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Review

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New Horizons of Arterial Stiffness Developed Using Cardio-Ankle Vascular Index (CAVI)

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Arterial stiffness is recognized mainly as an indicator of arteriosclerosis and a predictor of cardiovascular events. Cardio-ankle vascular index (CAVI), which reflects arterial stiffness from the origin of the aorta to the ankle, was developed in 2004. An important feature of this index is the independency from blood pressure at the time of measurement. A large volume of clinical evidence obtained using CAVI has been reported. CAVI is high in patients with various atherosclerotic diseases including coronary artery disease and chronic kidney disease. Most coronary risk factors increase CAVI and their improvement reduces CAVI. Many prospective studies have investigated the association between CAVI and future cardiovascular disease (CVD), and proposed CAVI of 9 as the optimal cut-off value for predicting CVD. Research also shows that CAVI reflects afterload and left ventricular diastolic dysfunction in patients with heart failure. Furthermore, relatively acute changes in CAVI are observed under various pathophysiological conditions including mental stress, septic shock and congestive heart failure, and in pharmacological studies. CAVI seems to reflect not only structural stiffness but also functional stiffness involved in acute vascular functions. In 2016, Spronck and colleagues proposed a variant index $CAVI_0$, and claimed that $CAVI_0$ was truly independent of blood pressure while CAVI was not. This argument was settled, and the independence of CAVI from blood pressure was reaffirmed. In this review, we summarize the recently accumulated evidence of CAVI, focusing on the proposed cut-off values for CVD events, and suggest the development of new horizons of vascular function index using CAVI.

Key words: **Cardio-ankle vascular index, Arterial stiffness, Stiffness parameter β, Cardiovascular disease, Heart failure**

Introduction

Previous studies have demonstrated the significance of arterial stiffness as an indicator of arteriosclerosis and a predictor of cardiovascular (CV) events[1)]. Several parameters have so far been utilized for clinical assessment of arterial stiffness[2)]. Since pulse wave velocity (PWV) can be measured noninvasively and easily, this method has been used clinically for several decades as a representative arterial stiffness marker[3)]. PWV contributed greatly to recognition of the importance of measuring arterial stiffness. However, PWV is dependent on blood pressure at the time of measurement. Therefore, use of this index is not appropriate in studies that examine the effect of hypertension or the effect of antihypertensive drugs on intrinsic arterial stiffness. To overcome this problem, Hayashi[4)] proposed the stiffness parameter β, an index reflecting arterial stiffness of local arterial segment, which is not influenced by blood pressure at the time of measurement. Subsequently, this theory has been applied to a new arterial stiffness index called cardio-ankle vascular index (CAVI) developed in 2004[5)], and this index reflects the stiffness of the arterial tree from the origin of the aorta to the ankle. The CAVI equation was essentially derived from the stiffness parameter β, and the changes of the artery caliber in the equation during the cardiac cycle were obtained

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from Bramwell-Hill's equation, in which PWV is related to caliber changes[6]. The calculation formula for CAVI is given in eq. 1.

$$CAVI = a \times \left(2\rho \times \frac{\ln\left(\frac{Ps}{Pd}\right)}{\Delta P} \times haPWV^2 \right) + b \quad (eq.1)$$

Ps: systolic blood pressure, Pd: diastolic blood pressure, ΔP: Ps − Pd, haPWV: heart-ankle PWV

The principle of CAVI and the calculation formula have been described in our previous review[2]. Independence of CAVI from blood pressure at the time of measurement was also confirmed by clinical experiments[7].

CAVI has been widely used in clinical medicine for the last 15 years as an index for the evaluation of cardiovascular diseases (CVD) and risk factors. Increased CAVI is observed in persons with CVD and risk factors, and a number of studies have investigated the association between CAVI and the occurrence of CV events, as summarized in the review published in 2016[2]. In the last decade, research using CAVI has continued to increase in depth and scope. Prospective studies aiming to determine the optimal cut-off values for predicting CVD have been accumulated[8-18]. Furthermore, the interaction between left ventricular (LV) function and CAVI has been reported, indicating that CAVI reflects not only organic stiffness but also functional stiffness. These studies may lead to the development of a new field of cardiovascular interaction using CAVI.

