Impact of Cardio-Ankle Vascular Index on Long-Term Outcome in Patients with Acute Coronary Syndrome

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Aim: The purpose of this study is to investigate the impact of arterial stiffness assessed using Cardio-ankle Vascular Index (CAVI) on long-term outcome after acute coronary syndrome (ACS).

Methods: A total of 387 consecutive patients (324 males; age, 64 ± 11 years) with ACS were enrolled. We examined CAVI and brachial-ankle pulse wave velocity (ba PWV) as the parameters of arterial stiffness. The patients were divided into two groups according to the cut-off value of CAVI determined using the receiver operating characteristic curve for the prediction of major adverse cardiovascular events (MACE): low-CAVI group, 177 patients with CAVI < 8.35; high-CAVI group, 210 patients with CAVI ≥ 8.35. The primary endpoint was the incidence of MACE (cardiovascular death, recurrence of ACS, heart failure requiring hospitalization, or stroke).

Results: A total of 62 patients had MACE. Kaplan–Meier analysis demonstrated a significantly higher probability of MACE in the high-CAVI group than in the low-CAVI group (median follow-up: 62 months; log-rank, \( p < 0.001 \)). Multivariate analysis suggested that CAVI was an independent predictor of MACE (hazard ratio [HR], 1.496; \( p = 0.02 \)) and cardiovascular death (HR, 2.204; \( p = 0.025 \)), but ba PWV was not. We investigated the incremental predictive value of adding CAVI to the GRACE score (GRS), a validated scoring system for risk assessment in ACS. Stratified by CAVI and GRS, a significantly higher rate of MACE was seen in patients with both higher CAVI and higher GRS than the other groups (\( p < 0.001 \)). Furthermore, the addition of CAVI to GRS enhanced net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (NRI, 0.337, \( p = 0.034 \); and IDI, 0.028, \( p = 0.004 \)).

Conclusion: CAVI was an independent long-term predictor of MACE, especially cardiovascular death, adding incremental clinical significance for risk stratification in patients with ACS.

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Key words: Arterial stiffness, Cardio-ankle vascular index, Prognosis, GRACE risk score, Acute coronary syndrome

Introduction

Acute coronary syndrome (ACS) is one of the leading causes of morbidity and mortality in most developed countries even in the era of optimal reperfusion therapy. Therefore, proper risk stratification is crucial for the assessment of long-term prognosis after ACS. Recent studies showed that arterial stiffness has attracted attention as a potentially useful parameter for risk stratification of patients with ACS. Cardio-ankle vascular stiffness index (CAVI) is a noninvasive measure of arterial stiffness that is not influenced by blood pressure at the time of examination. We previously reported that high CAVI was an independent predictor of cardiovascular (CV) events and non-fatal ischemic stroke in patients with ACS. However,
Aim

In this study, we explored the effect of arterial stiffness assessed using CAVI on CV events in patients with ACS during a long-term period. Furthermore, we investigated whether CAVI could improve the prognostic performance of the GRS.

Methods

Study Population

We studied 447 patients with ACS who underwent early coronary angiography in Yokohama City University Medical Center between April 2012 and February 2016. ACS was defined as ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina pectoris according to the current guideline. The presence of hypertension was defined as blood pressure >140/90 mm Hg or treatment with oral antihypertensive drugs. Dyslipidemia was defined as plasma levels of fasting triglycerides ≥ 150 mg/dL and/or fasting total cholesterol ≥ 200 mg/dL and/or low-density lipoprotein cholesterol ≥ 130 mg/dL. Diabetes mellitus was determined using the following criteria: medical history, fasting glucose value of ≥ 126 mg/dL, casual plasma glucose value of ≥ 200 mg/dL, or diabetic pattern based on 75-g oral glucose tolerance tests. We excluded patients with any of the following characteristics: (1) persistent atrial fibrillation (n=19), (2) severe aortic insufficiency (n=4), (3) peripheral arterial disease (Ankle Brachial index ≤ 0.9 or previous history of lower extremity bypass and/or endovascular therapy) (n=25), (4) CAVI data not available (n=3), or (5) informed consent was not given (n=6). A total of 390 patients with ACS met the eligibility criteria and were enrolled. Three patients were lost to follow-up, so we analyzed the cases of 387 patients in the current study (Fig. 1). All patients underwent calculation of GRS at admission, and a high GRS was defined as >140 based on previous reports. The study protocol was approved by the Yokohama City University Medical Center Institutional Review Board, and all patients provided written informed consent (UMIN-CTR ID: UMIN000016651).

