for the primary outcome, and a log-rank test was used to compare groups. Cox proportional hazards regression analysis was performed to investigate the association between clinical outcomes and the CAVI value. Proportional hazard assumption was evaluated on the basis of the log-log plot. Annualized incidence rates were calculated per 1000 patient-years of follow-up. The hazard ratios (HRs) and 95% CIs were calculated and reported. The incremental value of the CAVI for predicting cardiovascular events was assessed using the Akaike information criterion and the global χ^2 test. To assess the discrimination of events, receiver-operating characteristic curve analysis was performed. Similarly, we calculated the continuous net reclassification improvement and integrated discrimination improvement. A 2-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 25.0 (IBM Corporation, Tokyo, Japan) and JMP Pro version 15 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Patients

The median (interquartile range) follow-up period was 4.9 (4.6–5.2) years. In total, 94 patients were excluded because 60 patients had no follow-up data, and 34 withdrew consent. Finally, 2938 patients (2001 men and 937 women; mean [SD] age, 63.2 [8.0] years) were included in the analysis. The baseline characteristics of the patients are shown in Table S1. The baseline characteristics of patients included in the analysis according to the CAVI quintiles are shown in

Table 1. Baseline Characteristics According to the CAVI

Characteristics	CAVI					*P* Value for Trend
	Quintile 1 (≤7.55)	Quintile 2 (7.60–8.20)	Quintile 3 (8.25–8.80)	Quintile 4 (8.85–9.45)	Quintile 5 (≥9.50)	
	(N=579)	(N=578)	(N=614)	(N=577)	(N=584)	
Age, mean (SD), y	57.2 (9.3)	61.7 (7.9)	64.0 (7.0)	65.6 (6.2)	67.3 (5.2)	<0.001
Men	342 (59.1)	375 (64.9)	414 (67.4)	422 (73.1)	448 (76.7)	<0.001
Systolic blood pressure, mean (SD), mm Hg	130.5 (15.4)	131.3 (16.3)	132.0 (15.7)	134.8 (17.3)	137.3 (16.9)	<0.001
Diastolic blood pressure, mean (SD), mm Hg	80.2 (11.0)	79.9 (11.8)	78.9 (10.8)	80.4 (11.5)	80.5 (12.1)	0.089
Hypertension	499 (86.2)	512 (88.6)	533 (86.8)	513 (88.9)	540 (90.5)	0.002
Hypertension (high risk)	458 (79.1)	477 (82.5)	484 (78.8)	490 (84.9)	522 (89.4)	<0.001
Diabetes mellitus	430 (74.3)	416 (72.0)	458 (74.6)	438 (75.9)	467 (80.0)	0.007
Metabolic syndrome	183 (31.6)	150 (26.0)	172 (28.0)	161 (27.9)	154 (26.4)	0.148
Chronic kidney disease	198 (34.2)	219 (37.9)	222 (36.2)	233 (40.4)	253 (43.3)	0.001
History of coronary artery disease or cerebral infarction	197 (34.0)	216 (34.4)	231 (37.6)	224 (38.8)	247 (42.3)	0.005
Total cholesterol, mean (SD), mg/dL	188.4 (34.5)	184.0 (34.7)	183.9 (33.4)	182.6 (35.5)	180.3 (34.4)	0.002
HDL cholesterol, mean (SD), mg/dL	55.4 (15.1)	54.9 (16.0)	55.7 (15.5)	54.8 (15.5)	53.9 (14.7)	0.344
Obesity	163 (28.2)	69 (11.9)	54 (8.8)	43 (7.5)	30 (5.1)	<0.001
Smoking habits	246 (42.5)	244 (42.2)	279 (45.4)	277 (48.0)	264 (45.2)	0.086
Regular exercise	195 (33.7)	193 (33.4)	212 (34.5)	217 (37.6)	209 (35.8)	0.179
Medications						
Antihypertensive agents	443 (76.5)	454 (78.6)	473 (77.0)	427 (74.0)	463 (79.3)	0.850
Insulin	22 (3.8)	31 (5.4)	32 (5.2)	32 (5.6)	57 (9.8)	<0.001
Antidiabetic agents	179 (30.9)	189 (32.7)	22 (37.8)	237 (41.1)	272 (46.6)	<0.001
Lipid-lowering agents	345 (59.6)	372 (64.4)	376 (61.2)	334 (57.9)	378 (64.7)	0.545
Antiplatelet agents	190 (32.8)	213 (36.9)	229 (37.3)	214 (37.1)	246 (42.1)	0.003

Data are presented as the number (percentage) of participants, unless otherwise indicated. CAVI indicates cardio-ankle vascular index; and HDL, high-density lipoprotein.

Table 1. Patients with higher CAVI levels were older and were more likely to be men. The mean systolic blood pressure, prevalence of hypertension, diabetes mellitus, and obesity, use of insulin, and the use of antidiabetic as well as of antiplatelet agents increased significantly with a higher CAVI. The mean diastolic pressure and HDL cholesterol values, the prevalence of chronic kidney disease, history of CAD or cerebral infarction, smoking habits, regular exercise, and use of lipid-lowering agents did not differ among the CAVI quintile groups.

Association Between the CAVI and Primary Outcomes

During the follow-up, 82 participants experienced primary outcomes. These included 13 cardiovascular deaths, 44 nonfatal stroke cases, and 25 nonfatal myocardial infarction cases. The cumulative incidence rates of the primary outcomes are shown according to the CAVI levels in the Figure 1, and the rates were significantly higher in the fifth quintile group than in the first quintile group (*P* value for trend=0.01). Risk factors for cardiovascular events analyzed in the univariate Cox proportional hazard models are shown in Table S2. Male sex, HDL cholesterol, smoking habits, alcohol intake, and use of antiplatelet agents, but not systolic or diastolic blood pressure, were associated with cardiovascular events. The age- and sex-adjusted HRs increased linearly with elevating CAVI levels, and this relationship remained significant after adjusting for age, male sex, systolic blood pressure, type 2 diabetes mellitus, HDL cholesterol, smoking, history of CAD or cerebral infarction, and use of antihypertensive agents (Table 2). In the multivariable-adjusted model, the fifth quintile of CAVI (≥9.50) was associated with increased risk of the primary outcomes compared with the first quintile of CAVI (≤7.55), after adjusting for the above confounding factors (HR, 3.31 [95% CI, 1.26–8.71]; *P*=0.016). Every 1-point increment in the CAVI was similarly associated with an increased risk of the primary outcomes, after adjusting for the confounding factors (HR, 1.38 [95% CI, 1.16–1.65]; *P*<0.001).