On the other hand, Spronck *et al.*[19] proposed a variant index $CAVI_0$ in 2016. They claimed that $CAVI_0$ was an index truly independent from blood pressure while CAVI was not. Their report generated some controversies, but the issue was resolved. The independence of CAVI from blood pressure at the time of measurement was reaffirmed. We also add some comments in this review.

In this article, we review the new evidence that has been added in the last 5 years, and summarize the prospective studies aiming to determine the cut-off CAVI values for CVD events. Furthermore, we discuss the possibility of developing new horizons of vascular function index using CAVI.

Various Factors Affecting CAVI (Cross-sectional Studies)

A large number of cross-sectional studies have verified that numerous factors including arteriosclerotic diseases and coronary risk factors affect CAVI value. These studies are summarized in **Table 1**.

1. Age and Gender

Several studies have indicated that CAVI increases linearly with age[2, 20-22]. CAVI values are on average 0.2 higher in men than in women at all ages[21]. Moreover, male gender is an independent determinant of higher CAVI[22].

Age dependence of CAVI may be useful in the field of geriatric medicine. Nilsson[23] proposed a new concept of early vascular ageing (EVA) syndrome measured by carotid-femoral PWV (cfPWV) in European countries. Based on the definition of EVA, CAVI seems to be appropriate for its evaluation, since CAVI is independent of blood pressure. Furthermore, CAVI may also be used to evaluate the effects of anti-aging supplements on vascular aging. Resveratrol, an activator of sirtuin 1 (SIRT1)[24], and S-equol, a non-steroidal estrogen[25], are both reported to lower CAVI. The opposite phenotype of EVA is defined as super-normal vascular aging (SUPERNOVA). The use of CAVI may contribute to the search of protective mechanisms or new therapeutic targets against the aging process.

2. Arteriosclerotic Diseases

CAVI is known to be high in patients with various atherosclerotic diseases.

(a) Coronary Artery Disease

Several researchers have reported that CAVI is high in patients with coronary artery disease (CAD)[20, 21, 26, 27]. CAVI increases according to the number of stenotic vessels[26, 27]. Izuhara *et al.*[28] reported that CAVI, but not baPWV, is associated with the presence of carotid and coronary arteriosclerosis. In addition, Nakamura *et al.* reported that CAVI is an independent variable of coronary atherosclerosis severity, but mean intima-media thickness (IMT), maximum IMT and plaque score are not. CAVI correlates with coronary artery calcification[17, 29, 30]. A number of cross-sectional studies have determined the cut-off value of CAVI for the presence of CAD **(Table 2)**. CAVI ≥ 8.0 is associated with ≥ 50% coronary artery stenosis[31, 32], and CAVI ≥ 9.0 with ≥ 75% coronary artery stenosis[28]. In a study in Thailand, the cut-off value of CAVI for the presence of CAD is 8.0, and adding CAVI into the traditional risk score (RAMA-EGAT) improves the prediction of CAD incidence, increasing C-statistics from 0.72 to 0.85 and resulting in a net reclassification improvement (NRI) of 27.7% ($p < 0.0001$)[31]. From these findings, high CAVI is strongly associated with the presence of CAD, and the possible cut-off value is considered to be 8 or 9.

(b) Cerebral Infarction

CAVI values are high in patients with cerebral infarction[33]. CAVI is larger in patients with large artery atherosclerosis and small vessel occlusion than

