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REVIEW

Comparison of Predictive Ability of Arterial Stiffness Parameters Including Cardio-Ankle Vascular Index, Pulse Wave Velocity and Cardio-Ankle Vascular Index$_0$

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Abstract: Cardio-ankle vascular index (CAVI) was developed to reflect the stiffness of the arterial tree from the aortic origin to the ankle. This arterial stiffness parameter is useful for assessing the severity of cardiovascular disease (CVD) and its risk. However, compared to pulse wave velocity (PWV), the conventional gold standard of arterial stiffness parameter, there has been a concern regarding CAVI that there are fewer longitudinal studies for CVD. Furthermore, the accuracy of CAVI for atherosclerotic diseases compared to other parameters has not been well validated. This review article aims to summarize recent findings to clarify the predictive ability of CAVI in longitudinal studies. First, several large longitudinal studies have found that not only baseline CAVI but also CAVI changes during the observation period predict cardiovascular events. Second, CAVI may have superior discriminatory power for all-cause mortality and major adverse cardiovascular endpoints compared to PWV. Furthermore, one large longitudinal study found CAVI to be a stronger predictor for renal function decline compared to PWV as well as CAVI$_0$, a variant of CAVI that mathematically excludes BP dependence. Additionally, CAVI shows the properties that allow the elucidation of specific hemodynamics in aortic valve disease or hypovolemia. In conclusion, CAVI may be a modifiable arterial stiffness parameter not only for predicting and preventing atherosclerotic diseases but also for elucidating specific hemodynamic pathophysiology.

Keywords: cardio-ankle vascular index, pulse wave velocity, CAVI$_0$, longitudinal study, cardiovascular disease, renal function decline

Plain Language Summary

- Cardio-ankle vascular index (CAVI) is an arterial stiffness parameter in which the blood pressure dependence observed in pulse wave velocity (PWV) is eliminated.
- Many longitudinal studies revealed the independent contribution of CAVI for cardiovascular events.
- CAVI$_0$ is a variant of CAVI that theoretically corrects even more strongly for the dependence on blood pressure.
- CAVI may predict the development of atherosclerotic diseases more effectively than PWV and CAVI$_0$.

Preface

Arterial stiffness reflects the ageing and loss of elasticity in blood vessels, and is used as a predictor of cardiovascular disease (CVD).[1] The most commonly used arterial stiffness parameter is pulse wave velocity (PWV).[2] However, this parameter is inherently influenced by blood pressure (BP) at the time of measurement,[3] and may underestimate the degree of vascular dysfunction due to CVD risks other than hypertension. The cardio-ankle vascular index (CAVI) has been established to address this issue. CAVI reflects the stiffness of the whole arterial tree comprising the aorta, femoral artery and tibial artery.[4] The BP independence of CAVI has been confirmed both theoretically and

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experimentally.[3–5] CAVI can therefore clarify the intrinsic impact of BP on atherogenesis,[6] and has been reported to be associated positively with a number of CVD risk factors, severity of CVD and future cardiovascular (CV) events. Additionally, appropriate therapeutic interventions to reduce CAVI are expected to contribute to the prevention of future CV events.[7] However, there has been a concern regarding CAVI that there are fewer longitudinal studies for CV events compared to PWV. Moreover, a warning was issued that CAVI may lead to erroneous conclusions because it does not fully correct for BP dependence. Spronck et al[8] have proposed $CAVI_0$ as a variant of CAVI that theoretically corrects even more strongly for the BP dependence. The accuracy of these aforementioned arterial stiffness parameters has not yet been fully compared. Based on these backgrounds, this review article aims to summarize recent findings about CAVI in longitudinal studies for predicting atherosclerotic diseases. In addition, the predictive ability of the three arterial stiffness parameters (CAVI, PWV and $CAVI_0$) was compared.