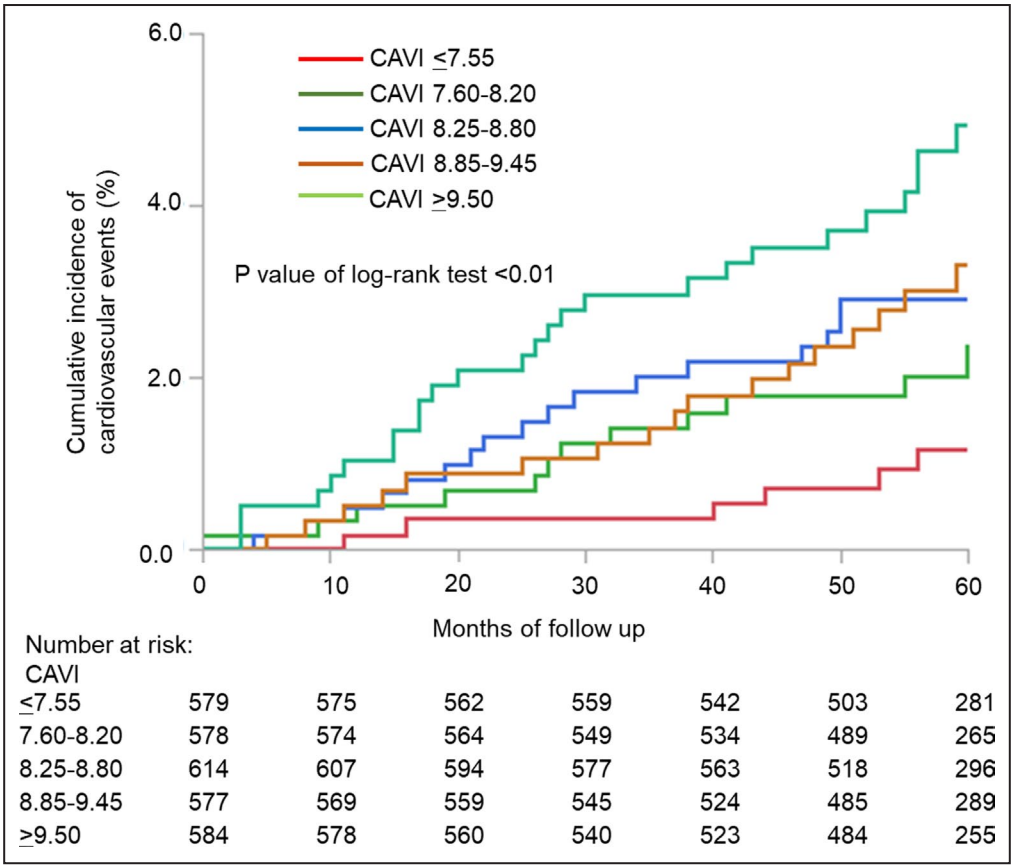

Figure. Kaplan-Meier plot of cumulative probability of cardiovascular events by quintiles of the cardio-ankle vascular index (CAVI).
Time to cardiovascular events, including cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction, according to baseline CAVI. The cumulative incidence rates of the primary outcomes according to the CAVI levels were significantly higher in the fifth quintile group (CAVI ≥9.50) than in the first quintile group (CAVI ≤7.55) (*P* value for trend=0.01).

Table 2. Association Between the CAVI and Cardiovascular Events

CAVI	Follow-Up Period, Median (IQR), mo	No. (%) of Events	No. of Participants	Incident Rate (per 10^3 PYs)	Age- and Sex-Adjusted		Multivariable-Adjusted*	
					HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Quintile 1 (≤7.55)	59 (55–63)	6 (1.03)	579	2.19	1.00 (Reference)		1.00 (Reference)	
Quintile 2 (7.60–8.20)	59 (54–63)	12 (2.07)	578	4.42	1.82 (0.67–4.91)	0.237	1.81 (0.67–4.90)	0.241
Quintile 3 (8.25–8.80)	59 (55–63)	18 (2.92)	614	6.26	2.43 (0.93–6.31)	0.069	2.43 (0.93–6.34)	0.071
Quintile 4 (8.85–9.45)	60 (54–62)	19 (3.28)	577	7.06	2.56 (0.98–6.74)	0.056	2.51 (0.95–6.66)	0.063
Quintile 5 (≥9.50)	59 (54–62)	27 (4.62)	584	10.04	3.49 (1.34–9.01)	0.011	3.31 (1.26–8.71)	0.016
Every 1-point increase in the CAVI		82 (2.79)	2932		1.42 (1.19–1.69)	<0.001	1.38 (1.16–1.65)	<0.001

CAVI indicates cardio-ankle vascular index; HR, hazard ratio; IQR, interquartile range; and PY, person-year.
*Adjusted for age, male sex, systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, smoking, history of coronary artery disease or cerebral infarction, and use of antihypertensive agents.

Association Between the CAVI and Each End Point

Subsequently, the association between the CAVI and each end point was assessed. After evaluating the proportional hazard assumption, the associations of the CAVI with cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, and heart failure with hospitalization were analyzed in the Cox proportional hazard models (Table 3). On the basis of the events included in the primary outcome, a CAVI >9.5 was significantly associated with the risk of cardiovascular death and nonfatal stroke (crude HR, 3.83 [95% CI, 1.28–11.40]; *P*=0.015; and crude HR, 2.07 [95% CI, 1.07–3.91]; *P*=0.024, respectively), but not with nonfatal myocardial infarction, as a CAVI ≤9.5 was considered as the reference. For the events included in the secondary outcome, a CAVI >9.5 was significantly associated with the incidence of all-cause mortality and heart failure with hospitalization (crude HR, 1.90 [95% CI, 1.11–3.26]; *P*=0.018; and crude HR, 3.38 [95% CI, 1.42–8.01]; *P*=0.005, respectively).

Estimation of the Risk Assessment Ability for Cardiovascular Events

To determine the incremental value of the CAVI for predicting cardiovascular events, the Akaike information criterion test, a likelihood ratio test, and receiver-operating characteristic curve analysis were performed (Table 4). The baseline model comprised the following parameters: age, male sex, systolic blood pressure, type 2 diabetes mellitus, HDL cholesterol, smoking, history of CAD or cerebral infarction, and use of antihypertensive agents. The addition of the CAVI to the baseline model improved the model fit, as indicated by a reduction in the Akaike information criterion from 731.3 to 721.9, and significantly increased the global χ^2 value from 33.8 to 45.2 (*P*<0.001). The increase in C-statistic was not significant (0.688 to 0.708; *P*=0.146). Addition of the CAVI yielded a category-free net reclassification index of 0.254 (95% CI, 0.034–0.472; *P*=0.024) and an integrated discrimination improvement of 0.006 (95% CI, 0.000–0.012; *P*=0.052).