Table1. Diseases and Coronary Risk Factors that Affect CAVI

Factors affecting CAVI	CAVI value	Main References
Age and gender		
Aging	↑	[2, 20, 21, 22]
Male	↑	[23, 24, 25]
Arteriosclerotic diseases		
Coronary artery disease	↑	[17, 20, 21, 26, 27, 28, 29, 30, 31, 32]
Cerebral infarction	↑	[33, 34]
Chronic kidney disease	↑	[35, 36, 37, 38]
Thickening of carotid intima-media thickness	↑	[20, 30, 39, 40, 41]
Coronary risk factors		
Hypertension	↑	[20, 36, 40, 42, 43, 44]
Diabetes mellitus	↑	[21, 32, 40, 54]
Diabetic retinopathy	↑	[55]
Diabetic neuropathy	↑	[56]
Diabetic nephropathy	↑	[29, 32, 39]
Postprandial hyperglycemia and high glycemic variability	↑	[57, 58, 59]
Dyslipidemia	↑	[66, 67]
Primary hypercholesterolemia	→	[66, 68, 69]
Uric acid	↑	[73, 74, 75, 76]
Only in females	↑	[77]
Nonalcoholic fatty liver disease	↑	[113]
Sleep apnea syndrome	↑	[78, 79]
Smoking	↑	[20, 81, 82]
Obesity and leanness		
Metabolic syndrome	↑ or →	[32, 84, 86, 87]
Obesity	↓	[83, 84]
Leanness	↑	[85]
Sarcopenia	↑	[89, 90, 91]
Cognitive decline	↑	[92, 93]
Autonomic nervous system		
Mental stress	↑	[94, 95, 97]
Sleep disturbance	↑	[96]
Septicshock	↓	[98]
Endocrine system		
Hypothyroidism	↑	[114]
Hypogonadism	↑	[115]
Collagen diseases		
Rheumatoid arthritis	↑	[99]
Systemic lupus erythematosus	↑	[100]
Psoriasis	↑	[116]
Tooth loss	↑	[117]

in controls[33, 34]. In the study of Saji *et al.*[34], the CAVI cut-off value for indicating silent brain infarct is 9.2, and that for white matter hyperintensities is 8.9.

(c) Chronic Kidney Disease

CAVI is higher in patients with chronic kidney disease (CKD) compared to patients with normal kidney function[35, 36], and is especially high in patients receiving hemodialysis[35, 37]. CAVI correlates with estimated glomerular filtration rate, urinary albumin creatinine ratio and cystatin C[35, 36, 38].

Table 2. Cross-Sectional Studies on the Association of CAVI with the Presence of Cardiovascular Disease

Author	Country	Subjects	Mean Age	Mean CAVI	Multivariate Analysis	What is Cut-off Value of CAVI for?	Cut-off Value	NRI
Nakamura *et al.* 2008 [26]	Japan	109 participants who underwent coronary angiography	58.0-67.6	Not described	CAVI was an independent variables of coronary atherosclerosis severity, but mean IMT, maximum IMT and plaque score were not.	Presence of CAD. (Significant coronary stenosis defined as ≥ 75%)	8.81	Not described
Takenaka *et al.* 2008 [118]	Japan	68 patients with end-stage renal diseases	60	7.8	Not described.	Presence of CVD.	7.55	Not described
Park *et al.* 2012 [32]	Korea	158 Normoglycemic Subjects and 373 subjects with abnormal glucose metabolism	56-58	7.5-7.9	Adjusted CAVI ≥ 8.0 was independently associated with significant coronary artery stenosis (OR 3.143).	Predicting ≥ 50% coronary artery stenosis.	8.0	Not described
Yingchoncharoen *et al.* 2012 [31]	Thailand	1,391 patients with a moderate to high risk for CAD	59	Not described	There was a correlation between CAVI and the prevalence of coronary stenosis after adjusting for traditional CAD risk factors (OR 3.29).	Presence of CAD. (Significant coronary stenosis defined as ≥ 50%)	8.0	0.277 ($p<$ 0.0001)
Gomez-Sanchez *et al.* 2015 [41]	Spain	500 subjects with intermediate level of CV risk factor	60.3	8.59	IMT and PWV maintained a positive association with adjusted CAVI.	Detecting mean IMT >0.90 mm and maxima IMT >0.90 mm.	8.95 (mean IMT > 0.90) (maxima IMT > 0.90)	Not described
Hitsumoto *et al.* 2019 [119]	Japan	405 patients with CV risk factors	64	8.7	CAVI was selected as independent factor for pulsatility index of common carotid artery as a subordinate factor.	High pulsatility index of common carotid artery (>1.60) as a risk value of stroke incidence.	9.1	Not described

CAVI, cardio-ankle vascular index; NRI, net reclassification improvement; IMT, intima-media thickness; CAD, coronary artery disease; CVD, cardiovascular disease; OR, odds ratio; CV, cardiovascular; PWV, pulse wave velocity

(d) Thickening of Carotid Intima-Media Thickness

IMT is associated with CAVI [20, 30, 39], and patients with carotid plaque have higher CAVI [40]. Spanish researchers have shown that IMT and PWV correlate positively with CAVI, and the cut-off CAVI values for detecting mean and maxima IMT >0.90 mm are 8.95 and 8.85, respectively [41].