CAVI as a Predictor of Cardiovascular Events

Table 1 shows large-scale longitudinal studies examining the predictive ability of CAVI in which there were more than 200 participants. In most studies, baseline CAVI was a predictor of future cardiovascular (CV) events or mortality, and was also associated with new-appearance of atrial fibrillation.[21]

Especially, some reports showed that the change in CAVI was also associated with CVD outcomes. Otsuka et al[10] demonstrated that persistent impairment of arterial stiffness was an independent risk for future CV events in 211 subjects with coronary artery disease. The study revealed that the incidence of CV events for 2.9 years was lower in the group with improved CAVI at 6 months compared to those without (Figure 1). Additionally, Saiki et al[20] also reported that the change in CAVI during the first year was associated with 3 point-major adverse cardiac events (MACE) in the 5-year prospective cohort trial enrolling 254 dyslipidemic patients. Furthermore, the annual change in CAVI throughout the observation period was significantly higher in subjects with CV events compared to those without (Figure 2). In other words, appropriate therapeutic interventions to reduce CAVI are expected to contribute to the prevention of future CVD events.

Measurement of the Three Arterial Stiffness Parameters

The methods for measuring arterial stiffness parameters cited in this review article are described.

CAVI and $CAVI_0$ are based on the stiffness index β and a wave equation derived from Newton's second law. CAVI is calculated by the following formula:[4]

$$\mathrm{CAVI} = \mathrm{a}\left\{2\rho \times \ln(\mathrm{Ps}/\mathrm{Pd})/\Delta\mathrm{P} \times \mathrm{PWV}^2\right\}+\mathrm{b}$$

where Ps is systolic blood pressure (SBP); Pd is diastolic blood pressure (DBP); ΔP is Ps - Pd; ρ is blood density; PWV is pulse wave velocity, and a and b are constants. On the other hand, $CAVI_0$ is calculated by the following formula:[8]

$$\mathrm{CAVI}_0 = 2\rho \times \mathrm{PWV}^2/\mathrm{Pd} - \ln(\mathrm{Pd}/\mathrm{Pref})$$

where Pref is reference pressure (ie, 100 mmHg).

There are several variants of PWV with different ranges of targeted vessels. Heart-ankle PWV (haPWV) and brachial-ankle PWV (baPWV) mainly cited in this article were calculated by the following formulas:[9]

$$\mathrm{haPWV} = \mathrm{Lha}/(\mathrm{Thb} + \mathrm{Tba})$$

$$\mathrm{baPWV} = (\mathrm{Lha} - \mathrm{Lhb})/\mathrm{Tba}$$

where Lha is the arterial path length from the aortic annulus to the midpoint of the right ankle cuff estimated by the subjects height, Thb is the time interval between the commencement of the second heart sound and the dicrotic notch on the right brachial arterial pressure wave, Tba is the "foot-to-foot" time interval between brachial and posterior-tibial arterial pressure waves, respectively, and Lhb is the arterial path length from the aortic annulus to the midpoint of right brachial cuff estimated by the subjects height.

Table 1 Summary on Association of CAVI with Cardiovascular Outcomes in Prospective Studies

References	Country	Population Characteristics	Mean Age (Years)	Baseline CAVI	Duration of Follow-Up	Outcomes	Incidence (%) (1000 Person-Years)	Prognostic Value	Cutoff Value
Kubota et al, 2011[9]	Japan	400 patients with CV risk or CAD history	63.2–73.9	Not described	27.2 months	CAD, stroke and death	54.0	HR of CVD was significantly higher in CAVI ≥ 10.0 group (HR: 2.25).	9.0
Otsuka et al, 2014[10]	Japan	211 CAD patients	65	9.87–10.05	2.9 years	Cardiac death, non-fatal MI, unstable AP, recurrent AP, requiring coronary revascularization or stroke	45.8	Persistently impaired CAVI was a significant independent predictor of CV events compared with improved CAVI at 6 months (HR: 3.3).	Not described
Laucevičius et al, 2015[11]	Lithuania	2106 MetS patients	53.83	7.92	3.8 years	MI, stroke or transient ischemic attack, and sudden cardiac death	11.6	CAVI was significantly associated with the occurrence of total CV events and MI.	7.95
Satoh-Asahara et al, 2015[12]	Japan	425 obese patients	51.5	7.6	5 years	AP, MI, stroke and arteriosclerosis obliterans	15.8	CAVI was a significant predictor of CV events (HR: 1.44 per 1 unit increase).	Not described
Sato et al, 2015[13]	Japan	1003 subjects with CV risk	62.5	9.25	6.7 years	MI and stable/unstable AP	13.4	CAVI was independently associated with future CVevent risk (HR: 1.126 per 1 unit increase).	Not described
Chung et al, 2015[14]	Taiwan	626 type 2 diabetic patients	64	8.8	4.1 years	Death, ACS, ischemic stroke, and any coronary, revascularization for CAD	38.2	Patients with CAVI ≥ 9.0 had greater CV events than those with CAVI <9.0 (OR: 1.23).	9.0
Gohbara et al, 2016[15]	Japan	288 patients with ACS	58–71	Not described	1.25 years	CV death, non-fatal MI, non-fatal ischemic stroke	52.8	Patients with CAVI ≥8.325 was an independent predictor of CV events (HR: 18.0) and nonfatal ischemic stroke (HR: 9.37).	8.325
Hitsumoto et al, 2018[16]	Japan	460 patients with CKD	74	9.7	60.1 months	Cardiovascular death, nonfatal MI, nonfatal ischemic stroke and heart failure hospitalization	39.5	A MACE was significantly higher in group CAVI ≥ 10 than in non-group CAVI < 10 (HR: 2.04).	9.7