DISCUSSION

We found that the CAVI was a predictor of the onset of cardiovascular events in patients with CVD risk factors. The analysis of the CAVI and different outcomes showed that CAVI was associated with incidence of cardiovascular death, nonfatal stroke, all-cause mortality, and heart failure with hospitalization. To our knowledge, all previous studies that have investigated the relationship between the CAVI and the incidence of cardiovascular events were smaller, single-center studies, and some of these studies failed to show a

Table 3. Association of CAVI >9.5 With Each End Point

End Point	No. (%) of Events	Crude HR (95% CI)	*P* Value
Cardiovascular death	13 (0.4)	3.83 (1.28–11.4)	0.015
Nonfatal stroke	44 (1.5)	2.07 (1.10–3.91)	0.024
Nonfatal myocardial infarction	25 (0.8)	1.13 (0.42–3.02)	0.080
All-cause mortality	64 (2.2)	1.90 (1.11–3.26)	0.018
Heart failure with hospitalization	21 (0.7)	3.38 (1.42–8.01)	0.005

CAVI indicates cardio-ankle vascular index; and HR, hazard ratio.

significant association between the CAVI and the risk of cardiovascular events.[23,24] Therefore, the study findings highlight the clinical usefulness of the CAVI in the risk assessment of cardiovascular events among patients at risk of cardiovascular events.

There have been several single-center, small-scale studies on the CAVI and the incidence of cardiovascular events.[15,20–24] A study, including 400 patients with hypertension, diabetes mellitus, or dyslipidemia, showed that patients with a CAVI ≥10.0 had a 1.73 relative risk of elevated cerebrovascular events compared with those with a CAVI <9.0.[34] A study including 626 patients with type 2 diabetes mellitus showed that a CAVI ≥9.0 was associated with increased cardiovascular events, compared with a CAVI <9.0 (HR, 1.23; 95% CI, 1.07–1.42).[22] A study including 425 obese patients showed that the CAVI was a significant factor for the incidence of cardiovascular events (HR, 1.44 per 1-point increase in the CAVI; 95% CI, 1.02–2.02).[20] In a study including 1562 patients with CVD risk factors, the CAVI was significantly associated with cardiovascular events (HR, 1.13 per 1-point increase in the CAVI; 95% CI, 1.01–1.26).[21] In the present study, a CAVI ≥9.50 was shown to be significantly associated with the increased incidence of cardiovascular events compared with CAVI ≤7.55. This finding was consistent with those of previous studies. However, there are several differences between the present study and the previous studies. First, this study was a multicenter, large-scale cohort. Second, this study included heterogeneous patients with several CVD risk factors and preexisting CVD. Thus, the present study demonstrated that CAVI is useful in the assessment of the risk for future cardiovascular events in patients with CVD risk factors.

In our study, CAVI was associated with the risk of nonfatal stroke, but not with that of nonfatal myocardial infarction. However, previous studies have shown that an increase in carotid-femoral PWV is associated with a greater risk of CAD rather than of stroke.[8,9] There are several explanations for the discrepancy. First, the definition of CAD in most previous studies was the composite outcome, including the incidence of acute coronary syndrome and the revascularization for chronic coronary syndrome. There were a few data about the impact of arterial stiffness on different end points. The substudy of the SPRINT (Systolic Blood Pressure Intervention Trial) showed that the estimated PWV was not associated with the incidence of myocardial infarction and acute coronary syndrome, which is consistent with our findings.[36] Second, longitudinal cohort studies in Asian populations have shown that an increase in brachial-ankle PWV was associated with a greater incidence of stroke than of CAD.[37,38] Several hypotheses underlying the association between arterial stiffness and atherosclerosis have been proposed. The arterial systolic pressure increases, and the diastolic pressure decreases, in the stiffened artery. Increased luminal pressure and shear stress accelerate the formation of atheroma and stimulate excessive collagen production and deposition in the arterial wall, leading to the progression of atherosclerosis.[39] In addition, increased pulse pressure may be associated with the development of plaque and its subsequent rupture.[40] Further clinical investigation will be needed to evaluate the clinical relevance of CAVI in the development of acute coronary syndrome.

This study demonstrated that increased CAVI was associated with heart failure with hospitalization. Heart

Table 4. Incremental Prognostic Value of the CAVI for Cardiovascular Events After Addition to a Model Incorporating Known Risk Factors

Model	AIC	Global χ^2 score		C-Statistic		NRI (95% CI)		IDI (95% CI)	
		P Value		*P* Value		*P* Value		*P* Value	
Age, sex, and risk factors*	731.3	33.8		0.688					
With CAVI added	721.9	45.2	<0.001	0.708	0.146	0.254 (0.034–0.472)	0.024	0.006 (0.000–0.012)	0.052

AIC indicates Akaike information criterion; CAVI, cardio-ankle vascular index; IDI, integrated discrimination improvement; and NRI, net reclassification index.
*Risk factors included age, male sex, systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, smoking, history of coronary artery disease or cerebral infarction, and use of antihypertensive agents.

failure is a growing public health problem worldwide because of its high mortality and morbidity.[41,42] The mechanisms underlying acute heart failure are manifold because this disease results from a complex of structural and functional alterations. Among them, increased arterial stiffness has been proposed as a potential and important noncardiac factor in the pathogenesis of heart failure.[43,44] Stiff aorta increases the systolic afterload and worsens ventricular-vascular coupling.[45] Although further investigations are needed, the measurements of CAVI might be helpful in identifying patients at increased risk for heart failure with hospitalization.

In the present study, the CAVI only mildly improved cardiovascular event discrimination over that by known risk factors. A recent meta-analysis of the association between brachial-ankle PWV and cardiovascular events demonstrated that the significant incremental prognostic value of brachial-ankle PWV for predicting cardiovascular events over that of the Framingham risk score was attenuated in participants with intermediate or high risk. This study included heterogeneous patients with several CVD risk factors and preexisting CVD, who had relatively moderate to high risks of cardiovascular events; this may explain the mild effect of the CAVI in the discrimination of cardiovascular events in this study. Further analyses, according to the magnitude of risks, will be needed.

There have been several techniques and methods applied to quantify arterial stiffness. A study demonstrated that CAVI was significantly correlated with carotid-femoral PWV and brachial-ankle PWV (Pearson correlation coefficients, 0.74 and 0.82, respectively).[46] However, there are notable differences among arterial stiffness measurements. Carotid-femoral PWV is obtained by applanation tonometry, which is a complicated technique compared with CAVI and brachial-ankle PWV. CAVI and brachial-ankle PWV are derived from plethysmography cuff automatically.[25] Meanwhile, CAVI is a noninvasive indicator of arterial stiffness. It has an advantage over PWV for measuring arterial stiffness as it is less dependent on blood pressure at the time of measurement.[14] An assessment of arterial properties by considering blood pressure and arterial stiffness may allow detailed monitoring of changes in arterial stiffness in daily practice. Furthermore, the CAVI measurement is simple. The CAVI is easily obtained automatically with a device, leading to its widespread use in clinical situations if cost constraints are ignored. Further investigations will be needed to elucidate this matter, with due consideration given to cost-effectiveness.

The measurement of CAVI has been included in the routine clinical setting in Japan. CAVI is measured for the risk stratification in patients with atherosclerotic risk factors and for the evaluation of therapeutic efficacy of medications and lifestyle modification in patients with cardiometabolic disorders on a regular basis. In addition, the VaSera device can evaluate the ankle-brachial index simultaneously, which helps to diagnose peripheral arterial disease. The measurement of CAVI has been covered by health insurance in Japan, and, thus, the measurement of CAVI is applied widely in clinical practice.

