



Article

# A Noninvasive Arterial Stiffness Index to Estimate the Severity of Coronary Atherosclerosis in Patients Undergoing Coronary Angiography

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**Abstract:** The early diagnosis and appropriate treatment of subclinical atherosclerosis before the onset of life-threatening cardiovascular (CV) diseases are major unmet medical needs in current clinical practice. Noninvasive arterial stiffness indices, the arterial velocity–pulse index (AVI) and the arterial pressure–volume index (API) have been associated with CV risks, conventional arterial stiffness indices, and the severity of coronary atherosclerosis. However, few studies have examined the relationship between these indices and the occurrence of CV events. We measured the AVI and API in 113 consecutive patients admitted to Yokohama City University Hospital for cardiac catheterization between June 2015 and March 2016. Patients were followed until September 2022, and the occurrence of CV events was assessed. The mean age was  $71.2 \pm 10.7$  years, and 83 patients (73.5%) were male. In total, 80 patients (70.8%) had hypertension, 87 (77.0%) had dyslipidemia, and 91 (80.5%) had a history of ischemic heart disease (IHD). The mean follow-up duration was  $1752 \pm 819$  days. Patients who received elective percutaneous coronary intervention (PCI) based on the results of coronary angiography (CAG) at the time of enrollment had significantly higher API than those who did not ( $38.5 \pm 12.6$ ,  $n = 17$  vs.  $31.3 \pm 7.4$ ,  $n = 96$ ,  $p = 0.001$ ). The API was independently associated with the risk of elective PCI in multiple logistic regression analysis. In conclusion, the API could be a useful indicator for estimating the need for coronary interventional treatment in patients with a high CV risk.

**Keywords:** atherosclerosis; cardiovascular disease; arterial stiffness; noninvasive; cuff oscillometry; arterial pressure-volume index



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## 1. Introduction

Atherosclerosis is a major disease that impedes human health and longevity. Atherosclerosis is a common pathological condition of lifestyle-related diseases, such as hypertension, diabetes, and dyslipidemia, that causes life-threatening cardiovascular (CV) events such as acute myocardial infarction and cerebral infarction [1]. Critical care for ischemic heart disease (IHD) and stroke in the acute phase requires enormous financial, time, and human resources. Even if these patients survive the acute disease, they frequently drop out of social life owing to serious sequelae. Thus, the early diagnosis and appropriate treatment of subclinical atherosclerosis before the onset of CV disease are major unmet medical needs in

current clinical practice [2–4]. To evaluate the severity of atherosclerosis and stratify the risk of CV events, various procedures have been used to assess arterial stiffness or endothelial dysfunction, including the pulse-wave velocity (PWV), flow-mediated dilatation (FMD), and carotid intima-media thickness (CIMT) [5–9]. However, their application in routine clinical practice remains challenging owing to factors such as the variability among investigators and the time-consuming nature of manual procedures. They are not suitable for use as screening tests to reveal latent atherosclerosis in asymptomatic outpatients because they can only be measured in facilities equipped with testing equipment. Because both the arterial velocity-pulse index (AVI) and arterial pressure-volume index (API) are measured using cuff oscillometry, the most advantageous aspects of both indices are their extreme versatility and utility in clinical settings.

The AVE-1500 system (Shisei Datum, Tokyo, Japan) is a recently developed device that can evaluate arterial stiffness and endothelial dysfunction using new indices, measured as the AVI and API, using cuff oscillometry and a single blood pressure (BP) measurement. The AVI is an index calculated from the pulse-wave pattern characteristics under high cuff pressure exceeding the systolic blood pressure (SBP). An earlier computational model revealed that the oscillation wave generated by a suprasystolic cuff pressure resembles the blood pressure wave in the proximal brachial artery and is characterized by two systolic peaks [10]. Accordingly, the AVI was calculated as the ratio of the differential pressure to the differential time ( $dp/dt$ ) of the brachial artery during systole and diastole [11]. The latter systolic waveform increased and then rapidly decreased with the enhanced reflected wave resulting from atherosclerosis and increased peripheral resistance. Thus, the AVI reflects the arterial stiffness of the central and peripheral arteries. For the API, the relationship between the cuff pressure and arterial volume shows a sigmoidal pattern [12]. As atherosclerosis progresses, the change in arterial volume becomes gradual, and the inclination of the sigmoidal curve slows. Komine et al. reported an equation for the sigmoid curve, and the API was defined as the reciprocal value of the inclination of the sigmoidal curve, suggesting that the API reflects the reactive vasodilation and stiffness of the peripheral artery [13]. Therefore, the AVI and API are indicators that reflect central and peripheral arterial stiffness, respectively [10,11,13].