Two-Dimensional Echocardiography

A standardized complete echocardiographic examination was performed at the same phase as CAVI measurement by experienced sonographers blinded to the clinical data and CAVI following a standard protocol. All images were obtained using a commercial ultrasound system (Vivid q or Vivid E9, GE Healthcare). The left ventricular ejection fraction was calculated using the biplane modified Simpson method. The peak early diastolic velocity (E) was imaged at the tip of the mitral leaflets from the apical four-chamber view. Tissue Doppler imaging was applied to the apical four-chamber view to determine peak early (e') velocities at the septal mitral valve annulus. E/e' (septal) was calculated as an index of left ventricular diastolic function.
Measurement of Arterial Stiffness (CAVI and Brachial-Ankle Pulse Wave Velocity)

CAVI was measured automatically using VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan). Cuffs were placed bilaterally on the upper arms and ankles while the subjects were lying supine and their heads held in midline position. Electrocardiography electrodes were placed on both wrists, and a microphone was placed to detect heart sounds over the sternum.

CAVI was determined using the following equation:

\[
\text{CAVI} = a \left( \frac{2\rho}{\Delta P} \right) \ln \left( \frac{P_s}{P_d} \right) + b,
\]

where \( a \) and \( b \) are constants, \( \rho \) is the blood density, \( \Delta P = P_s - P_d \), \( P_s \) is the systolic blood pressure, \( P_d \) is the diastolic blood pressure, and PWV is the pulse wave velocity.

The actual measurement method of CAVI has been previously reported\(^\text{12}\). In the current study, CAVI was measured more than 1 week after admission in a stable condition. The average of the right and left CAVI values was adopted for analyses.

The brachial-ankle pulse wave velocity (ba PWV) was measured using a volume-plethysmography device (BP-203RPEII, OMRON COLIN Co., Ltd., Tokyo, Japan). The details of the measurements and the reproducibility of this automatic method have been previously described\(^\text{12}\). The average of the right and left ba PWV values was used for analyses.

Follow-Up

Major adverse outcomes were evaluated for a median follow-up of 62 months (interquartile range [IQR], 60 to 64 months). The primary endpoint was the occurrence of major adverse CV events (MACE), defined as CV death, recurrence of ACS, heart failure (HF) requiring hospitalization, or stroke. CV death was defined as death from acute myocardial infarction, HF, stroke, or documented sudden death without apparent cardiovascular cause\(^\text{13}\). Stroke was defined as documented focal neurologic deficit and clinically relevant brain imaging of infarction or hemorrhage. The most severe endpoint was selected for primary endpoint analysis if >1 MACE endpoint occurred during follow-up. We defined CV death for the most severe endpoint, HF requiring hospitalization for the second, stroke for the third and recurrence of ACS was the mildest. All events were followed by hospital visits or telephone interviews with experienced cardiovascular physicians who were not informed of the clinical details and results.

Statistical Analysis

Statistical analyses were performed using JMP pro 12 (SAS Institute, Inc., Cary, NC) and EZR, which is a graphical user interface for R (version 3.1.2, The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation for normally distributed variables and as median (IQR) for skewed distributed variables. Differences between the two groups were tested using the \( t \)-test for normally distributed variables, Mann–Whitney \( U \) test for skewed distributed variables, and chi-square test or Fisher exact test as appropriate for categorical variables. Receiver operating characteristic (ROC) curves were analyzed to assess the cut-off value of CAVI for the prediction of MACE. The optimal cut-off value was defined as the value that gives the maximal sum of sensitivity and specificity. The area under the curve (AUC) of CAVI was 0.663, sensitivity = 0.790, and 1-specificity = 0.495. Accordingly, we divided the patients into two groups by CAVI ≥ 8.35: low-CAVI group, 177 patients with CAVI < 8.35; high-CAVI group, 210 patients with CAVI ≥ 8.35. We used Cox proportional-hazards models to estimate hazard ratios (HR) for endpoints and 95% confidence intervals (CI) using univariate and multivariate models. Coronary risk factors (age, male sex, hypertension, body mass index (BMI), current smoker, dyslipidemia, diabetes mellitus, and estimated glomerular filtration rate (eGFR)), GRS, ba PWV, and CAVI were entered in the univariate analysis. Baseline variables that were considered clinically relevant were entered into the multivariate analysis (forced inclusion model) together with CAVI (model 1: age, male sex, current smoker, hypertension, dyslipidemia, diabetes mellitus, BMI, eGFR, ba PWV and CAVI; model 2: GRS and CAVI). GRS was not included in multivariate analysis model 1 because of its high covariance with the coronary risk factors. The cumulative incidence of a clinical event was assessed using the Kaplan–Meier method and compared using the log-rank test. We evaluated whether the combination of CAVI and GRS gives a better predictive accuracy for MACE compared with each parameter alone. In addition, the incremental effect of adding CAVI to GRS to predict future deaths and CV events was evaluated using the net reclassification index (NRI) as previously described\(^\text{14}\). As a sensitivity analysis, we used a logistic regression model on MACE using the combination of CAVI and GRS as a predictor variable. The cumulative incidence for all analyses (\( p < 0.05 \)) was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of all patients are listed in Table 1. Patients in the high-CAVI group...
Table 1. Baseline Clinical and Angiographic Characteristics of Patients with Acute Coronary Syndrome Who Underwent Cardio-Ankle Vascular Stiffness Index Measurement