This study had several limitations. First, as this was an observational cohort study, a causal relationship between an increased CAVI and increased cardiovascular events could not be proved. Second, the study population comprised only Japanese patients. Although several studies of non-Asian populations have recently been reported,[47,48] the generalizability of our data to other races/ethnicities remains uncertain. Third, the present study examined arterial stiffness only by the CAVI. Therefore, we could not compare the impact of the CAVI with those of other stiffness markers. Finally, we failed to estimate a threshold for each event because of the modest number of events. Hence, a further study with longer follow-up or a larger sample is warranted.

In conclusion, our findings demonstrated that, in patients with CVD risk factors, patients with a higher CAVI (≥9.50) have elevated risks of cardiovascular events. These data suggest that the CAVI is clinically useful in the assessment of the risk of cardiovascular events among patients with CVD risk factors.

APPENDIX

The Investigators and Institutions Involved in the CAVI-J (Prospective Multicenter Study to Evaluate Usefulness of Cardio-Ankle Vascular Index in Japan)

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Supplementary Material

Data S1
Tables S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

- **Study protocol Study protocol and Outcome definitions for adverse events**

Protocol for evaluating the cardio–ankle vascular index to predict cardiovascular events in Japan: A prospective multicenter cohort study

Brief tile: CAVI-J study

Study Title	Protocol for evaluating the cardio–ankle vascular index to predict cardiovascular events in Japan: A prospective multicenter cohort study
Protocol Date	01/April/2013 (Ver. 1.0) 27/March/2014 (Ver. 1.1)
Study Chair	Hajime Orimo, MD
Funding	The Japan Vascular Disease Research Foundation
Clinical and Data Coordinating Center	2-5-1 Shikata-cho, Okayama, Okayama University
ClinicalTrials.gov Identifier	NCT01859897

TABLE OF CONTENTS

1. STUDY SYNOPSIS

Title	Protocol for evaluating the cardio–ankle vascular index to predict cardiovascular events in Japan: A prospective multicenter cohort study (CAVI-J)
Coordinating Center	2-5-1 Shikata-cho, Okayama, Okayama University
Study Chair	Hajime Orimo, MD
Overall Objective	An open label, international, multicenter observational registry designed to examine the benefits of cardio–ankle vascular index (CAVI) as a predictor of cardiovascular events in high-risk patients.
Study Design	A multicenter observational registry. The study will be conducted in up to 50 sites in Japan.
Study Cohorts	A total of 3,000 subjects undergoing CAVI will be enrolled.
Eligibility	**Inclusion Criteria:** 1. Adult individual between 40 and 74 years of age 2. Type 2 diabetes mellitus 3. Metabolic syndrome 4. Hypertension categorized as high-risk 5. Chronic kidney disease (stage 3) 6. History of coronary artery disease or cerebral infarction **Exclusion Criteria:** 1.Under 40 years of age or over 75 years of age 2.Ankle brachial index $\leq$ 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/1.73m^2 7.Chronic hemodialysis 8.Treatment with systemic steroids or immunosuppressants 9.Liver cirrhosis 10.History of PCI/CABG within 6months 11.Severe valvular stenosis or regurgitation 12.Determined as unsuitable for this study by a physician
Duration of Study	Accrual is expected to take 6 years. All subjects enrolled will be followed-up for 5 years. Total duration of the study will be 6 years.
Primary Endpoint	1. Cardiovascular death 2. Nonfatal myocardial infarction 3. Nonfatal stroke
Secondary Endpoint	1. All cause death 2. Stable 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 (chronic dialysis or kidney transplantation)
Sample size	3,000 subjects

2. BACKGROUND AND RATIONALE

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 disease consist of 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.

3. STUDY DESIGN

CAVI-J is a prospective multicenter cohort study with central registration in Japan. The targeted population is heterogeneous, given the clinical use of CAVI across a number of indications. As such, patients referred for clinically indicated CAVI and meet the inclusion and the exclusion criteria will include those undergoing evaluation for atherosclerotic diseases. The study is considered non-significant risk because: 1) CAVI is a non- invasive diagnostic modality; 2) this is an observational registry with no targeted downstream alteration to the clinical care pathway of the patient or additional interventions. Up to 50 medical centers from Japan will participate in the study, 3,000 subjects will be enrolled into the study. Each Center may not enroll more than 20% of the total number of subjects.

4. STUDY OBJECTIVES

Primary Objective. To examine the benefits of CAVI as a predictor of primary endpoints (cardiovascular death, nonfatal myocardial infarction, and non-fatal stroke).

Secondary Objectives. The secondary objectives of CAVI-J include:

1) To determine the clinical implication of CAVI in each cardiovascular event, including
   a) Primary endpoints: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke
   b) Secondary endpoints: all cause death, stable angina pectoris with revascularization, new incidence of peripheral arterial disease (arteriosclerosis obliterans), aortic aneurysm, aortic dissection, heart failure with hospitalization, Deterioration in renal function (dialysis or renal transplantation)
2) To determine the clinical implication of CAVI in different patient subgroups, including:
   a) Type 2 diabetes mellitus

b) Metabolic syndrome

c) Hypertension categorized as highest-risk

d) Chronic kidney disease (stage 3)

e) History of coronary artery disease or cerebral infarction

f) Sex

g) Age

h) Physical activity

i) Alcohol consumption

j) Medication at baseline

3) To examine the association of change in CAVI over time and cardiovascular events

5. STUDY ENDPOINTS

Primary Endpoint (Definition of each event is defined in Appendix file.)

1. Cardiovascular death
2. Nonfatal myocardial infarction
3. Nonfatal stroke

Secondary Endpoint (Definition of each event is defined in Appendix file.)

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 kidney transplantation)

6. PATIENT POPULATION

This study will prospectively enrol 3,000 patients undergoing CAVI. Sites participating in the CAVI-J of the study will be selected based on data quality and quantity of CAVI.

7. ELIGIBILITY

Patient Eligibility and Screening.

Patients who have presented or are presenting at a clinic or a hospital for clinical indication — and who meet the inclusion criteria and none of the exclusion criteria — will be included into CAVI-J study.

Enrollment.

3,000 subjects will be enrolled, with no more than 20% of the total study population enrolled per site. Consecutive consenting adult patients who meet the inclusion criteria and none of the exclusion criteria will be asked to participate in the study.

Ethical Considerations.

The study will be 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).

Informed Consent

Study-specific data collection cannot be started until the patient has met all clinical inclusion criteria and written informed consent has been obtained. The investigator, or a person designated by the investigator who has been trained on the Investigational Plan, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions from the patient. If the patient agrees to participate, the informed consent form must be signed and personally dated prior to enrollment by the patient or his/her legally authorized representative and the investigator or a person designated by the investigator. A copy of the fully executed informed consent form must be provided to the patient. All patients must provide written informed consent in accordance with the ethics committee.