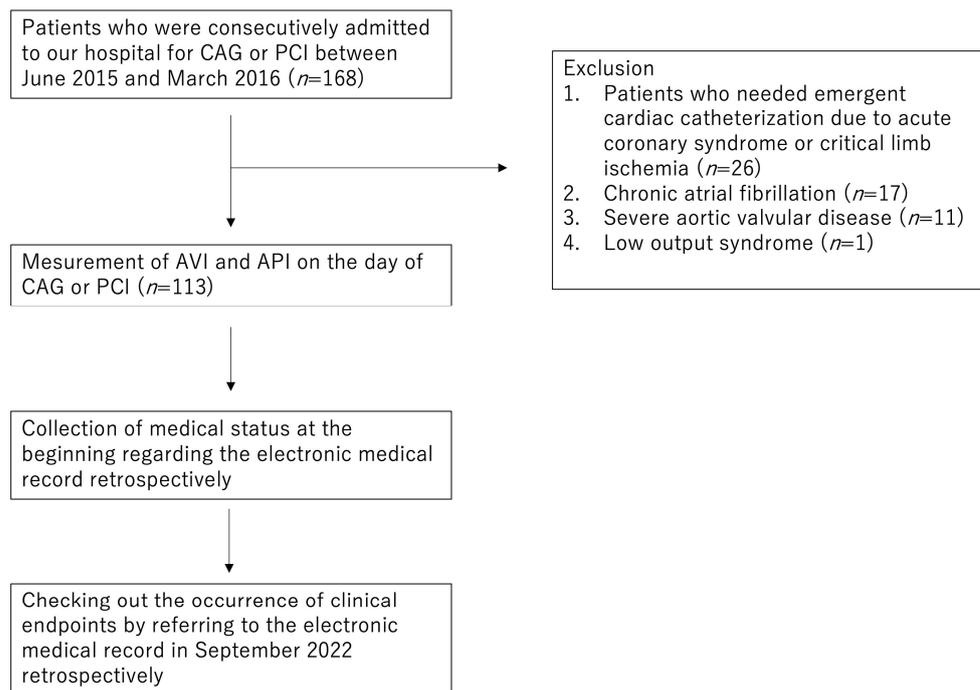
Previous studies, including ours, have reported that these indices are useful for evaluating CV risk, other atherosclerotic indices, and the severity of coronary artery lesions [14–18] in Japan. The associations of API and AVI with established cardiovascular disease risk factors were examined at annual medical checkups and an outpatient clinic at a single medical institution in Japan; the API and AVI were significantly correlated with risk factors, atherosclerotic risk scores, and high test-retest reliabilities, suggesting their potential usefulness as vascular risk markers, warranting further research [14,15]. Additionally, for patients undergoing coronary angiography (CAG) in the hospital, significant differences were identified in both the API and AVI, suggesting a significant correlation with the degree of coronary artery atherosclerosis [16–18].

However, few studies have examined the relationship between these measures and the occurrence of CV events [19,20]. In the present retrospective cohort study, we aimed to investigate the relationship between the arterial stiffness indices (AVI and API) and the occurrence of CV events in patients with apparent or subclinical atherosclerosis in Japan.

## 2. Materials and Methods

### 2.1. Patients

This retrospective cohort study was performed at the Yokohama City University Hospital, Japan. The study protocol was registered and approved by the ethics committee of Yokohama City University Hospital in 2015 (B150701005). Participants were provided the means to opt out on the website via notifications for guaranteed withdrawal. Owing to the noninvasive observational study design, additional informed consent was not obtained from the participants. The detailed inclusion and exclusion processes of the study are shown in Figure 1.



**Figure 1.** Flowchart showing inclusion and exclusion processes of the current study.

We used a multifunctional blood pressure monitoring device, the AVE-1500 (Shisei Datum, Tokyo, Japan), to estimate the AVI and API in patients consecutively admitted to our hospital for CAG or percutaneous coronary intervention (PCI) between June 2015 and March 2016 ( $n = 113$ ). On the day of CAG or PCI, the AVI and API were measured twice for each patient in the supine position in the catheterization laboratory. Patients who required emergency cardiac catheterization due to acute coronary syndrome or critical limb ischemia were excluded from the study. Patients with chronic atrial fibrillation, severe aortic valvular disease, or low-output syndrome were also excluded. We checked out the occurrence of the following clinical CV events of all the patients who met the inclusion criteria by referring to the electronic medical record in September 2022 retrospectively. We determined that observation was censored when the patient ceased attending our hospital.

Data on each patient's general status, medical history, blood test results, concomitant medications, and clinical outcomes were retrospectively obtained from the electronic medical records. Hypertension (HT) was defined as an SBP of  $\geq 140$  mmHg, diastolic blood pressure (DBP) of  $\geq 90$  mmHg, or ongoing medical treatment for HT. Dyslipidemia (DL) was defined as a low-density lipoprotein (LDL) cholesterol level of  $\geq 140$  mg/dL, a triglyceride level of  $\geq 150$  mg/dL, a high-density lipoprotein (HDL) cholesterol level of  $\leq 40$  mg/dL, or ongoing medical treatment for DL. Diabetes mellitus (DM) was defined as a blood glucose level  $\geq 200$  mg/dL, a hemoglobin A1c level  $\geq 6.5\%$ , or ongoing medical treatment for DM. Chronic heart failure (CHF) was defined as a B-type natriuretic peptide (BNP) level of  $\geq 40$  pg/mL caused by CV disease. Valvular heart disease (VHD) was defined as valve regurgitation or stenosis of at least a moderate degree. Plasma glucose and triglyceride levels were measured by routine blood sampling without overnight fasting.