|                          | Low CAVI group (n = 177) | High CAVI group (n = 210) | p value |
|--------------------------|--------------------------|---------------------------|---------|
| Age, years               | 57 ± 10                  | 71 ± 8                    | <0.001  |
| Male, n (%)              | 155 (87)                 | 168 (80)                  | 0.054   |
| BMI, kg/m²                | 25.8 ± 3.9               | 23.6 ± 3.2                | <0.001  |
| Current smoker, n (%)    | 98 (55)                  | 75 (35)                   | <0.001  |
| Hypertension, n (%)      | 90 (50)                  | 136 (65)                  | 0.005   |
| Systolic BP at admission, mmHg | 146 ± 34                | 148 ± 34                  | 0.641   |
| Diastolic BP at admission, mmHg | 90 ± 24                  | 85 ± 22                   | 0.023   |
| Dyslipidemia, n (%)      | 86 (48)                  | 77 (36)                   | 0.22    |
| LDL cholesterol, mg/dl   | 134 ± 38                 | 122 ± 34                  | <0.001  |
| HDL cholesterol, mg/dl   | 44 ± 11                  | 46 ± 11                   | 0.013   |
| Triglycerides, mg/dl     | 168 (151-186)            | 137 (114-161)             | 0.032   |
| Diabetes mellitus, n (%) | 63 (35)                  | 94 (44)                   | 0.077   |
| HbA1c, %                 | 6.2 ± 1.3                | 6.1 ± 1.0                 | 0.479   |
| History of cerebral infarction, % | 2 (1)                  | 10 (4)                    | 0.043   |
| History of myocardial infarction, % | 15 (8)                  | 21 (10)                   | 0.606   |
| Clinical presentation    |                          |                           | 0.993   |
| Unstable angina pectoris, n (%) | 13 (7)                  | 15 (7)                    |         |
| ST-segment elevation MI, n (%) | 132 (74)                 | 153 (72)                  |         |
| Non-ST-segment elevation MI, n (%) | 32 (18)                  | 41 (19)                   |         |
| Culprit artery, n (%)    |                          |                           | 0.321   |
| Left anterior descending coronary artery | 86 (48)                  | 119 (56)                  |         |
| Right coronary artery    | 65 (36)                  | 66 (31)                   |         |
| Left circumflex coronary artery | 22 (12)                  | 18 (8)                    |         |
| No. of diseased vessels, n (%) | 0.550                   |                           |         |
| 1                        | 136 (60)                 | 85 (55)                   |         |
| 2                        | 58 (25)                  | 47 (30)                   |         |
| 3                        | 30 (13)                  | 20 (13)                   |         |
| In-hospital procedure, n (%) |                          |                           |         |
| In-hospital PCI, %       | 167 (94)                 | 189 (90)                  | 0.116   |
| In-hospital CABG, %      | 8 (4)                    | 10 (4)                    | 0.902   |
| hs-CRP at admission, mg/dl | 0.521 (0.303-0.739)     | 0.593 (0.340-0.845)       | 0.679   |
| eGFR at admission, ml/min/1.73 m² | 75.9 ± 19.0             | 67.6 ± 18.3               | <0.001  |
| peak CK-MB, IU/l         | 175 (144-206)            | 181 (154-208)             | 0.755   |
| LVEF, %                  | 52.3 ± 10.5              | 52.1 ± 11.6               | 0.841   |
| E/e'                     | 10.1 ± 3.3               | 12.2 ± 3.8                | <0.001  |
| Medications on discharge, n (%) |                          |                           |         |
| Aspirin                  | 172 (97)                 | 200 (95)                  | 0.192   |
| Thienopyridine           | 155 (88)                 | 181 (86)                  | 0.584   |
| β-blocker                | 106 (59)                 | 133 (63)                  | 0.483   |
| ACEI or ARB              | 134 (75)                 | 162 (77)                  | 0.739   |
| Statin                   | 165 (93)                 | 194 (92)                  | 0.750   |