(*Continued*)

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Table 1 (Continued).

References	Country	Population Characteristics	Mean Age (Years)	Baseline CAVI	Duration of Follow-Up	Outcomes	Incidence (%) (1000 Person-Years)	Prognostic Value	Cutoff Value
Kirigaya et al, 2019[17]	Japan	387 patients with ACS	64	8.4–9.0	62 months	CV death, ACS recurrence, heart failure hospitalization, or stroke	31.0	CAVI was an independent predictor of MACE (HR: 1.496) and CV death (HR: 2.204), but baPWV was not. The addition of CAVI to GRACE score enhanced NRI (0.337).	8.35
Miyoshi et al, 2021[18]	Japan	2932 patients with CV risk	63	Not described	4.9 years	CV death, nonfatal stroke, or nonfatal MI	5.7	CAVI predicted the primary outcome (HR: 1.38). The addition of CAVI to known CV risks enhanced NRI (0.254).	9.5
Murakami et al, 2021[19]	Japan	242 hemodialysis patients	60	8.64–9.64	6 years	All-cause mortality	26.2	CAVI was a significant predictor of mortality (HR:1.595 per 1 SD increase).	9.2
Saiki et al, 2021[20]	Japan	254 subjects with CV risk	64.8	9.56	5 years	CV death, nonfatal stroke or nonfatal MI	7.9	Change in CAVI during the first year tended to be an independent predictor of 3P-MACE (HR: 1.736, $p = 0.079$).	Not described
Nagayama et al, 2021[21]	Japan	5418 subjects receiving health screening	48	7.6–8.7	4 years	New-appearance of AF	1.0	CAVI ≥ 8.0 was an independent predictor of new-appearance of AF.	8.0
Sumin AN et al, 2021[22]	Russia	238 patients after elective CABG	56.5–62.0	Not described	5 years	CV mortality, MI, Stroke or transient ischemic attack, percutaneous coronary intervention, carotid endarterectomy, pulmonary embolism, hospitalizations for CVD	79.8	CAVI ≥ 9.0 was an independent factor associated with the combined endpoint (OR: 1.78)	9.0
Watanabe et al, 2021[23]	Japan	223 heart failure patients	58.0–69.0	7.31–9.62	Median 1623 days	Cardiac death or unplanned re-hospitalization for HF treatment, ischemic coronary events and all-cause mortality	58.5	CAVI ≥ 8.9 was an independent predictor of cardiac events (HR: 1.845).	8.9

Sato et al, 2021[24]	Japan	557 heart failure patients	65.6–73.0	Not described	Median 1415 days	Ischemic or hemorrhagic stroke	11.6	CAVI ≥ 9.64 was an independent predictor of stroke (HR: 3.599) compared to CAVI < 9.64.	9.64
Tabara et al, 2021[25]	Japan	7249 urban residents	59.8	7.91	Median 8.53 years	First-ever MI, coronary artery bypass grafting or angioplasty, Ischemic or hemorrhagic stroke	3.5	CAVI was significant predictor of incident CVD (HR: 1.23 per 1 unit).	Not described
Aiumtrakul et al, 2022[26]	Thailand	4898 subjects with CV risk	60.2–70.0	7.05–10.06	60 months	eGFR decline over 40%, eGFR less than 15 mL/min/1.73 m^2, doubling of serum creatinine, initiation of dialysis and death related to renal causes	15.7	Subjects with CAVI ≥ 9 had a 1.45-fold significant risk for the primary composite outcome and 1.72-fold risk for all-cause mortality, compared with subjects with CAVI < 8.	Not described
Rerkasem et al, 2022[27]	Thailand	347 adults with HIV	Aged ≥50	Not described	5 years	A composite of total deaths and hospitalizations due to myocardial infarction, coronary revascularization, stroke, and heart failure	25.9	Subjects with CAVI ≥ 8.0 was a independent predictor of MACE (HR = 2.11, 95% CI 1.06–4.20).	Not described