## 2.2. AVI and API

The AVE-1500 is a recently developed device that can noninvasively evaluate arterial stiffness and endothelial dysfunction of the central arteries (AVI) and peripheral arteries (API) using conventional cuff oscillometry and a single BP measurement [10,11,13]. The AVE-1500 can evaluate the SBP, DBP, AVI, API, and pulse rate in a single measurement within two minutes. The AVI and API were measured by an AVE-1500 with the patients in the supine position in a quiet, temperature-controlled room (24.0–26.8 °C) in the current

study. Measurements were performed twice for each participant, and the average AVI and API measurements at the time of participant enrollment were used for subsequent analyses.

### 2.3. Calculation of SYNTAX and Gensini Scores

The SYNTAX and Gensini scores were used to quantitatively measure the degree of coronary atherosclerosis in each patient.

To calculate the Gensini score, a severity score was established for each coronary lesion according to the degree of stenosis, and the score was multiplied by a coefficient that considered the importance of the position of the lesion in the coronary circulation. Finally, the Gensini score was calculated by summing the scores of individual coronary segments. Gensini et al. previously described the detailed calculation method [21].

The SYNTAX score considered more detailed anatomical risk factors, such as the presence of bifurcation lesions, calcification, thrombus, and tortuosity, in addition to the position and degree of coronary stenosis. The SYNTAX score was calculated for each patient using the calculator on the website (<https://syntaxscore.org>, accessed on 1 June 2015).

### 2.4. Clinical Events and Endpoints

First, we investigated whether elective PCI was performed during the follow-up period according to CAG findings at the time of enrollment. Indications for PCI were determined according to the conventional Japanese Circulation Society (JCS) guidelines, which were generally consistent with the European Society of Cardiology (ESC) guidelines from the same period [22,23].

Second, we investigated clinical endpoints, which were defined as the first occurrence of any of the following events: CV death, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization due to unstable angina pectoris (UAP), hospitalization due to heart failure (HF), and repeated coronary revascularization (RRV). CV death, nonfatal MI, nonfatal stroke, and hospitalization due to UAP were collectively considered major adverse cardiovascular events (MACE).

### 2.5. Statistical Analysis

A  $p$ -value  $< 0.05$  was considered to indicate statistical significance. Data are shown as the mean  $\pm$  standard deviation for continuous variables and as frequencies and percentages for categorical variables. Quantitative data were compared between two groups using an unpaired  $t$ -test. A chi-square test was used to compare categorical data between the two groups. The correlations of AVI and API with all other variables were analyzed using Pearson's correlation coefficients. Finally, multivariate analyses were performed to investigate the independent variables responsible for clinical outcomes. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 29.0; SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Baseline Characteristics

The baseline patient characteristics are shown in Table 1. The mean patient age was  $71.2 \pm 10.7$  years, and 83 (73.5%) were male. Overall, 80 patients (70.8%) had HT, 87 (77.0%) had DL, and 46 (40.7%) had DM. Moreover, 91 patients (80.5%) had a history of IHD and 85 (75.2%) received oral antiplatelet treatment. The mean AVI and API were  $33.9 \pm 10.3$  and  $32.4 \pm 8.7$ , respectively. The mean Gensini and SYNTAX scores were  $49.7 \pm 42.7$  and  $14.4 \pm 13.1$ , respectively.

**Table 1.** Baseline characteristics.

$n = 113$			
Age (years)	$71.2 \pm 10.7$	BMI ( $\text{kg}/\text{m}^2$ )	$23.9 \pm 4.3$
Male (%)	83 (73.5)	SBP (mmHg)	$139.7 \pm 23.7$

**Table 1.** *Cont.*

<i>n</i> = 113			
Follow-up period (day)	1752 ± 819	DBP (mmHg)	70.0 ± 12.4
HT (%)	80 (70.8)	HR (/min)	66.5 ± 11.2
DL (%)	87 (77.0)	AVI	33.9 ± 10.3
DM (%)	46 (40.7)	API	32.4 ± 8.7
Smoking (%)		Gensini score	49.7 ± 42.7
Current	6 (5.3)	SYNTAX score	14.4 ± 13.1
Previous	65 (57.5)	Laboratory data	
Never	42 (37.2)	LDL-C (mg/dL)	97.6 ± 35.8
IHD (%)	91 (80.5)	HDL-C (mg/dL)	54.4 ± 17.3
VHD (%)	16 (14.2)	TG (mg/dL)	133.3 ± 73.4
OMI (%)	24 (21.2)	BS (mg/dL)	129.0 ± 37.4
CHF (%)	24 (21.3)	HbA1c (%)	6.31 ± 0.80
Hemodialysis (%)	7 (6.2)	CRP (mg/dL)	0.43 ± 0.86
Medication		Cr (mg/dL)	1.34 ± 1.99
RAS inhibitors (%)	55 (48.7)	eGFR (mL/min/1.73m <sup>2</sup> )	61.4 ± 22.7
β-blockers (%)	58 (51.3)	BNP (pg/mL)	106 ± 155
Diuretics (%)	31 (24.8)		
Nitrites (%)	31 (27.4)		
Ca antagonists (%)	48 (42.5)		
Statins (%)	73 (64.6)		
Antiplatelet drugs (%)	85 (75.2)		