Values are the mean ± standard deviation (SD), n (%), or median (interquartile range) as appropriate. ACEI, angiotensin-converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAVI, cardio-ankle vascular stiffness index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous intervention.
Nonfatal stroke. MACE occurred less frequently in the low-CAVI group than in the high-CAVI group (7.3% vs 23.3%, \( p < 0.001 \)). The average CAVI values were 9.0 ± 1.1 in the group with MACE and 8.4 ± 1.2 in the group without MACE. CAVI was significantly higher in the MACE group than in the without-MACE group (\( p < 0.001 \)).

Kaplan–Meier Estimate for Event-Free Rate

Kaplan–Meier curves for patients with high and low CAVI values are shown in Fig. 3. MACE more frequently occurred in patients with high CAVI than in those with low CAVI (log-rank, \( p < 0.001 \)) (Fig. 3A). CV death also occurred more often in patients with high CAVI than in those with low CAVI (log-rank, \( p < 0.001 \)) (Fig. 3B).

Follow-Up and Major Adverse Cardiovascular Events

During the median follow-up of 62 months, 62 patients (16%) experienced MACE: 15 (3.8%) had cardiovascular death, 24 (6.3%) had recurrence of ACS, 10 (2.5%) had heart failure, and 13 (3.3%) had nonfatal stroke. MACE occurred less frequently in the low-CAVI group than in the high-CAVI group (7.3% vs 23.3%, \( p < 0.001 \)). The average CAVI values were 9.0 ± 1.1 in the group with MACE and 8.4 ± 1.2 in the group without MACE. CAVI was significantly higher in the MACE group than in the without-MACE group (\( p < 0.001 \)).
In multivariate analysis of CV death without ba PWV, CAVI was an independent predictor of CV death after adjustment for coronary risk factors (HR, 2.309; 95% CI, 1.273–4.487; \( p = 0.008 \), Model 1 in Supplementary Table 2). However, ba PWV was not a significant predictor of CV death in multivariate analysis without CAVI (HR, 1.001; 95% CI, 0.999–1.003; \( p = 0.109 \), Model 2 in Supplementary Table 2). When adjusted for GRACE risk score, ba PWV was also not an independent predictor of CV death (HR, 1.000; 95% CI, 0.999–1.001; \( p = 0.051 \), Model 3 in Supplementary Table 1). In multivariate analysis of CV death without ba PWV, CAVI was an independent predictor of CV death after adjustment for coronary risk factors (HR, 2.309; 95% CI, 1.273–4.487; \( p = 0.008 \), Model 1 in Supplementary Table 2). However, ba PWV was not a significant predictor of CV death in multivariate analysis without CAVI (HR, 1.001; 95% CI, 0.999–1.003; \( p = 0.109 \), Model 2 in Supplementary Table 2). When adjusted for GRACE risk score, ba PWV was an independent predictor of CV death (HR, 1.002; 95% CI, 1.000–

Table 2. Univariate and multivariate logistic regression analysis—estimate hazard ratio for major adverse cardiovascular events