Inclusion Criteria:

patients between 40 and 74 years of age who have at least one of the following

1.Type 2 diabetes mellitus
2.Metabolic syndrome
3.Hypertension categorized as high-risk [c)]
4.Chronic kidney disease (stage 3) [d)]
5.History of coronary artery disease or cerebral infarction [e)]

Exclusion Criteria:

1.Under 40 years of age or over 75 years of age
2.Ankle brachial index $\leq$ 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/1.73m^2
7.Chronic hemodialysis
8.Treatment with systemic steroids or immunosuppressants
9.Liver cirrhosis
10.History of PCI/CABG within 6months
11.Severe valvular stenosis or regurgitation
12.Determined as unsuitable for this study by a physician

Definition of inclusion criteria

Type 2 diabetes mellitus: Diabetes mellitus was defined according to the American Diabetes Association. [20]

Metabolic syndrome: Metabolic syndrome was defined with the modified criteria of the Japanese Expert

Committee on the Diagnosis and Classification of Metabolic Syndrome for the clinical diagnosis of metabolic syndrome. [8] Waist circumference ≥ 85cm (men) or ≥ 90cm and at least two of following additional risks: fasting glucose ≥ 110mg/dL, triglyceride ≥ 150 mg/dL or HDL < 40mg/dL, and systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥ 85mmHg.

Hypertension categorized as high-risk: Hypertension categorized as high-risk was defined as a complication of diabetes mellitus or chronic kidney disease, or organ damages or multiple risk factors according to the guidelines of the Japanese Society for Hypertension 2009. [21]

Table 2-7 Prognostic factors for risk stratification to use in plannin hypertension management

A. *Risk factors for cardiovascular disease*
- Advanced age
- Smoking
- Systolic/diastolic blood pressure levels
- Dyslipidemia
  - Low-HDL-cholesterol (<40 mg per 100 ml)
  - High-LDL-cholesterol (⩾140 mg per 100 ml)
  - High triglyceride (⩾150 mg per 100 ml)
- Microalbuminuria
  - CKD
  - Obesity (BMI⩾25) (especially, abdominal obesity)
- Metabolic syndrome[a]
- Family history of premature cardiovascular disease
- Diabetes
  - Fasting plasma glucose: ⩾126 mg per 100 ml or glucose tolerance test: 2-h value ⩾200 mg per 100 ml

B. *Target organ damages/cardiovascular disease*
- Brain
  - Cerebral hemorrhage/cerebral infarction
  - Asymptomatic cerebrovascular diseases
  - Transient ischemic attack
- Heart
  - Left ventricular hypertrophy (electrocardiogram, echocardiogram)
  - Angina pectoris/myocardial infarction/coronary revascularization
  - Heart failure
- Kidney
  - Proteinuria (including microalbuminuria)
  - Decreased eGFR[b] (<60 ml per min per 1.73 m^2)
  - CKD, established kidney disease (diabetic nephropathy/renal failure)
- Blood vessels
  - Atheromatous plaque
  - Carotid intima–media thickness >1.0 mm
  - Aortic disease
  - Arteriosclerosis obliterans (decreased ABI<0.9)
- Ocular fundus
  - Advanced hypertensive retinopathy

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Metabolic syndrome: Patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level, and/or impaired glucose tolerance that does not lead to diabetes) and/or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[b]The eGFR is calculated using the following formula for Japanese:
$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ (×0.739; females).

Table 2-8 Stratification of cerebrovascular/cardiovascular risk in four categories on the basis of (clinic) blood pressure classification and risk strata

Blood pressure classification / *Risk strata (risk factors other than blood pressure)*	*High-normal blood pressure 130–139/85–89 mm Hg*	*Grade I hypertension 140–159/90–99 mm Hg*	*Grade II hypertension 160–179/100–109 mm Hg*	*Grade III hypertension ⩾180⩾110 mm Hg*
Risk stratum-1 (no other risk factors)	No additive risk	Low risk	Moderate risk	High risk
Risk stratum-2[a] (one to two risk factors (other than diabetes) or metabolic syndrome)[b]	Moderate risk[c]	Moderate risk	High risk	High risk
Risk stratum-3[a] (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)	High risk[c]	High risk	High risk	High risk

Abbreviation: CKD, chronic kidney disease.
[a]When obesity and dyslipidemia are present in the absence of other risk factors, risk factors other than the blood pressure level are counted as two, and the risk is classified as the risk stratum-2. However, when other risk factors are present, the total of risk factors is calculated as three or more, and the risk is classified as the risk stratum-3.
[b]Metabolic syndrome in risk stratum-2 indicates patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110–125 mg dl^{-1} and/or impaired glucose tolerance that does not lead to diabetes), or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[c]Treatment in moderate- and high-risk groups with high-normal blood pressure values is based on the algorithm for treatment of hypertension at initial visit. The management of common cardiovascular risks is important here.

Chronic kidney disease (stage 3): Chronic kidney disease (stage 3) was defined as including patients with estimated glomerular filtration rates from 30 to 60 mL/min/1.73 m^2 in accordance with clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012 [22]

History of coronary artery disease or cerebral infarction: History of coronary artery disease was defined as condition over 6 months after percutaneous coronary intervention or coronary artery bypass surgery. Coronary artery disease included angina pectoris, myocardial infarction, and unstable angina. Non-cardiogenic cerebral infarction is defined as cerebral infarction with an evidence by imaging modality (CT and MRI) except for cardioembolic infarction and intracerebral hemorrhage.

Patient Discontinuation

Every subject should remain in the study until completion of the required study period. However, a subject's participation in any Clinical Investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit.

8. STUDY DURATION

The anticipated duration of this study will be 6 years. Qualifying patients will be enrolled in the study for the first 1 years, and followed for an additional 5 years through follow up visits and/or phone calls.

Activity	Start Day	Finish Day	Comments
Site activation	June 2013		
Subject enrollment	June 2013	December 2014	
Data monitoring	June 2013	May 2019	Simultaneous with enrollment and follow up
Data analysis	December 2019	---	
Abstracts / Publications	February 2020	**---**	

9. DATA COLLECTION

The following data will be collected:

	Enrollment/Baseline	Year 1-5
Inclusion and Exclusion Criteria	**x**	
CAVI	**x**	**x****
Clinical Presentation	**x**	
Demographics	**x**	
CAD Risk Factors	**x**	
Other Medical Conditions	**x**	
Height and Weight	**x**	
Laboratory Tests*	**x**	
Medications	**x**	

Drinking habit/physical activity	**x**	
Primary and secondary outcomes	**x**	**x**

* Laboratory test must be performed at same date of CAVI. ** Annual measurement of CAVI is not mandatory.