Data are presented as mean ± standard deviation or n (%). HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus; IHD, ischemic heart disease; VHD, valvular heart disease; OMI, old myocardial infarction; CHF, chronic heart failure; RAS, renin-angiotensin system; BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate; AVI, arterial velocity pulse index; API, arterial pressure volume index; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, triglyceride; BS, blood sugar; HbA1c, hemoglobin A1c; CRP, C-reactive protein; Cr, creatinine; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

**3.2. Differences in AVI, API, and Gensini and SYNTAX Scores between Patients with and without Clinical Events**

The mean follow-up duration was 1752 ± 819 days (Table 1). Table 2 shows the frequency of clinical events. Seventeen subjects (15.0%) underwent elective PCI based on CAG results at the time of enrollment. MACEs were observed in 8 patients (7.1%), and 15 patients (13.3%) received RRV during the follow-up period. Patients who underwent elective PCI had significantly higher API and Gensini scores than those who did not (38.5 ± 12.6 vs. 31.3 ± 7.4, *p* = 0.001 and 69.6 ± 45.0 vs. 46.1 ± 41.6, *p* = 0.036, respectively) (Table 3 and Figure 2). This trend was the same for elective PCI and RRV and the composite of elective PCI, RRV, and MACE for the API and the Gensini and SYNTAX scores. In clinical cardiology, trials are conducted with composite endpoints as outcomes; however, distinguishing between endpoints related to revascularization using PCI and MACE, including CV death, nonfatal MI, nonfatal stroke, and hospitalization due to UAP, based on events from plaque rupture of atherosclerotic lesions is biologically possible. The results in Table 3 suggest that the noninvasive index, the API, rather than AVI, is comparable in value to invasively defined indices of coronary atherosclerosis, such as the Gensini and Syntax scores, for noninvasive evaluation. In contrast, the AVI and API were not significantly different between patients with and without MACE, RRV, hospitalization due to HF, or any of the events described in the upper column of Table 3.

Additionally, we performed receiver operating characteristics (ROC) analyses to assess the efficacy of using AVI and API as indicators of the need for elective PCI (Table 4). The area under the curve (AUC) for API was 0.653, which was significant (95% CI, 0.503–0.803; *p* = 0.045).

**Table 2.** Frequency of clinical events.

	Number (%)
Elective PCI	17 (15.0)
All-cause death	14 (12.4)
MACE	8 (7.1)
Cardiovascular death	1 (0.9)
Nonfatal myocardial infarction	1 (0.9)
Nonfatal stroke	3 (2.7)
Hospitalization due to UAP	3 (2.7)
Hospitalization due to HF	6 (5.3)
Repeated coronary revascularization (RRV)	15 (13.3)

PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events; UAP, unstable angina pectoris; HF, heart failure.

**Table 3.** Differences in AVI, API, and Gensini and SYNTAX scores between the patients with and without clinical events.

	Number (%)	AVI		API	
		Event (–)	Event (+)	Event (–)	Event (+)
All-cause death	14 (12.4)	34.0 ± 10.1	33.9 ± 12.0	32.5 ± 8.7	31.7 ± 8.9
MACE	8 (7.1)	33.8 ± 10.0	36.5 ± 14.0	32.3 ± 8.7	33.7 ± 9.8
HF	6 (5.3)	33.9 ± 10.4	34.8 ± 9.8	32.5 ± 8.8	30.0 ± 7.5
RRV	15 (13.3)	33.9 ± 10.4	34.5 ± 10.3	32.2 ± 8.7	33.8 ± 8.9
MACE + HF	13 (11.5)	33.6 ± 10.1	36.3 ± 11.7	32.5 ± 8.8	31.2 ± 8.1
MACE + HF + RRV	27 (23.9)	33.7 ± 10.2	34.8 ± 10.6	32.3 ± 8.8	32.6 ± 8.6
Elective PCI (ePCI)	17 (15.0)	33.9 ± 10.4	34.4 ± 10.1	<b>31.3 ± 7.4 *</b>	<b>38.5 ± 12.6 *</b>
All PCI (ePCI + RRV)	27 (23.9)	33.5 ± 10.4	35.5 ± 10.0	<b>31.2 ± 7.3 *</b>	<b>36.2 ± 11.5 *</b>
All PCI + MACE	32 (28.3)	33.6 ± 10.1	34.9 ± 10.8	<b>31.3 ± 7.3 *</b>	<b>35.1 ± 11.3 *</b>
All PCI + MACE + HF	39 (34.5)	33.2 ± 10.3	35.4 ± 10.3	31.2 ± 7.2	34.6 ± 10.8