| Variable                  | Univariate | Multivariate (Model 1) | Multivariate (Model 2) |
|---------------------------|------------|------------------------|------------------------|
|                           | HR    | 95% CI | \( p \) value | HR    | 95% CI | \( p \) value | HR    | 95% CI | \( p \) value |
| Age, per 1 year           | 1.031 | 0.854-1.066 | 0.014 | 0.989 | 0.953-1.026 | 0.569 | 1.001 | 1.000-1.002 | 0.002 |
| Male                      | 1.036 | 0.513-2.276 | 0.924 | 1.194 | 0.550-2.797 | 0.666 | 0.900 | 0.900-1.000 | 0.001 |
| Current smoker            | 0.848 | 0.543-1.631 | 0.829 | 1.227 | 0.660-2.281 | 0.514 | 1.001 | 1.000-1.002 | 0.002 |
| Hypertension              | 0.909 | 0.526-1.584 | 0.734 | 0.721 | 0.391-1.329 | 0.293 | 0.988 | 0.971-1.005 | 0.019 |
| Dyslipidemia              | 0.845 | 0.479-1.465 | 0.533 | 1.015 | 0.557-1.833 | 0.958 | 0.988 | 0.971-1.005 | 0.019 |
| Diabetes mellitus         | 1.069 | 0.611-1.849 | 0.811 | 1.015 | 0.562-1.811 | 0.957 | 0.988 | 0.971-1.005 | 0.019 |
| BMI, per 1 kg/m²          | 0.879 | 0.806-0.953 | 0.001 | 0.900 | 0.817-0.988 | 0.030 | 0.988 | 0.971-1.005 | 0.019 |
| eGFR, per 1 mL/min per 1.73 m² | 0.986 | 0.971-1.001 | 0.073 | 0.988 | 0.971-1.005 | 0.019 | 0.988 | 0.971-1.005 | 0.019 |
| ba PWV                    | 1.001 | 1.000-1.001 | 0.004 | 1.000 | 0.999-1.001 | 0.009 | 1.012 | 1.004-1.020 | 0.002 |
| GRACE risk score          | 1.015 | 1.008-1.023 | <0.001 | 1.494 | 1.067-2.120 | 0.021 | 1.399 | 1.093-1.802 | 0.008 |
| mean CAVI                 | 1.595 | 1.271-2.022 | <0.001 | 1.494 | 1.067-2.120 | 0.021 | 1.399 | 1.093-1.802 | 0.008 |

ba PWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; HR, hazard ratio; 95% CI, 95% confidence interval.
The integrated discrimination improvement (IDI) again showed that the diagnostic performance of the model was significantly improved by adding CAVI to the GRS (IDI: 0.028, \( p < 0.004 \)). For the sensitivity analysis, CAVI, comparing to GRS, was more strongly and gradually associated with MACE, in which the odds ratios (95% CIs) of higher GRS and lower CAVI, lower GRS and higher CAVI, and higher GRS and higher CAVI against lower GRS and lower CAVI were 1.238 (0.359–3.891), 3.076 (1.246–8.088), and 4.816 (2.232–11.621), respectively.

We evaluated the incremental effect of adding CAVI to the GRS for predicting MACE. When we divided all patients into four groups according to the cut-offs for CAVI and GRS >140, significantly higher MACE rates were seen in patients with both higher CAVI and higher GRACE risk score (n=35, 26.1% of all patients) than the other groups (\( p < 0.001 \)). CAVI, cardio-ankle vascular index; GRACE, global registry of acute coronary events; MACE, major adverse cardiovascular events.

### Table 3. Univariate and multivariate logistic regression analysis-estimate hazard ratio for cardiovascular death

| Variable                  | Univariate |                       |                       |                       |                       |
|---------------------------|------------|------------------------|------------------------|------------------------|------------------------|
|                           | HR         | 95% CI                 | \( p \) value          | HR                     | 95% CI                 | \( p \) value          | HR                     | 95% CI                 | \( p \) value          |
| Age, per 1 year           | 1.145      | 1.073-1.240            | < 0.001                | 1.076                   | 0.990-1.181            | 0.097                  |                       |                       |                       |
| Male                      | 0.784      | 0.240-3.516            | 0.713                  | 1.413                   | 0.352-7.696            | 0.651                  |                       |                       |                       |
| Current smoker            | 0.607      | 0.186-1.743            | 0.370                  | 1.564                   | 0.406-5.701            | 0.498                  |                       |                       |                       |
| Hypertension              | 1.444      | 0.502-4.712            | 0.509                  | 0.844                   | 0.235-3.310            | 0.798                  |                       |                       |                       |
| Dyslipidemia              | 0.487      | 0.133-1.453            | 0.225                  | 0.689                   | 0.167-2.375            | 0.572                  |                       |                       |                       |
| Diabetes mellitus         | 1.710      | 0.601-4.973            | 0.309                  | 1.522                   | 0.467-4.980            | 0.479                  |                       |                       |                       |
| BMI, per 1 kg/m\(^2\)     | 0.795      | 0.669-0.932            | 0.006                  | 0.909                   | 0.748-1.098            | 0.331                  |                       |                       |                       |
| eGFR, per 1 mL/min per 1.73 m\(^2\) | 0.968      | 0.940-0.996            | 0.027                  | 0.991                   | 0.955-1.025            | 0.617                  |                       |                       |                       |
| ba PWV                    | 1.020      | 1.008-1.032            | < 0.001                | 1.000                   | 0.998-1.002            | 0.687                  |                       |                       |                       |
| mean CAVI                 | 3.276      | 2.032-5.680            | < 0.001                | 2.173                   | 1.126-4.500            | 0.027                  | 2.899                  | 1.755-5.109           | 0.001                  |

ba PWV, brachial-ankle pulse wave velocity; BMI, body mass index; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; HR, hazard ratio; 95% CI, 95% confidence interval.