10. STUDY-SPECIFIC VARIABLES

Data dictionaries and case report forms will be provided to study investigators. These will include:

Baseline Data and Laboratory Assessments

Laboratory assessment and collection will be in accordance with standard hospital policy. In addition, the following assessments will be collected:

- Creatinine
- Total cholesterol
- HDL-C
- Triglycerides
- HbA1c
- Uric acid
- Urine protein (semi-quantitative)

Electrocardiogram

Medical History and Clinical Presentation

Demographics:

- Age
- Sex
- Weight
- Height
- Weight circumflex
- Blood pressure
- Heart rate

History of CAD:

- Myocardial infarction
- Percutaneous coronary intervention
- Coronary artery bypass graft

History of ischemic stroke

Concomitant medications:

- Lipid-lowering agents – statins, ezetimibe, omega-3 fatty acid, etc.
- Antiplatelet therapy – aspirin, P2Y12-inhibitors
- Oral anti-coagulants – warfarin, DOACs
- Anti-hypertensive agents
- Diabetic agents – metformin, SGLT2 inhibitor, insulin, etc.
- Anti-osteoporosis agents

CAD Risk Factors:

- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Smoking
- Atrial fibrillation
- Peripheral arterial disease
- Sleep apnea syndrome
- Chronic kidney disease
- Family history of diabetes, hypertension, and cardiovascular diseases

Drinking habits: how many times per week, how much volume per once converted as alcohol

Physical activity:

Moderate physical activity (≥150 minutes per week), vigorous physical activity (≥ 75 minutes per week) or no physical activity (< 75 minutes per week) will be recorded [23].

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 supine and the head held in the midline position. The examinations were performed after resting for 10 minutes. The pressure of all cuffs was kept low at 50 mmHg to minimize the effect of cuff pressure on hemodynamics. Blood pressure was then measured. Pulse wave velocity (PWV) 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 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, and Pd is diastolic blood pressure.

11. DATA HANDLING AND RECORD KEEPING

The CAVI-J office will perform data management activities including documentation of the systems and procedures to be used. All e case report form (CRF) data collection will be performed through a secure web portal and all authorized personnel with access to the electronic data capture (EDC) system must use an electronic signature access method to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system. Completed eCRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the Investigator's site and a backup copy archived with the CAVI-J office.

Electronic Case Report Form Completion.

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by the clinical site personnel trained on the protocol and eCRF completion. eCRF data will be collected for all patients that are registered into the study.

Record Retention.

The sponsor will archive and retain all documents pertaining to the study for the time of the study under evaluation, and for lifetime during the post-study phase. The Investigator must obtain permission from Executive Steering Committee (ESC) in writing before destroying or transferring control of any study investigation records.

Publication Policy.

All publications and other public disclosures related to the Study shall be by the decision of the ESC, in cooperation with the study investigators and clinical site. All publications or other disclosures must be approved in advance by the ESC.

Study investigators may use all study-related data for the purposes of scientific investigations, scientific abstracts, and scientific publications as has been approved by the ESC.

The CAVI-J office will be responsible for registering the study on clinicaltrials.gov, or any other clinical investigations, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines.

12. STUDY ORGANIZATION

Study Investigators.

The Investigator(s) undertake(s) to perform CAVI-J in accordance with this protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory local requirements.

The Investigator is required to ensure compliance with all procedures required by this protocol. The Investigator agrees to provide reliable data and all images into the EDC system in an accurate and timely fashion. The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the study. All Sub-Investigators shall be appointed and listed. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a CAVI-J Protocol and all necessary information to successfully perform the study.

Data Coordinating Center (DCC).

As the DCC, CAVI-J office bears responsibility for monitoring interim data and analyzing the study's results in conjunction with the Investigators. Issues relating to regulatory reporting are the responsibility of both the Investigator and the DCC will aim to support these activities. The DCC will coordinate and monitor the study activities in alliance with the Principal Investigators, the ESC, and the sub-committees.

Organizational and Leadership Design.

The CAVI-J study organizational structure will comprise a study chair, principal investigators, an ESC; as well as

dedicated disease-specific sub-committees.

Study Chairs.

The Study Chair will be responsible for the overall leadership of the study. The Study Chairs will work with site investigators and subcommittees, and will be responsible for reporting any pertinent findings to the ESC.

The Study Chair will be:

Hajime Orimo, MD

Principal Investigators.

Principal Investigators will be from investigative sites.

Executive Steering Committee.

The ESC is charge with the responsibility for ensuring scientific quality and study fairness. It is composed of the Study Chair, Principal Investigators, and Site Investigators. The ESC will meet at once a year to review study progress and conduct. The ESC will provide feedback to the CAVI-J office and study investigators after each meeting and on an *ad hoc* basis. In that capacity, The ESC will address and resolve scientific issues encountered during the study. All final decisions regarding trial or protocol modifications rest with the ESC.

All proposed research investigations for CAVI-J study must be approved by the ESC.

The ESC membership will be comprised of the following (in alphabetical order):

1. Shigeo Horinaka, MD
2. Kohji Shirai, MD
3. Hiroshi Ito, MD
4. Jitsuo Higaki, MD

Clinical Endpoint Review Committee

The Clinical Endpoint Review Committee (CEC), consisting of members blinded to information about the patients, will assess the appropriateness of the clinical judgment of the cardiovascular events according to prespecified criteria.

The CEC membership will be comprised of the following:

1. Masanobu Takata, MD
2. Kuniaki Otsuka, MD
3. Shinichi Oikawa, MD

Statistical consulting

Shigeo Yamamura, PhD (Josai International University)

13. Quality Control and Assurance

Site Qualification.

Each clinical center will be required to obtain ethics committee approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the EDC system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). Each participating site contributing patient-level data to CAVI-J study should meet the following site requirements:

- ability to organize data required for completion of CAVI-J case report form
- ability to perform de-identification of Protection Health Information (PHI) securely on-site in a manner in keeping with local regulations

Investigator Profile.

The following information will be collected for all investigators who participate in the study: CVs, contact information including address, telephone, and email, Conflict of Interest Statement and Financial Disclosure Certifications prior to initiation of enrollment.

Qualifications and Training.

Clinical investigators will be cardiology investigators with expertise in vascular function test including CAVI.
All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the EDC system.

Safety Monitoring.

Study Investigators and their site designees will be responsible for monitoring safety data throughout the course of the study.

Delegation of Authority and PI Oversight.

Principal Investigators are responsible for all study activities at their sites. They may delegate study tasks to qualified staff members while continuing to oversee all study activities. The Delegation of Authority Log will list each staff member’s title and responsibilities for the study. The PI is responsible for careful review of each staff member’s qualifications.

Site Approval.

The following documents must be collected prior to site approval and opening to patient enrollment:

- Signed Research and Data Use Study Agreement
- Signed Conflict of Interest Statements
- Completed Delegation of Authority Log
- Signed and dated CVs for all staff on Delegation of Authority Log
- Ethics committee approval for protocol, informed consent document
- Study-specific training documents
- Other regulatory and training documentation may be required prior to site initiation

Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators, and any other health care professionals who may be involved in the study.

Patient Confidentiality.

All patients' records will be kept confidential. Study Investigators, CAVI-J representatives may review source documentation as necessary, but all unique patient and hospital identifiers will be removed from source documents which are sent to the CAVI-J office. The aggregate data from this study may be published as per publication policy documented in this Protocol; however, no data with patient identifiers will be published.