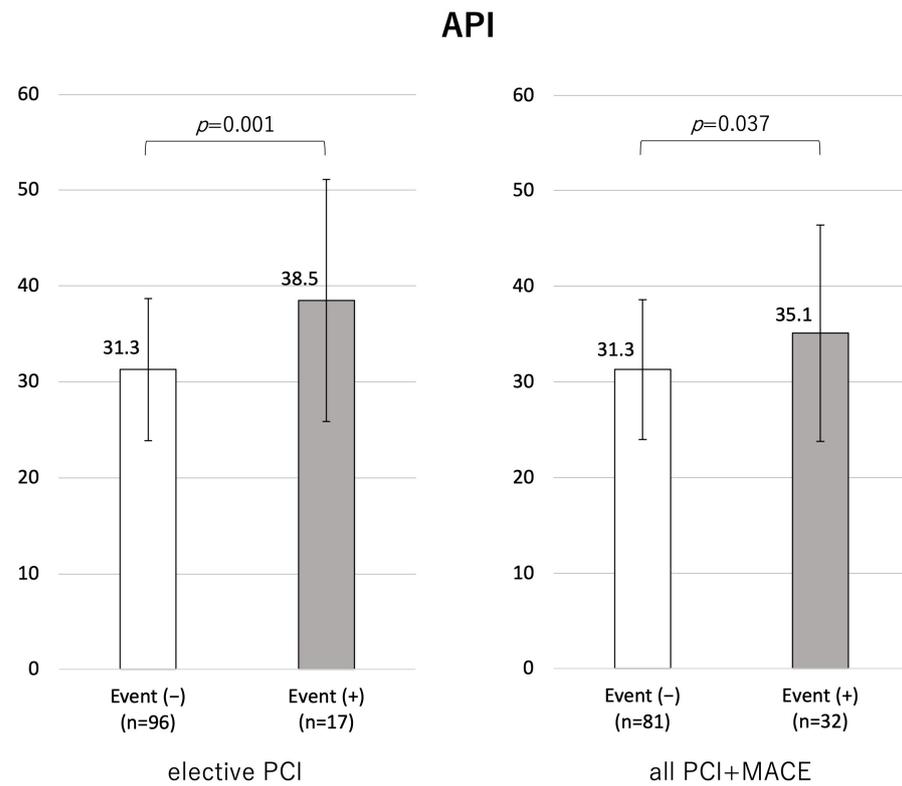
	Gensini score		SYNTAX score	
	Event (–)	Event (+)	Event (–)	Event (+)
All-cause death	47.4 ± 42.6	65.4 ± 42.2	13.6 ± 13.0	19.5 ± 13.3
MACE	49.6 ± 43.1	50.7 ± 40.9	14.3 ± 13.1	15.7 ± 13.5
HF	50.7 ± 43.1	31.5 ± 31.8	14.7 ± 13.3	9.0 ± 7.8
RRV	47.0 ± 42.3	67.0 ± 43.0	<b>13.4 ± 12.2 *</b>	<b>20.6 ± 17.4 *</b>
MACE + HF	48.5 ± 41.0	58.8 ± 55.4	14.2 ± 13.0	15.7 ± 14.3
MACE + HF + RRV	45.9 ± 40.3	61.7 ± 48.7	13.4 ± 12.1	17.5 ± 15.7
Elective PCI (ePCI)	<b>46.1 ± 41.6 *</b>	<b>69.6 ± 45.0 *</b>	13.7 ± 13.6	18.3 ± 9.0
All PCI (ePCI + RRV)	<b>43.7 ± 41.9 *</b>	<b>68.6 ± 40.5 *</b>	<b>12.6 ± 12.3 *</b>	<b>20.1 ± 14.1 *</b>
All PCI + MACE	<b>44.2 ± 42.1 *</b>	<b>63.6 ± 41.7 *</b>	<b>12.8 ± 12.5 *</b>	<b>18.4 ± 14.0 *</b>
All PCI + MACE + HF	<b>41.8 ± 39.3 *</b>	<b>64.5 ± 45.6 *</b>	<b>12.4 ± 12.3 *</b>	<b>18.1 ± 13.9 *</b>

MACE, major adverse cardiovascular events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization due to unstable angina; RRV, repeated coronary revascularization; HF, hospitalization due to heart failure; PCI, percutaneous coronary intervention. \* Red bold/italics indicate  $p < 0.05$ .

**Table 4.** Receiver operating characteristics (ROC) analyses between patients with and without elective PCI.

Event	Variables	AUC	95%CI	p-Value
Elective PCI	AVI	0.516	0.371–0.661	0.829
	API	0.653	0.503–0.803	0.045 *
	Gensini score	0.664	0.539–0.788	0.010 *
	SYNTAX score	0.643	0.530–0.755	0.013 *

AUC, area under the curve; CI, confidence interval. \*  $p < 0.05$ .