### Fig. 4. Relation of high or low CAVI and GRACE risk score

When we divided all patients into four groups according to the cut-offs for CAVI and GRACE risk score >140, significantly higher MACE rates were seen in patients with both higher CAVI and higher GRACE risk score (n=35, 26.1% of all patients) than the other groups (\( p < 0.001 \)). CAVI, cardio-ankle vascular index; GRACE, global registry of acute coronary events; MACE, major adverse cardiovascular events.
Discussion

The main finding of the current study was that arterial stiffness assessed using CAVI was a significant and independent predictor of long-term incidence of MACE, especially CV death in patients with ACS. Furthermore, the results demonstrated that the prognostic performance of CAVI was independent of the GRS and the addition of CAVI to the GRS improved risk stratification in ACS patients. To the best of our knowledge, this is the first study to reveal the role of arterial stiffness evaluated using CAVI in long-term incidence of MACE and CV death in patients with ACS.

The Role of CAVI in the Prognosis

Previously, some studies reported that arterial stiffness was a significant predictor of adverse events in patients with coronary artery disease. However, the prognostic role of this parameter in patients with ACS has not been fully understood. In the current study, we demonstrated the independent predictive value of CAVI after adjustment for classic CV risk factors. In addition, the combined use of CAVI and GRS improved risk stratification in patients with ACS. These results suggested that CAVI has an adjunctive value in the assessment of traditional CV risk factors. This may be because CAVI reflects damage in the arterial wall over a long period. By contrast, blood pressure, glycemia, and lipids cannot reflect the genuine damage on the arterial wall because their values may fluctuate depending on the timing. Therefore, we think that CAVI can serve as an additional prognostic tool to stratify patients with ACS at risk of the development of events, beyond the assessment of traditional atherosclerotic risk factors.

Organ damage caused by increased arterial stiffness may worsen the prognosis of patients with ACS. Previous studies showed that increased arterial stiffness determined using CAVI was associated with atherosclerotic diseases such as cerebral infarctions and chronic kidney disease (CKD). In the current study, more patients with a high CAVI had a history of cerebral infarctions and renal insufficiency as compared with patients with a low CAVI. Previous studies revealed that cerebral infarctions and CKD were predictors of CV events in ACS. Hence, in the current study, atherosclerotic organ damage induced by increased arterial stiffness may adversely affect the prognosis of patients with ACS.

In addition, LV diastolic dysfunction induced by increased arterial stiffness may worsen the prognosis of patients with ACS. Previous studies reported that an increased LV afterload caused by elevated arterial stiffness induced higher LV filling pressure and diastolic dysfunction. A number of studies demonstrated that diastolic dysfunction was associated with a poor prognosis in patients with ACS. In our study, E/e', which was previously shown to be an indicator of LV diastolic dysfunction, was significantly elevated in the high-CAVI group as compared to that in the low-CAVI group.

Comparison with Previous Studies

Previous studies investigated the effect of arterial stiffness on CV outcomes in patients with ACS. Tomiyama et al. reported that ba PWV was an independent predictor of the prognosis of patients with ACS. In our study, there was a significant relationship between ba PWV and major adverse events in the univariate analysis but not in the multivariate analysis that included CAVI. In addition, when we performed multivariate analysis of major adverse events without ba PWV, CAVI was a significant predictor of MACE after adjustment for the established coronary risk factors. Although there was a similar trend for ba PWV, it did not reach statistical significance. These findings may be related to some as-yet undetermined effects on blood pressure at the time of the examination or the superiority of CAVI over ba PWV as a method of measuring arterial stiffness.

Hans-Josef et al. reported that aortic PWV measured by cardiac magnetic resonance imaging (MRI) was an independent predictor of MACE comprising all-cause death, nonfatal myocardial reinfarctions, new congestive heart failure, and strokes. Another study found that phase-contrast cardiac MRI could provide an accurate and reproducible method for the determination of PWV. However, aortic stiffness measured by cardiac MRI requires more time and complex calculations. In addition, it can be performed in specific situations. Therefore, cardiac MRI is not suitable for all types of acutely hospitalized patients with ACS. However, CAVI can easily be measured in the clinical setting. Thus, we think that CAVI is a more useful predictive tool than cardiac MRI for all types of ACS.