3. Coronary Risk Factors

Overall, CAVI is high in patients with coronary risk factors. However, some conventional risk factors do not affect CAVI. In addition, the effect on CAVI differs depending on the type of treatment, even when the degree of risk factor improvement is similar. Accumulated studies reporting treatments and behavior modifications that affect CAVI are summarized in **Table 3**. CAVI may reveal the impact of each risk factor on arterial stiffness.

(a) Hypertension

Hypertension is well known to be a major risk factor for CVD. Numerous studies have reported high CAVI in hypertensive patients [20, 36, 40, 42, 43]. Logistic regression models show that 1-standard deviation increments in systolic (SBP), diastolic (DBP) and

mean blood pressure (MBP) indices contribute independently to high CAVI (≥ 90th percentile)[43]. Moreover, most of these reports show that CAVI has a lower correlation coefficient with blood pressure than PWV[5, 36, 40, 44]. Since PWV depends on blood pressure at the time of measurement and CAVI does not, the lower correlation of CAVI with blood pressure is reasonable. CAVI may accurately assess whether antihypertensive agents improve arterial stiffness.

Many studies have consistently reported that renin-angiotensin-aldosterone system inhibitors such as angiotensin II receptor antagonists lower CAVI[45-49]. Among calcium channel blockers (CCBs), amlodipine, the most commonly used L-type blocker, does not lower CAVI[45, 50-52]. On the other hand, CAVI is significantly reduced by the T-channel blocker efonidipine[50]. CAVI may indicate the differential effects of various types of CCBs on arterial stiffness. Recent studies also report that novel antihypertensive agents, mineralocorticoid receptor blocker and direct renin inhibitor, also lower CAVI[51-53].

(b) Diabetes Mellitus

CAVI is higher in patients with diabetes than in those without[21, 40], and CAVI is associated with HbA1c[32, 54]. Elevated CAVI (≥ 8.0) is independently associated with diabetes[54]. In patients with diabetes, CAVI is related to diabetic microvascular complications such as retinopathy, peripheral neuropathy and microalbuminuria[32, 39, 55, 56], and correlates with estimated glomerular filtration rate[29]. Furthermore, a few studies show the association of CAVI with postprandial hyperglycemia[57-59]. Tsuboi *et al.*[57] reported that 1-hour postprandial glucose levels are associated with increased CAVI in non-diabetic subjects.

The response of CAVI to glucose-lowering treatment depends on the type of agent used[60]. Alpha-glucosidase inhibitor[61] and rapid-acting insulin analog[58, 59] reduce CAVI through improvement of postprandial hyperglycemia. An insulin-sensitizer pioglitazone also decreases CAVI accompanying the adiponectin increasing effect[62]. Whether dipeptidyl peptidase 4 (DPP-4) inhibitors and sulfonylurea reduce CAVI remains controversial[63, 64]. Nagayama *et al.*[64] reported that glimepiride, a third generation sulfonylurea, improves CAVI and markers of insulin resistance and oxidative stress, but glibenclamide, a conventional sulfonylurea, has no such effects. A recent study shows that switching DPP-4 inhibitors to the sodium-glucose cotransporter-2 inhibitor tofogliflozin ameliorates CAVI that correlates with the level of advanced glycation end products[65]. These findings suggest that postprandial hyperglycemia, insulin resistance and oxidative stress may influence CAVI in patients with diabetes.