Abbreviations: CAVI, cardio-ankle vascular index; CV, cardiovascular; CAD, coronary artery disease; CVD, cardiovascular disease; HR, hazard ratio; AP, angina pectoris; MI, myocardial infarction; MetS, metabolic syndrome; ACS, acute coronary syndrome; NRI, net reclassification improvement; ACS, acute coronary syndrome; CKD, chronic kidney disease; OR, odds ratio; SD, standard deviation; MACE, major adverse cardiovascular events; GRACE, global registry for acute coronary events; baPWV, brachial-ankle pulse wave velocity; AF, atrial fibrillation; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

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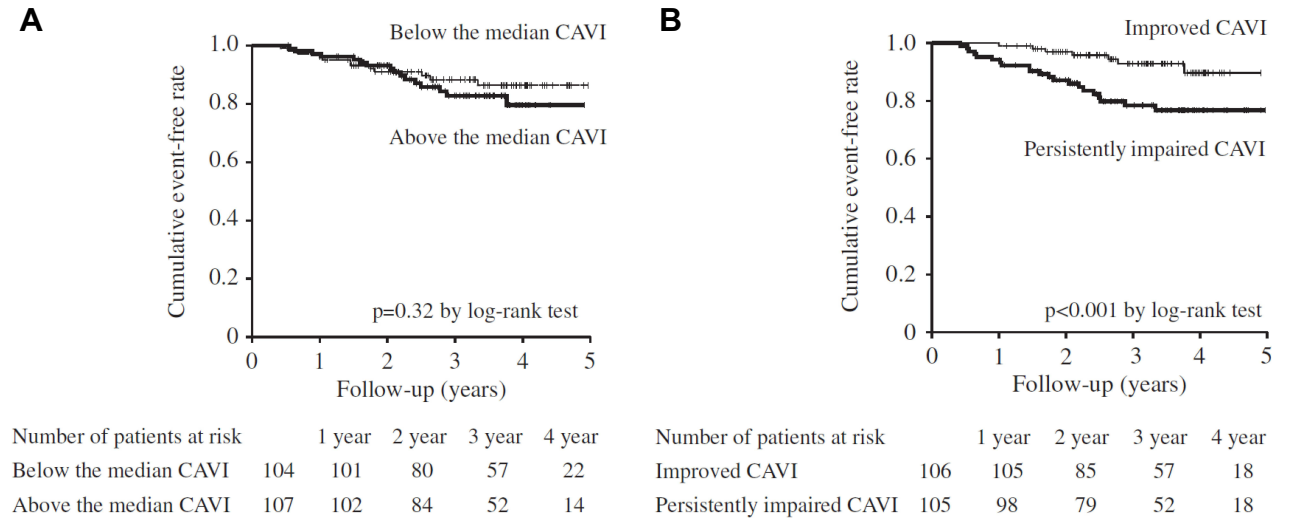


Number of patients at risk		1 year	2 year	3 year	4 year
Below the median CAVI	104	101	80	57	22
Above the median CAVI	107	102	84	52	14

Number of patients at risk		1 year	2 year	3 year	4 year
Improved CAVI	106	105	85	57	18
Persistently impaired CAVI	105	98	79	52	18

Figure 1 Kaplan–Meier curves of event-free survival according to CAVI. 211 patients with coronary artery disease (age 65±10 years, 118 men). (**A**) Comparison of Kaplan–Meier curves of event-free survival between patients above the median and below the median CAVI value in the first CAVI test. (**B**) Comparison of Kaplan–Meier curves of event-free survival between patients with persistently impaired CAVI and improved CAVI. Reprinted with permission from Otsuka T, Fukuda S, Shimada K et al. Serial assessment of arterial stiffness by cardio-ankle vascular index for prediction of future cardiovascular events in patients with coronary artery disease. *Hypertens Res*. 2014;37(11):1014–1020.[10]

Abbreviation: CAVI, cardio-ankle vascular index.