As noted earlier, previous studies revealed the significance of arterial stiffness in the prognosis of patients with ACS. However, no previous studies examined the association between arterial stiffness and CV mortality in patients with ACS. Moreover, other previous studies were based on smaller study populations and shorter follow-up duration than ours. Furthermore, critically ill patients, such as those with HF or CKD, were excluded in the previous studies. In the current study, we could explore the role of arterial stiffness in such seriously ill patients using CAVI, which is an easy and noninvasive measurement of
arterial stiffness. We believe that our study using CAVI as a marker of arterial stiffness is most reliable and reproductive in the current era.

Clinical Implications
The GRS is widely used, simple to assess, and effective in risk estimation of mortality and is recommended for all types of patients with ACS\(^8\). However, this score, which is based on common traditional risk factors for CV disease, was derived in the early 21st century. Since that time, many novel risk factors, including arterial stiffness, have been studied. The GRS does not include any of these new risk factors. Our study was the first to demonstrate that the addition of CAVI could improve risk stratification based on the GRS.

CAVI, which is not influenced by blood pressure at the time of the examination, integrates measurements of CV risk factors such as aging, hypertension, diabetes mellitus, and dyslipidemia\(^5, 15\). Therefore, it is reasonable that CAVI has better predicted values than each of these classic risk factors and shows the added value to GRS.

Otsuka et al. reported that persistent impairment of arterial stiffness assessed using CAVI was associated with future CV events, even after comprehensive management of traditional atherosclerotic risk factors in patients with stable coronary artery disease\(^26\). This suggested that serial assessments of arterial stiffness using CAVI could serve as an indicator of the need for treatment. Moreover, several interventional studies showed that nonpharmacological and pharmacological treatments were associated with an improvement in CAVI\(^27-29\). To determine the utility of CAVI in patients with ACS, more clinical and experimental studies are required. In addition, a therapeutic strategy for improving arterial stiffness in ACS needs to be developed.

Limitations
This study has limitations that need to be acknowledged. First, this study was based on a relatively small sample size at a single center. However, in comparison with previous studies, our study included the largest number of patients and had a longer follow-up duration so that we could clearly reveal the significance of arterial stiffness measured by CAVI. Second, we excluded patients with severe aortic insufficiency, peripheral artery disease, and persistent atrial fibrillation because it was difficult to accurately measure CAVI in these patients. It remains uncertain if our results apply to these subgroups of patients. Third, dyslipidemia, which is thought to be a conventional risk factor of recurrent atherosclerotic events, was less observed in the high-CAVI group than in the low-CAVI group. The relationship between CAVI and dyslipidemia has not been consistent with past studies\(^30, 31\). The higher proportion of elderly people in the high-CAVI group may affect the lipid profile\(^32\). Forth, compared to other recent studies, the rate of major adverse events in our study was relatively low\(^2, 18\). This better outcome may be explained by the extremely high proportion of patients who underwent percutaneous coronary intervention (92.1%) or coronary artery bypass grafting (4.8%).

Conclusion
Arterial stiffness determined using CAVI was an independent long-term predictor of MACE in patients with ACS. Furthermore, we demonstrated that the additional usefulness of CAVI can improve risk stratification based on the GRS.

Acknowledgements
Not applicable.

Conflict of Interest
The authors have no conflicts of interest to declare.

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**Supplementary Table 1.** Univariate and multivariate logistic regression analysis—estimate hazard ratio for major adverse cardiovascular events