14. Statistical Plan

Sample size

Sample size calculations: The relative risk of cerebrovascular event in patients with CAVI>10 has been estimated to be 1.73 compared with patients with CAVI ≤10; thus, the study enrolled 2.5 times as many patients with CAVI ≤10 as patients with CAVI>10, [19] in whom the risk of cerebrovascular events is anticipated to be 4.6% in 5 years [24]. From these data, the risks of cerebrovascular events in patients with CAVI ≤10 and 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 CAVI ≤10 and 2024 for CAVI >10 groups with a two-sided alpha of 5%, 80% power and 20% dropout rate [25]. On the basis of these assumptions, a sample size of 3000 was chosen for this study.

Analysis plan

Data collection: categorical data will be presented as absolute numbers and percentages. Continuous data will be presented as mean ± standard deviation. Participants will be classified into several groups based on CAVI value. Baseline characteristics was compared among them. The effect of CAVI on each endpoint will be analyzed using the proportional hazard model. Incremental prognostic value was analyzed with likelihood ratio test, ROC (receiver operating characteristic) curve analysis, NRI (net reclassification improvement), and IDI (integrated discrimination improvement). The cutoff for CAVI against the incidence of cardiovascular events will be determined by ROC analysis.

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Appendix: Definition of adverse events

Primary Endpoint	1. Cardiovascular death 2. Nonfatal myocardial infarction 3. Nonfatal stroke
Secondary Endpoint	1. All cause death 2. Stable 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)

Cardiovascular death

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

1. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days1 after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the MI, it will be considered a death due to myocardial infarction. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

a. Death witnessed and occurring without new or worsening symptoms

b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

d. Death after unsuccessful resuscitation from cardiac arrest

e. Death 30 days after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology

f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific noncardiovascular cause of death (information regarding the patient's

clinical status preceding death should be provided, if available)

General Considerations

o Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see Heart Failure Event Definition). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions (unless ≤30 days after an MI, see definition for Death due to Acute MI above), ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Cerebrovascular Event Definition).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure unless procedure is to treat a myocardial infarction.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Cerebrovascular Event Definition), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade. 7. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Non-CV death

Non-CV death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to determine the most likely cause of non-CV death. Examples of non-CV death are pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious causes (e.g., systemic inflammatory response syndrome), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, non-CV organ failure (e.g., hepatic failure) or non-CV surgery.

Myocardial infarction (non-fatal)

1. General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

The term acute myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.
Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy

2. Criteria for Myocardial Infarction

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from

the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

c. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a diagnosis of MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):
  o ST elevation
  New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
  o ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- Criteria for pathological Q-wave
  o Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  o Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)

- ECG changes associated with prior myocardial infarction
  o Pathological Q-waves, as defined above
  o R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T wave in the absence of a conduction defect
- Criteria for prior myocardial infarction
  Any one of the following criteria meets the diagnosis for prior MI:
  o Pathological Q waves with or without symptoms in the absence of nonischemic causes
  o Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  o Pathological findings of a prior myocardial infarction

Stroke (non-fatal)

The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or

cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies must be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.

Diagnosis of stroke. For the diagnosis of stroke, the following four criteria should be fulfilled:

- Rapid onset of a focal/global neurological deficit with at least one of the following:
  – Change in level of consciousness
  – Hemiplegia
  – Hemiparesis
  – Numbness or sensory loss affecting one side of the body
  – Dysphasia/aphasia
  – Hemianopia (loss of half of the field of vision of one or both eyes)
  – Other new neurological sign(s)/symptom(s) consistent with stroke

Note: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥24 hours OR <24 hours if attributable to at least one of the following therapeutic interventions:
  – Pharmacologic (i.e., thrombolytic drug administration)
  – Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)

or

  – Available brain imaging clearly documents a new hemorrhage or infarct

or

  – The neurological deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
- Confirmation of the diagnosis by at least one of the following:
  – Neurology or neurosurgical specialist
  – Brain imaging procedure (at least one of the followings):
    1 CT scan
    2 MRI scan
    3 Cerebral vessel angiography
  – Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus will be mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

- Persisted for more than one week

or

- Persisted for more than 24 hours and accompanied by an appropriate new CT or MRI finding

Classification of stroke. Strokes are sub-classified as follows:

- Ischemic (non-hemorrhagic): A stroke caused by an arterial obstruction attributable to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic stroke with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)
- Hemorrhagic: A stroke caused by a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes attributable to primary intracerebral hemorrhage (intraparenchymal or intraventricular), subdural hematoma and primary subarachnoid hemorrhage
- Not assessable: The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

Stable angina pectoris with coronary revascularization

- Angina pectoris includes stable and unstable angina pectoris.

For diagnosis of unstable angina, the subject must first have had an episode of ischemic discomfort consistent with unstable angina (ischemic discomfort either at rest, of new onset, or in an accelerating pattern) lasting ≥10 minutes, which occurred before the subject presented to the hospital. However, if an increase of biomarkers >5 × 99th percentile URL (troponin or CK-MB >5 × 99th percentile URL) is observed, diagnosis will be myocardial infarction.

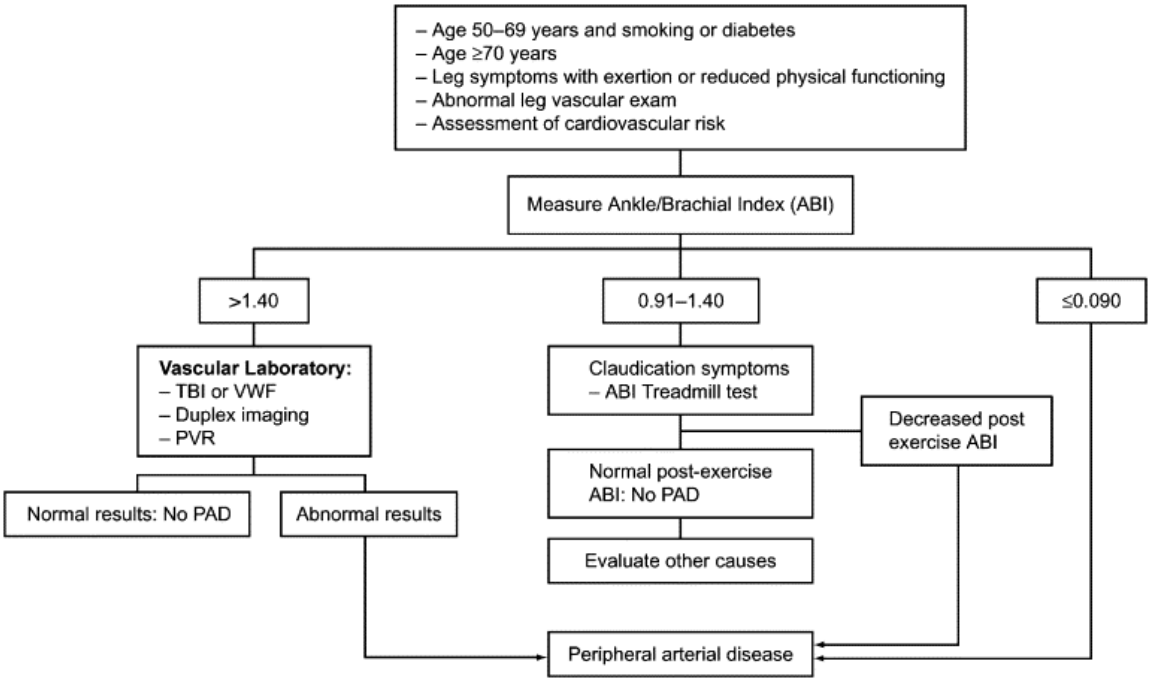
- Coronary Revascularization

Attempted revascularization procedures, even if not successful, will be counted. Revascularization is divided by type and urgency. Planned revascularization is defined as ischemia-driven coronary revascularization (PCI or CABG). The evaluation of invasive or non-invasive functional ischemia is essential before PCI. Urgent revascularization is defined as coronary revascularization (PCI or CABG) that occurred during a hospitalization prompted by unstable angina with an episode of ischemic discomfort at rest lasting at least 10 minutes.