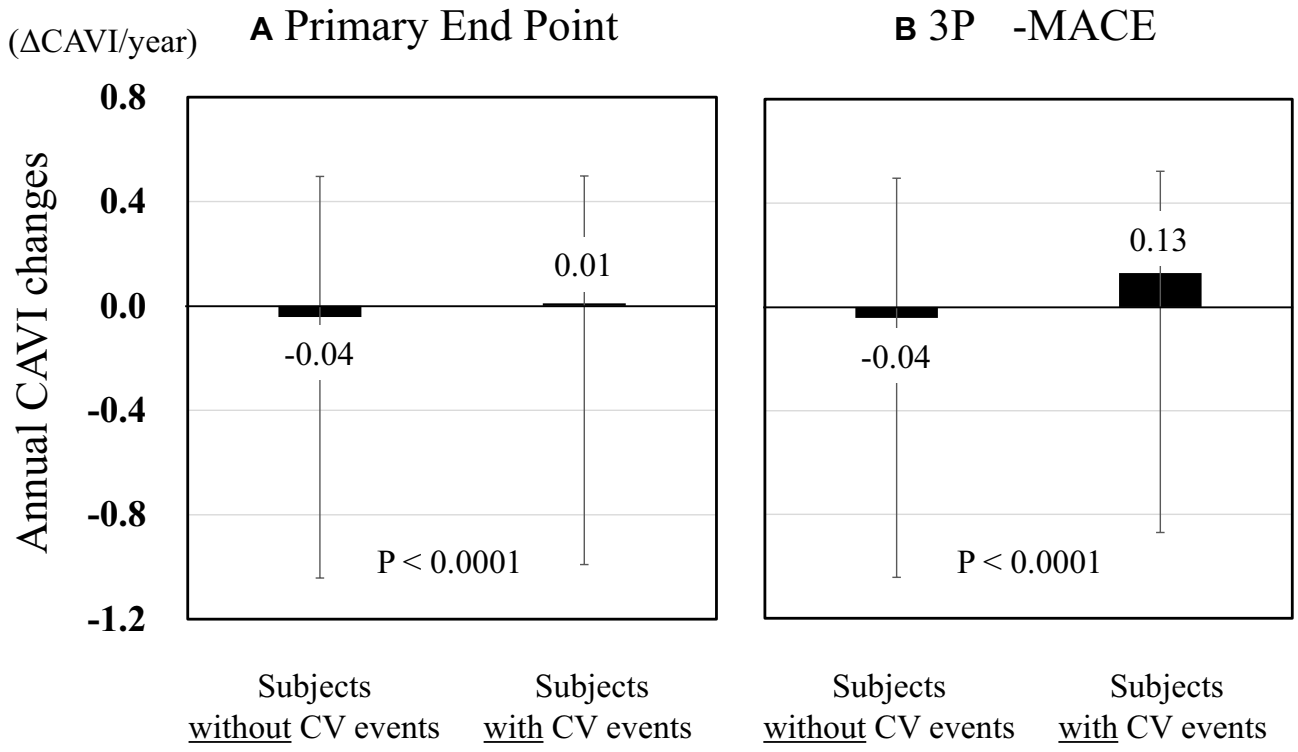


Figure 2 Differences in the annual CAVI changes in patients with or without CV events. 254 patients with CVD risk (age 64.8 ± 9.3 years, 118 men). (**A**) Primary end points and (**B**) 3P-MACE. Mean ± SD, Mann–Whitney *U*-test. Annual CAVI change was defined as the annual change in CAVI until the occurrence of any CV event or the end of 5-year study period. Primary end point: composite of cardiovascular death, sudden death of unknown origin, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, and heart failure requiring hospitalization. 3P-MACE: three-point major cardiac adverse events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke). Reprinted with permission from Saiki A, Watanabe Y, Yamaguchi T et al. CAVI-Lowering Effect of Pitavastatin May Be Involved in the Prevention of Cardiovascular Disease: Subgroup Analysis of the TOHO-LIP. *J Atheroscler Thromb*. 2021;28(10):1083–1094. Creative Common.[20]

Abbreviations: CAVI, cardio-ankle vascular index; CV, cardiovascular.

