SUPPLEMENTAL MATERIAL
Data S1.

- 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                                                                                                                           |
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Appendix: Definition of adverse events
### 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 < 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/1.73m²
7. Chronic hemodialysis
8. Treatment with systemic steroids or immunosuppressants
9. Liver cirrhosis
10. History of PCI/CABG within 6 months
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], 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
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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
- Type 2 diabetes mellitus
- Metabolic syndrome
- Hypertension categorized as high-risk
- Chronic kidney disease (stage 3)
- History of coronary artery disease or cerebral infarction

Exclusion Criteria:

- Under 40 years of age or over 75 years of age
- Ankle brachial index < 0.9
- Chronic atrial fibrillation
- Heart failure (NYHA class III or IV) or left ventricular dysfunction (EF below 40%)
- Medical history of cancer and/or treatment for cancer within the last 5 years
- Estimated glomerular filtration rate <30 ml/min/1.73m²
- Chronic hemodialysis
- Treatment with systemic steroids or immunosuppressants
- Liver cirrhosis
- History of PCI/CABG within 6 months
- Severe valvular stenosis or regurgitation
- 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
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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 planning hypertension management

| A. Risk factors for cardiovascular disease | Advanced age | Smoking | Systolic/diastolic blood pressure levels | Dyslipidemia | Diabetes | Metabolic syndrome | Family history of premature cardiovascular disease | Diabetes |
|------------------------------------------|--------------|---------|-----------------------------------------|-------------|----------|-------------------|-----------------------------------------------|----------|
|                                          |              |         | Low-HDL cholesterol (< 40mg per 100 ml) | High-LDL cholesterol (> 140mg per 100 ml) | High triglyceride (> 150mg per 100 ml) |                   |                                 |            |
|                                          |              |         |                                         |             |          |                   |                                 |            |

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 | High-normal blood pressure | Grade I hypertension | Grade II hypertension | Grade III hypertension |
|-------------------------------|----------------------------|-----------------------|-----------------------|------------------------|
|                               | 130-139/85-89 mm Hg        | 140-159/90-99 mm Hg   | 160-179/100-109 mm Hg | ≥ 180/110 mm Hg        |

**Risk strata (risk factors other than blood pressure):**

- **Risk stratum-1** (no other risk factors)
  - No additive risk
  - Low risk

- **Risk stratum-2** (one to two risk factors other than diabetes or metabolic syndrome)
  - Moderate risk
  - Moderate risk

- **Risk stratum-3** (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)
  - High risk

**Abnormalities:**

- **ABI:** Ankle-brachial index
- **eGFR:** Estimated glomerular filtration rate
- **HDL:** High-density lipoprotein
- **LDL:** Low-density lipoprotein
- **Metabolic syndrome:** Patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110-125 mg/dL 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).
- **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
- eGFR: estimated glomerular filtration rate
- Metabolic syndrome: Patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110-125 mg/dL 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).
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 m² 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:

| 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 |     |
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:**
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- 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: \( CAVI = a((2\rho/\Delta P) \times \ln(Ps/Pd) \times PWV^2) + b \), where \( a \) and \( b \) are constants, \( \rho \) is blood density, \( \Delta P \) 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 electronic 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
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**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.

**15. References**

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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 days 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
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:
CAVI-J protocol ver. 1.1

- 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)):
  - **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.
  - **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**
  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - 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**
  - Pathological Q-waves, as defined above
  - 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:
    - Pathological Q waves with or without symptoms in the absence of nonischemic causes
    - 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
    - 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)
  - Available brain imaging clearly documents a new hemorrhage or infarct
  - 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
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 | Patients who failed to complete | 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)            | 660 (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  |
| **Medications** | **Number (Percentage)** | **Number (Percentage)** | **P-value** |
|-----------------|-------------------------|-------------------------|------------|
| Regular Exercise | 1026 (37.2)             | 27 (31.8)               | .209       |
| 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 (1.00‒1.02)  | .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
| Category               | HR (95% CI)       | P-value |
|------------------------|-------------------|---------|
| 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.