**Figure 2.** Differences in API between patients with and without clinical events.

**3.3. Differences in Each Variable between Patients with and without Clinical Events and Multivariate Analyses**

Table 5 shows the differences in each variable between patients with and without elective PCI. As previously mentioned, API and Gensini scores were significantly higher in patients who underwent elective PCI than in those who did not, and remained significantly associated with the risk of elective PCI in multiple logistic regression analysis (Table 6).

**Table 5.** Differences between patients with and without elective PCI.

	Event (-) (n = 96)	Event (+) (n = 17)	p-Value
Age (years)	71.3 ± 11.1	70.9 ± 7.9	0.907
Male (%)	72 (75.0)	11 (64.7)	0.376
BMI (kg/m <sup>2</sup> )	23.9 ± 4.5	23.9 ± 3.2	0.960
HT (%)	68 (70.8)	12 (70.6)	0.984
DL (%)	72 (75.0)	15 (88.2)	0.192
DM (%)	39 (40.6)	7 (41.2)	0.966
Current smoker (%)	6 (6.2)	0	0.367
IHD (%)	75 (78.1)	16 (94.1)	0.109
VHD (%)	14 (14.6)	2 (11.8)	0.554
OMI (%)	22 (22.9)	2 (11.8)	0.246
CHF (%)	22 (22.9)	2 (11.8)	0.246
Hemodialysis (%)	6 (6.3)	1 (5.9)	0.691
Medication			
RAS inhibitors (%)	49 (51.0)	6 (35.3)	0.231
β-blockers (%)	48 (50.0)	10 (58.8)	0.502
Diuretics (%)	26 (27.1)	2 (11.8)	0.147
Nitrites (%)	25 (26.0)	6 (35.3)	0.431
Ca antagonists (%)	40 (41.7)	8 (47.1)	0.679
Statins (%)	59 (61.5)	14 (82.4)	0.079

**Table 5.** Cont.

	Event (–) (n = 96)	Event (+) (n = 17)	p-Value
Antiplatelet drug (%)	71 (74.0)	14 (82.4)	0.344
SBP (mmHg)	138.5 ± 24.7	146.7 ± 15.9	0.187
DBP (mmHg)	70.4 ± 12.5	68.1 ± 11.6	0.497
HR (/min)	67.2 ± 10.4	62.7 ± 14.8	0.127
AVI	33.9 ± 10.4	34.4 ± 10.1	0.841
API	31.3 ± 7.4	38.5 ± 12.6	0.001 *
Gensini score	46.1 ± 41.6	69.6 ± 45.0	0.036 *
SYNTAX score	13.7 ± 13.6	18.3 ± 9.0	0.185
Laboratory data			
LDL-C (mg/dL)	97.5 ± 37.4	98.4 ± 26.3	0.924
HDL-C (mg/dL)	55.2 ± 17.9	49.7 ± 12.8	0.227
TG (mg/dL)	129.5 ± 74.8	154.9 ± 62.6	0.189
BS (mg/dL)	128.5 ± 36.5	131.7 ± 43.4	0.744
HbA1c (%)	6.29 ± 0.79	6.41 ± 0.88	0.558
CRP (mg/dL)	0.46 ± 0.90	0.23 ± 0.52	0.312
Cr (mg/dL)	1.39 ± 2.13	1.09 ± 0.82	0.556
eGFR (mL/min/1.73 m <sup>2</sup> )	61.7 ± 23.4	59.5 ± 19.0	0.709
BNP (pg/mL)	114.4 ± 165.2	60.8 ± 65.9	0.191

\* p < 0.05.

**Table 6.** Multiple logistic regression analysis of the risk of elective PCI.

	OR	95% CI	p-Value
Age	0.969	0.917–1.024	0.267
API	1.103	1.032–1.179	0.004 *
LDL-C	1.005	0.989–1.022	0.549
HbA1c	0.761	0.371–1.560	0.456
Gensini score	1.015	1.000–1.029	0.046 *

OR, odds ratio; CI, confidence interval. \* p < 0.05.

Table 7 shows the differences in each variable between participants with and without composite events of MACE, RRV, and hospitalization due to HF. Serum creatinine levels were significantly higher and eGFR values were lower in patients with these events than in those without. In the multivariate Cox proportional hazard regression analysis, the eGFR was independently associated with the risk of composite events of MACE, RRV, and hospitalization due to HF (Table 8).