Comparison of the Predictive Ability of CAVI with Other Arterial Stiffness Parameters

This section lists longitudinal studies comparing the arterial stiffness parameters.

Comparison of CAVI and PWV

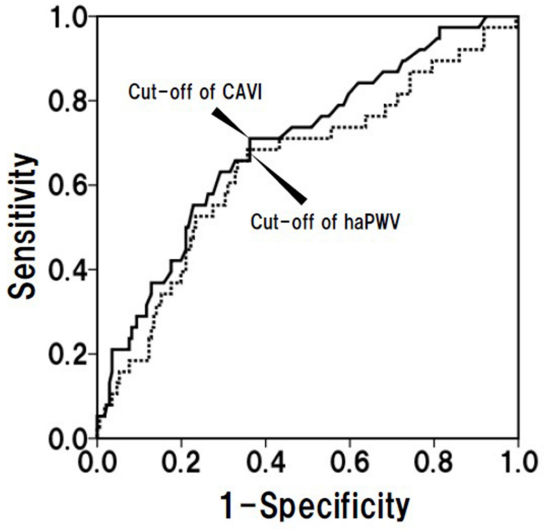
The Nagahama study,[25] a five-year longitudinal study of 8850 Japanese community residents, showed that baPWV and CAVI were similarly associated with future CVD events. However, it was concluded that the association was clearer for baPWV. On the other hand, several longitudinal studies have been reported showing the superiority of CAVI.

We have previously conducted a longitudinal study comparing CAVI with haPWV, an index incorporated into the CAVI structural equation including central and peripheral arteries.[19] Of the 209 hemodialysis patients, 38 died for 6 years. Resultantly, in the Cox-proportional hazards analyses, 1 SD increase in both parameters contributed almost equally to all-cause mortality [CAVI: hazards ratio (HR) 1.595, haPWV: HR 1.695]. On the other hand, receiver operating characteristic analysis showed that CAVI had better discriminatory power for all-cause mortality compared to haPWV (Figure 3).

Kirigaya et al[17] also compared the predictive ability of CAVI and baPWV in 387 consecutive patients with history of acute coronary syndrome (ACS) in a longitudinal study. Resultantly, MACE (CV death, recurrence of ACS, heart failure requiring hospitalization or stroke) occurred in 62 patients (16.0%) during a median follow-up of 62 months. Multivariate analysis suggested that mean CAVI was a significant predictor of MACE (HR = 1.494) and CV death (HR = 2.217), but baPWV was not.

Comparison of CAVI, PWV and $CAVI_0$ (Part 1)

Spronck et al[28] compared the three arterial stiffness parameters including haPWV, CAVI and $CAVI_0$ in 154 outpatients during an average of 2.53 years of observation, and the predictive ability of each parameter for the composite endpoint



Line	Cut-off	Sensitivity	Specificity	AUC (95% CI)	NRI (95% CI)	IDI (95% CI)
····· : haPWV	8.90	68.4%	64.3%	0.647 (0.544−0.750)	-	-
—— : CAVI	9.15	71.1%	63.7%	0.698* (0.605−0.791)	0.573† (0.235−0.911)	0.040† (0.019−0.060)

Figure 3 Discriminatory powers of arterial stiffness parameters for the prediction of all-cause mortality. Of the 209 hemodialysis patients (mean age 60 years, 129 men), 38 patients died during the 6-year period. Curves represent receiver-operating-characteristics analyses for discriminating the probability of all-cause mortality. The Youden's J statistic was used to select the optimum cutoff point of each arterial stiffness parameter. *P < 0.05, †P < 0.001 between haPWV and CAVI. Reprinted with permission from Dove Medical Press. Murakami K, Inayama E, Itoh Y et al. The Role of Cardio-Ankle Vascular Index as a Predictor of Mortality in Patients on Maintenance Hemodialysis. *Vasc Health Risk Manag*. 2021;17:791–798.[19]

Abbreviations: AUC, area under curve; NRI, net reclassification index; IDI, integrated discrimination improvement; 95% CI, 95% confidence interval; haPWV, heart-ankle pulse wave velocity; CAVI, cardio-ankle vascular index.