New incidence of peripheral arterial disease (arteriosclerosis obliterans)

Diagnosis of PAD. Follow the below work flow of TASC II (J Vasc Surg. 2007 Jan;45 Suppl S:S5-67.)

The ankle–brachial index is a mandatory test.



Aortic aneurysm

Aneurysm is defined as a segmental, full-thickness dilation of a blood vessel that is 50 percent greater than the normal aortic diameter (> 30 mm in abdominal aorta and >45 mm in thoracic aorta).

For diagnosis of aortic aneurysm, CT scan or MRI scan are mandatory.

Aortic dissection

Aortic dissection can result either from a tear in the intima and propagation of blood into the media or from intramural haemorrhage and haematoma formation in the media followed by perforation of intima; the former is more common. The characteristic picture of aortic dissection is the presence of an intimal flap in the aorta.

CT scan with contrast image enhancement is required to identify the extent of the dissection along with the true and false lumens

Classification of aortic dissection. DeBakey classification:

- Type I involves ascending aorta, aortic arch, and descending aorta.
- Type II is confined to ascending aorta only.
- Type III is confined to descending aorta distal to the left subclavian artery only; IIIa extends up to diaphragm, IIIb extends beyond the diaphragm.

Heart failure with hospitalization

The date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit. Heart failure with hospitalization is defined as an event that meets all of the

following criteria:

- Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-hour stay (or a date change if the time of admission/discharge is not available)
- Clinical manifestations of heart failure (new or worsening), including at least one of the followings:
  - Dyspnea
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Edema
  - Pulmonary basilar crackles
  - Jugular venous distension
  - Third heart sound or gallop rhythm
  - Radiological evidence of worsening heart failure
- Additional/increased therapy: at least one of the followings:
  - Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy
  - Up-titration of oral diuretic or intravenous therapy, if already on therapy
  - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function); or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at the treatment of heart failure

Changes in a biomarker (e.g., brain natriuretic peptide) consistent with CHF will support this diagnosis.

Requirement for Renal Replacement Therapy

Definition of renal replacement therapy:

- Kidney transplantation

  Definitive renal replacement therapy prescribed when uremic symptoms have already occurred, or are anticipated to occur, due to the progression of irreversible chronic kidney disease. Death during the transplant surgery will be considered kidney transplantation.

- Chronic dialysis

  ESKD will be diagnosed if dialysis is performed for 30 days or more and is not subsequently known to recover. Indications for dialysis are indicated in section below.

Onset of ESKD

The mode of onset of ESKD will be adjudicated into the following categories:

- Chronic progression
- Acute deterioration, diagnosed when the decline in kidney function is sudden and acute kidney injury is superimposed on chronic kidney disease resulting in renal replacement therapy.

Table S1. Characteristics of patients who completed and who failed to complete the study

Characteristic	Patients who completed n = 2932	Patients who failed to complete n = 94	p
Age, mean (SD), y	63.2 (8.0)	61.3 (9.7)	.014
Male	2001 (68.3)	62 (66.0)	.639
Systolic blood pressure, mean (SD), mmHg	133.2 (16.5)	134.9 (20.1)	.329
Diastolic blood pressure, mean (SD), mmHg	80.0 (11.4)	80.0 (13.2)	.979
Diabetes mellitus	2209 (75.3)	66 0 (70.2)	.275
Metabolic syndrome	1395 (47.6)	58 (61.7)	.007
Hypertension categorized as high-risk	2431 (82.9)	62 (66.0)	<.001
Hypertension	2597 (88.6)	70 (74.5)	.001
Chronic kidney disease stage 3	1125 (38.4)	35 (37.2)	.824
History of coronary artery disease or cerebral infarction	1115 (38.0)	24 (25.5)	.014
Total cholesterol, mean (SD),	183.8 (34.6)	190.7 (38.1)	.061
HDL cholesterol, mean (SD),	55.0 (15.4)	54.3 (17.8)	.704
Obesity	359 (12.2)	12 (12.8)	.879
Smoking habits	1310 (46.2)	38 (41.8)	.414

Regular Exercise	1026 (37.2)	27 (31.8)	.209
Medications			
Anti-hypertensive agents	2260 (77.1)	52 (55.3)	<.001
Insulin	174 (6.0)	11 (12.1)	.022
Anti-diabetic agents	1109 (37.8)	39 (41.5)	.471
lipid-lowering agents	1805 (61.6)	42 (44.7)	.001
Antiplatelet agents	1092 (37.2)	20 (21.3)	.002

Data are presented as number (percentage) of participants unless otherwise indicated.

HDL, high-density lipoprotein; SD, standard deviation

Table S2. Univariate cox regression analysis for the primary outcome

Characteristic	HR (95%CI)	P
Age (per year)	1.02 (1.00–1.06)	.065
Male	3.38 (1.74–6.54)	<.001
Systolic blood pressure (per mmHg)	1.01 (1.0–1.02)	.142
Diastolic blood pressure (per mmHg)	1.00 (0.98–1.01)	.660
Diabetes mellitus	1.12 (0.67-1.90)	.659
Hypertension	1.64 (0.71-3.76)	.245
Chronic kidney disease	1.29 (0.83-2.00)	.251
History of coronary artery disease or cerebral infarction	1.49 (0.97-2.30)	.071
Total cholesterol (per mg/dL)	1.00 (0.99-1.01)	.766
HDL cholesterol (per mg/dL)	0.97 (0.96-0.99)	.002
Obesity	0.88 (0.44-1.77)	.729
Smoking habits	1.80 (1.16-2.79)	.009
Regular Exercise	1.08 (0.69-1.69)	.747
Medications		
Anti-hypertensive agents	1.48 (0.83-2.64)	.179

Insulin	1.98 (0.99-3.95)	.053
Anti-diabetic agents	1.17 (0.75-1.81)	.486
lipid-lowering agents	0.88 (0.56-1.36)	.554
Antiplatelet agents	1.87 (1.21-2.88)	.005

HDL, high-density lipoprotein; HR, hazard ratio.