**Table 7.** Differences in each variable between patients with and without composite events of MACE, HF, and RRV.

	Event (–) (n = 86)	Event (+) (n = 27)	p-Value
Age (years)	70.6 ± 11.2	73.3 ± 8.4	0.257
Male (%)	63 (73.3)	20 (74.1)	0.933
BMI (kg/m <sup>2</sup> )	24.1 ± 4.6	23.1 ± 3.1	0.301
HT (%)	65 (75.6)	15 (55.6)	0.046 *
DL (%)	69 (80.2)	18 (66.7)	0.144
DM (%)	36 (41.9)	10 (37.0)	0.656
Current smoker (%)	5 (5.8)	1 (3.7)	0.558
IHD (%)	67 (77.9)	24 (88.9)	0.164
VHD (%)	10 (11.6)	6 (22.2)	0.168
OMI (%)	19 (22.1)	5 (18.5)	0.692
CHF (%)	18 (20.9)	6 (22.2)	0.886

**Table 7.** Cont.

	Event (–) (n = 86)	Event (+) (n = 27)	p-Value
Hemodialysis (%)	3 (3.5)	4 (14.8)	0.055
Medication			
RAS inhibitors (%)	46 (53.5)	9 (33.3)	0.068
β-blockers (%)	45 (52.3)	13 (48.2)	0.705
Diuretics (%)	20 (23.3)	8 (29.6)	0.503
Nitrites (%)	22 (25.6)	9 (33.3)	0.431
Ca antagonists (%)	33 (38.4)	15 (55.6)	0.115
Statins (%)	58 (67.4)	15 (55.6)	0.185
Antiplatelet drug (%)	63 (73.3)	22 (81.5)	0.388
SBP (mmHg)	140.3 ± 24.1	138.0 ± 22.8	0.658
DBP (mmHg)	71.1 ± 12.5	66.6 ± 11.4	0.101
HR (/min)	65.9 ± 11.5	68.4 ± 9.9	0.301
AVI	33.7 ± 10.2	34.8 ± 10.6	0.618
API	32.3 ± 8.8	32.6 ± 8.6	0.896
Gensini score	45.9 ± 40.3	61.7 ± 48.7	0.092
SYNTAX score	13.4 ± 12.1	17.5 ± 15.7	0.156
Laboratory data			
LDL-C (mg/dL)	97.8 ± 37.4	97.3 ± 30.9	0.949
HDL-C (mg/dL)	55.0 ± 16.1	52.5 ± 21.0	0.512
TG (mg/dL)	136.9 ± 76.9	122.0 ± 60.9	0.360
BS (mg/dL)	128.9 ± 39.5	129.1 ± 30.3	0.980
HbA1c (%)	6.36 ± 0.83	6.12 ± 0.69	0.173
CRP (mg/dL)	0.39 ± 0.90	0.53 ± 0.70	0.464
Cr (mg/dL)	1.11 ± 1.51	2.07 ± 2.99	0.029 *
eGFR (mL/min/1.73 m <sup>2</sup> )	64.0 ± 20.7	52.8 ± 26.9	0.025 *
BNP (pg/mL)	91.0 ± 151.9	156.2 ± 158.1	0.060

\*  $p < 0.05$ .

**Table 8.** Multivariable Cox proportional hazard regression analysis of the risk of composite events of MACE, HF, and RRV.

	HR	95% CI	p-Value
Male	1.372	0.538–3.500	0.508
Age	1.022	0.972–1.074	0.390
LDL-C	1.002	0.991–1.014	0.714
HbA1c	0.550	0.289–1.046	0.068
eGFR	0.977	0.959–0.996	0.016 *
BNP	1.001	0.999–1.003	0.321

HR, hazard ratio; CI, confidence interval. \*  $p < 0.05$ .

#### 4. Discussion

We performed a single-center retrospective cohort study of patients admitted to our hospital for cardiac catheterization to investigate the relationship between noninvasive vascular indices and CV events. Most of this population had a history of IHD, HT, or DL and were considered to have a high risk of CV events with apparent or subclinical atherosclerosis. In the present study, we found a significant association between the API and indications for elective PCI, but not for AVI. In an additional analysis, we found that the group of patients who underwent PCI at enrollment or who underwent elective PCI based on CAG at enrollment ( $n = 46$ ) had significantly higher API compared to the other patient group ( $n = 67$ ) ( $34.7 \pm 9.4$  vs.  $30.8 \pm 7.9$ ,  $p = 0.017$ ). Based on these results, the API, but not AVI, could be a useful indicator for estimating the severity of coronary atherosclerosis requiring coronary interventional treatment.

The AVE-1500 is a recently developed device that can noninvasively evaluate arterial stiffness and endothelial dysfunction of the central arteries (AVI) and peripheral arteries (API) using cuff oscillometry and a single BP measurement. These indices were derived by

quantitatively analyzing the specific characteristics of the cuff oscillation waves detected at different cuff operating pressures. The relationship between the cuff pressure and arterial volume showed a sigmoidal pattern [12]. As atherosclerosis progresses, the change in arterial volume becomes gradual, and the inclination of the sigmoidal curve slows. Komine et al. reported an equation to approximate the sigmoidal curve and defined the reciprocal value of the slope of the curve as the API, which reflects the reactive vasodilation and stiffness of the peripheral arteries [13]. Consistent with this measurement principle, several studies have reported a significant correlation between API and PWV, a known arterial stiffness index [13,16]. Our previous studies reported that the API was significantly and independently associated with CV risk scores, such as the Framingham CV risk score and Suita score [15], and the severity of coronary atherosclerosis calculated using Gensini and SYNTAX scores [18]. Similarly, another study showed that the API was significantly higher in patients with moderate or greater coronary stenosis than in those without coronary stenosis [17]. These reports support the findings of this study, that the API was significantly higher in patients requiring coronary revascularization.