[death (n = 21) and heart failure requiring hospitalization (n = 18)] was examined. Resultantly, after adjustment for baseline heart failure status assessed by Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and systolic BP, only right sided haPWV (HR = 1.58) and right sided CAVI (HR = 1.44) remained predictive, whereas only $CAVI_0$ was not a significant factor.

Comparison of CAVI, PWV and $CAVI_0$ (Part 2)

Most renal impairment is attributable to renal atherosclerosis, and renal function can be quantified using estimated glomerular filtration rate (eGFR). The predictive ability of three arterial stiffness parameters for renal function decline was therefore validated.[29] A total of 27,864 Japanese urban residents without renal impairment at baseline who participated in two to eight consecutive (mean 3.5 ± 1.7 times) annual health examinations were studied, and 6.6% of them developed renal function decline (eGFR < 60 mL/min/1.73m^2).

The discriminatory power for renal function decline showed a decreasing trend of CAVI to haPWV to $CAVI_0$ (C-statistic: 0.740 vs 0.734 vs 0.726). The cutoffs defined using Youden's J statistic were CAVI 8.0, haPWV 7.23, and $CAVI_0$ 11.6 (Table 2A). The results of the analyses showed that CAVI was most strongly associated with renal function decline, followed by haPWV and $CAVI_0$, in that order (Table 2B). Furthermore, the contribution of each parameter (increase above cutoff or by 1 SD) to renal function decline was assessed using Cox-proportional hazards analysis (Table 3). If the arterial stiffness parameter is not significant in Model 1 [confounders: age, sex, BMI, proteinuria, systolic BP, fasting plasma glucose and high-density lipoprotein cholesterol (HDL-C)], it implies a lack of predictive ability beyond any metabolic parameters including BP, for renal function decline. Alternatively, if the arterial stiffness parameter is significant in Model 1 but not in Model 2 (confounders: treatments for hypertension, diabetes and dyslipidemia replaced by systolic BP, FPG and HDL-C in Model 1), it implies that the parameter depends on any metabolic abnormality. In other words, if the arterial stiffness parameter is not extracted as a significant factor in both Model 1 and 2, the parameter can be considered as having no value as a new risk factor. The results confirmed that only CAVI significantly contributed to the renal function decline in both models. On the other hand, haPWV and $CAVI_0$ were not necessarily significant contributors.

The cutoff is defined by the intersection point in the frequency distribution curves of arterial stiffness parameter in each of the two groups with and without renal function decline. Since arterial stiffness is strongly age-dependent, the cutoffs vary widely across age groups. In other words, the cutoff for predicting renal function decline is higher when restricted to older

Table 2 Comparison of Associations of Arterial Stiffness Parameters with Renal Function Decline

(A)					
	C-statistics (95% CI)	***p* value**	**Cutoff**	**Sensitivity**	**Specificity**
CAVI	0.740 (0.729–0.751)	<0.001	8.0	0.672	0.690
haPWV	0.734 (0.722–0.775)	<0.001	7.23	0.726	0.632
$CAVI_0$	0.726 (0.714–0.738)	<0.001	11.6	0.657	0.688
(B)					
	***p* value for C-statistics**	**NRI (95% CI)**	***p* value for NRI**	**IDI (95% CI)**	***p* value for IDI**
CAVI vs haPWV	0.038	0.159 (0.112–0.206)	<0.001	0.004 (0.002–0.006)	<0.001
CAVI vs $CAVI_0$	<0.001	0.477 (0.430–0.523)	<0.001	0.007 (0.006–0.009)	<0.001
haPWV vs $CAVI_0$	0.095	0.201 (0.154–0.248)	<0.001	0.003 (0.004–0.006)	0.023

Notes: 27,864 Japanese urban residents (median age 46.0 years) without renal impairment at baseline who participated in 2 to 8 consecutive (mean 3.5±1.7 times) annual health examinations. (A) Discriminatory powers and cutoff values of arterial stiffness parameters for renal function decline. Youden's J statistic was used to select the optimum cutoff point for each arterial stiffness parameter. (B) Comparisons of discriminatory power between arterial stiffness parameters for renal function decline. Adopted from reference.[29]

Abbreviations: CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval.