| Variable                      | Multivariate (Model 1) |          |          |          | Multivariate (Model 2) |          |          |          | Multivariate (Model 3) |          |          |          |
|-------------------------------|------------------------|----------|----------|----------|------------------------|----------|----------|----------|------------------------|----------|----------|----------|
|                               | HR                     | 95% CI   | P value  |          | HR                     | 95% CI   | P value  |          | HR                     | 95% CI   | P value  |          |
| Age, per 1 year               | 0.990                  | 0.955-1.027 | 0.618 |          | 1.004                  | 0.971-1.039 | 0.796 |          | 1.014                  | 1.007-1.022 | <0.001 |          |
| Male                          | 1.172                  | 0.543-2.730 | 0.697 |          | 1.318                  | 0.617-3.051 | 0.493 |          | 1.000                  | 0.999-1.001 | 0.051 |          |
| Current smoker                | 1.209                  | 0.653-2.235 | 0.542 |          | 1.248                  | 0.674-2.311 | 0.477 |          | 0.988                  | 0.971-1.005 | 0.188 |          |
| Hypertension                  | 0.738                  | 0.405-1.349 | 0.322 |          | 0.748                  | 0.408-1.371 | 0.346 |          | 0.988                  | 0.971-1.005 | 0.188 |          |
| Dyslipidemia                  | 1.015                  | 0.557-1.832 | 0.958 |          | 1.009                  | 0.555-1.816 | 0.974 |          | 0.988                  | 0.971-1.005 | 0.188 |          |
| Diabetes mellitus             | 1.014                  | 0.562-1.807 | 0.962 |          | 1.120                  | 0.628-1.979 | 0.695 |          | 2.309                  | 1.273-4.487 | 0.008 |          |
| BMI, per 1 kg/m²              | 0.900                  | 0.817-0.988 | 0.030 |          | 0.890                  | 0.809-0.975 | 0.001 |          | 0.988                  | 0.971-1.005 | 0.188 |          |
| eGFR, per 1 mL/min per 1.73 m²| 0.988                  | 0.971-1.005 | 0.179 |          | 0.988                  | 0.971-1.005 | 0.188 |          |                      |          |          |          |
| GRACE risk score              |                        |          |          |          |                        |          |          |          |                        |          |          |          |
| ba PWV                        | 1.000                  | 0.999-1.001 | 0.082 |          | 1.000                  | 0.999-1.001 | 0.051 |          |                      |          |          |          |
| mean CAVI                     | 1.549                  | 1.149-2.109 | 0.004 |          |                      |          |          |          |                        |          |          |          |

Model 1 age, male, current smoker, hypertension, dyslipidemia, diabetes mellitus, BMI, eGFR and CAVI, Model 2 age, male, current smoker, hypertension, dyslipidemia, diabetes mellitus, BMI, eGFR and ba PWV, Model 3 GRACE risk score and ba PWV. GRACE, global registry of acute coronary events; HR, hazard ratio; 95% CI, 95% confidence interval; Other abbreviations as in Table 1

**Supplementary Table 2.** Univariate and multivariate logistic regression analysis—estimate hazard ratio for cardiovascular death

| Variable                      | Multivariate (Model 1) |          |          |          | Multivariate (Model 2) |          |          |          | Multivariate (Model 3) |          |          |          |
|-------------------------------|------------------------|----------|----------|----------|------------------------|----------|----------|----------|------------------------|----------|----------|----------|
|                               | HR                     | 95% CI   | P value  |          | HR                     | 95% CI   | P value  |          | HR                     | 95% CI   | P value  |          |
| Age, per 1 year               | 1.079                  | 0.994-1.183 | 0.083 |          | 1.105                  | 1.020-1.210 | 0.020 |          | 1.017                  | 1.004-1.031 | 0.006 |          |
| Male                          | 1.381                  | 0.347-7.423 | 0.670 |          | 1.534                  | 0.403-7.826 | 0.560 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| Current smoker                | 1.524                  | 0.398-5.485 | 0.520 |          | 1.559                  | 0.411-5.613 | 0.496 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| Hypertension                  | 0.884                  | 0.249-3.410 | 0.851 |          | 0.880                  | 0.262-3.204 | 0.839 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| Dyslipidemia                  | 0.678                  | 0.165-2.323 | 0.555 |          | 0.741                  | 0.186-2.504 | 0.643 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| Diabetes mellitus             | 1.531                  | 0.473-4.984 | 0.470 |          | 2.003                  | 0.646-6.387 | 0.226 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| BMI, per 1 kg/m²              | 0.907                  | 0.748-1.094 | 0.314 |          | 0.875                  | 0.730-1.044 | 0.141 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| eGFR, per 1 mL/min per 1.73 m²| 0.989                  | 0.955-1.023 | 0.559 |          | 0.989                  | 0.955-1.022 | 0.534 |          | 1.000                  | 1.000-1.003 | <0.001 |          |
| GRACE risk score              |                        |          |          |          |                        |          |          |          |                        |          |          |          |
| ba PWV                        | 1.000                  | 0.999-1.003 | 0.109 |          | 1.002                  | 1.000-1.003 | <0.001 |          |                      |          |          |          |
| mean CAVI                     | 2.309                  | 1.273-4.487 | 0.008 |          |                      |          |          |          |                        |          |          |          |

BMI, body mass index; eGFR, estimated glomerular filtration rate; ba PWV, brachial-ankle pulse wave velocity; GRACE, global registry of acute coronary events; HR, hazard ratio; 95% CI, 95% confidence interval.