In contrast, the AVI is an index of the characteristics of pulse waves at cuff pressures higher than SBP. The pulse wave was detected as a composite of the ejection wave from the heart and the reflected wave from the periphery. As arterial stiffness progresses and vascular resistance increases, the amplitude of the reflected wave is enhanced, leading to an enhancement and steep descent of the latter systolic pulse waveform [10,24]. The AVI was defined as the value obtained by dividing the slope of the descending phase of the pulse wave by the slope of the rising phase [11]. Previous studies, including ours, have reported that the AVI is significantly associated with the augmentation index (AI) [15,16] and central BP [11,17,25]. In addition, significant negative correlations between the AVI and peak oxygen uptake in patients undergoing cardiac rehabilitation for cardiac diseases have been reported in other studies [26,27]. Based on the measurement principle and these results, the AVI can be considered as a vascular index that reflects central arterial stiffness and cardiac afterload. Our previous study reported that the AVI has a predictive value for the risk of composite events of MACE and hospitalization due to HF in cardiology outpatients [19]. Another study reported that the AVI was a strong predictor of the composite of all-cause death and rehospitalization for HF in patients admitted for acute HF [20]. Similar to existing vascular indices, such as PWV and CIMT, the AVI can be a predictive index of CV events. When comparing the API and AVI, owing to the measurement principle, the API quantifies the pressure–volume relationship of the brachial artery, whereas the AVI quantifies the velocity ratio of the ejection and reflection waves of the central artery. Therefore, regarding revascularization using PCI, the API is more specifically involved than the AVI.

However, in the present study, we found no significant differences in the AVI or API between subjects with and without CV events. One possible reason for this discrepancy may be the selection bias of the target patients. To determine the indications for invasive cardiac catheterization, noninvasive tests, such as echocardiography, treadmill exercise tests, stress cardiac scintigraphy, and coronary computed tomography angiography, are usually performed beforehand. Based on the results of these tests, patients with low CV damage may have been excluded from this study, which could explain why neither AVI nor API had a predictive value for the risk of CV events in our population. Another reason may be the low rate of CV events due to risk reduction by cardiac catheterization and guideline-directed medical therapy at the beginning of the follow-up in this study. We employed RRV as a clinical outcome to compensate for the low event rate, but did not detect a significant difference in the AVI or API between patients with and without CV events.

One study found that brachial-ankle PWV, an index of arterial stiffness, was an independent predictor of CV events in patients with treated hypertension, a history of coronary artery disease (CAD), and a BP < 130/80 mmHg [28]. This suggests that brachial-ankle PWV could potentially be used to predict repeat revascularization in patients with similar conditions, and the 2021 ESC prevention guidelines suggest that arterial stiffness metrics, such as AI, can predict CV events [29]. While the study does not specifically

mention repeat revascularization, these metrics may be used to predict such events, given their association with CV risk. However, although these metrics can provide valuable insights, they should be used in conjunction with other clinical assessments and patient histories for a comprehensive evaluation. Within the Subclinical Atherosclerosis section of the most recent guidelines published in 2022 by the Japan Atherosclerosis Society [30], the utility of vascular indices such as brain MRI (magnetic resonance imaging), CIMT, CAC (coronary artery calcification), PWV, CAVI (cardio-ankle vascular index), and ABI (ankle-brachial index) is discussed from the perspective of their contribution to the risk of existing atherosclerotic diseases. However, none of these indices adequately contribute to the risk of atherosclerotic disease. The distinctive feature of the API/AVI index lies in its use of cuff oscillometry, rendering it significantly more versatile than the existing vascular indices. By leveraging its noninvasive and repeatable measurement capabilities, it may reveal unique values that are not found in existing vascular indices.

Our study had several limitations. First, our population was relatively small and heterogeneous because it was selected from a single center. Second, this study was designed as a retrospective cohort and had a selection bias, as described previously. Third, our study did not evaluate the correlation of AVI and API with other conventional arterial stiffness indices. Despite these limitations, this is the first study to determine the potential usefulness of the API in estimating the need for coronary revascularization. The AVE-1500 can easily measure the AVI and API in a single BP measurement without requiring special techniques. If the predictive value of these indices for CV events is proven, they could be measured in a wide range of facilities as a screening test for arterial stiffness, allowing for the early diagnosis of subclinical atherosclerosis, which could lead to the prevention of life-threatening CV events. Therefore, the prognostic value of the AVI and API for CV disease needs to be confirmed in a well-designed prospective study involving larger populations, including healthy volunteers.

## 5. Conclusions

In conclusion, the API may be a useful indicator for estimating the severity of coronary atherosclerosis requiring revascularization in patients at a high risk of CV disease with apparent or subclinical atherosclerosis.

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