Table 3 Adjusted Hazard Ratios of Arterial Stiffness Parameters for Renal Function Decline

	CAVI		haPWV		$CAVI_0$	
	≥ 8.0	1 SD Increase	≥ 7.23	1 SD Increase	≥ 11.6	1 SD Increase
Model 1	1.182 (1.010–1.383)*	1.115 (1.039–1.197)*	1.120 (0.946–1.325)	1.144 (1.050–1.246)*	1.147 (0.985–1.336)	1.023 (0.968–1.080)
Model 2	1.188 (1.043–1.353)*	1.108 (1.041–1.179)*	1.238 (1.088–1.409)*	1.115 (1.054–1.179)*	1.151 (1.014–1.306)*	1.023 (0.974–1.074)

Notes: 27,864 Japanese urban residents (median age 46.0 years) without renal impairment at baseline who participated in 2 to 8 consecutive (mean 3.5±1.7 times) annual health examinations. *$p < 0.05$. Hazards ratios (95% confidence interval) estimated using Cox-proportional hazards analyses are shown. Renal function decline is defined as eGFR < 60 mL/min/1.73m^2 during the study period. Cutoff of each parameter was defined using Youden's J statistic. Model 1: Confounders include age, sex, BMI, proteinuria, systolic blood pressure, fasting plasma glucose and HDL-C. Model 2: Confounders include age, sex, BMI, proteinuria, and treatments for hypertension, diabetes and dyslipidemia. Adopted from reference.[29]

Abbreviations: CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity; SD, standard deviation; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

people. Therefore, when the cutoff of arterial stiffness parameter estimated in this study is treated for predicting renal function decline, the interpretation should only be targeted to the middle aged general Japanese population.

In summary, haPWV, a remarkable BP dependent arterial stiffness parameter, was more predictive for renal function decline than $CAVI_0$, which has been proposed to theoretically eliminate BP dependence. However, CAVI was most strongly associated with renal function decline compared with haPWV and $CAVI_0$. The major difference between CAVI and $CAVI_0$ is that CAVI employs β over a range of diastolic to systolic pressures, whereas $CAVI_0$ employs β at only diastolic pressure. This difference in structural formula might cause the divergence of predictive ability between CAVI and $CAVI_0$.

Comparison of the Predictive Ability for Hemodynamic Changes

Finally, the predictive ability of arterial stiffness parameters for the specific hemodynamic is discussed.

Mestanik et al[30] reported that cold pressor test caused a transient increase in CAVI, but not in $CAVI_0$. Since the cold pressor test inherently induces vascular smooth muscle contraction through sympathetic activation,[31] this result therefore means that CAVI, not $CAVI_0$, is influenced by short-term arterial smooth muscle contraction. This finding is consistent with our previous report revealing that CAVI can be reduced by α1- adrenergic receptor blocker, but not by β1 blocker.[3] In other words, CAVI accurately reflects not only organic stiffness (ie, arteriosclerosis) but also functional stiffness (ie, vascular smooth muscle contraction).

Plunde et al[32] reported that aortic valve replacement (AVR) for aortic valve disease increased CAVI. The prolonged pulse wave caused by preoperative aortic valve disease leads to an extended and larger arterial dilatation to comply with the systolic flow and consequently resulting in a modified measurement of arterial stiffness. Relief of obstruction by AVR therefore leads to true arterial stiffness can be measured by CAVI.[33] However, carotid-femoral PWV, which essentially lacks information on the aortic valve and ascending aorta, remained unchanged after AVR in the same population.

Nagasawa et al[34] used a rabbit model to assess the effect of changes in intra-aortic blood volume on arterial stiffness. When blood was removed, BP and blood flow in the common carotid artery gradually decreased. At that point, CAVI increased during blood removal, whereas haPWV conversely decreased slightly as the decreased BP. The finding suggests that CAVI, not haPWV, accurately reflects the acute response of conduit artery elasticity to changes in intra-aortic blood volume.

Conclusions

As discussed in this chapter, CAVI may predict the development of atherosclerotic diseases more effectively compared to PWV and $CAVI_0$, and is also useful for assessing the pathophysiology of hemodynamics in relation to left ventricular function and peripheral organ blood flow. This index is a suitable arterial stiffness parameter reflecting the Windkessel effect, and may therefore open up a new horizons of vascular function research.

Disclosure

The authors report no conflicts of interest in this work.

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