(c) Dyslipidemia

CAVI is higher in patients with dyslipidemia than in controls[66]. Using a trend test, Nagayama *et al.*[67] demonstrated linear relations between CAVI and all the conventional lipid parameters, and that these parameters contributed independently to high CAVI (≥ 90th percentile). Among their subjects with high low-density lipoprotein cholesterol (LDL-C), those with concurrent high triglycerides (TG) had higher CAVI, and receiver operating characteristic (ROC) analysis determined TG level of 93 mg/dl as the optimal cut-off value in predicting high CAVI **(Fig. 1)**. On the other hand, several researchers found no elevation of CAVI in patients with primary hypercholesterolemia[66, 68, 69]. On the contrary, CAVI is low in patients with familial hypercholesterolemia (FHC) due to "lipidosis" in the early stage, but CAVI increases after the development of inflammation, fibrous cap or complicated lesion. Therefore, a low CAVI in FHC does not indicate a low risk of future CVD[69].

Among cholesterol-lowering agents, pitavastatin lowers CAVI, which is associated with changes in malondialdehyde-LDL[70]. Triglyceride-lowering agents also decrease CAVI. Eicosapentaenoic acid decreases CAVI together with a reduction in oxidized LDL[71]. Yamaguchi *et al.*[72] reported that bezafibrate ameliorates CAVI accompanied by improvement of remnant-like particle cholesterol and diacron-reactive oxygen metabolites. In patients with dyslipidemia, coexisting abnormal glycolipid metabolism and oxidative stress may affect CAVI.

(d) Uric Acid

Uric acid as a risk factor for arteriosclerosis is controversial because uric acid is known to have both antioxidant[73] and pro-oxidative actions in the process of production[74]. Several researchers documented that uric acid increases arterial stiffness measured by CAVI[75, 76]. Nagayama *et al.*[76] reported that CAVI increases progressively with increasing serum uric acid tertile as shown in a multiple regression analysis, but CAVI tends to be high in male patients with lower serum uric acid. Zheng *et al.*[77] also reported a positive association between elevated serum uric acid and higher CAVI risk only in females.

(e) Sleep Apnea Syndrome

Sleep apnea syndrome is one of important risk factors of atherosclerosis. CAVI is also high in patients with sleep apnea syndrome[78, 79]. Alberto *et al.*[79] reported that multivariable-adjusted odds ratio of increased CAVI in patients with severe nocturnal intermittent hypoxia is remarkably increased when

Table 3. Effects of Various Treatments and Behavior Modifications on CAVI

Treatments and behavior modifications	CAVI value	Main References
Body weight reduction		
Calorie restriction (metabolic syndrome)	↓	Satoh N. Hypertens Res 2008 [84]
Calorie restriction (obesity with diabetes)	↓	Nagayama D. Obes Res Clin Pract 2011 [88]
Bariatric Surgery	→	Streese L. Obes Surg 2019 [126]
Glucose control		
Rapid-acting insulin analog	↓	Ohira M. Metabolism 2011 [58]
	↓	Akahori H. Diabetolo Int 2014 [59]
Dipeptidyl peptidase 4 inhibitors	↓ or →	Shigiyama F. J Diabetes Investig 2016 [63]
Sulfonylurea	↓ or →	Nagayama D. Int J Clin Pract 2010 [64]
Pioglitazone	↓	Ohira M. Diabetes Metab Syndr Obes 2014 [62]
α-glucosidase inhibitor	↓	Uzui H. J Diabetes Investig 2011 [61]
Sodium-glucose Cotransporter-2 Inhibitors	↓	Bekki M. Current Vascular Pharmacology 2018 [65]
Blood pressure control		
Ca blocker (L-type calcium channel blocker)	→	Sasaki H. J Atheroscler Thromb 2009 [50]
	→	Miyashita Y. J Atheroscler Thromb 2009 [45]
	→	Shibata T. Intern Med 2015 [51]
	→	Bokuda K. Hypertens Res 2018 [52]
Ca blocker (T-type calcium channel blocker)	↓	Sasaki H. J Atheroscler Thromb 2009 [50]
Renin-angiotensin-aldosterone system inhibitors	↓	Bokuda K. Vasc Health Risk Manag 2010 [46]
	↓	Miyashita Y. J Atheroscler Tromb 2009 [45]
	↓	Ogihara T. Exert Rev Cardiovasc Ther 2008 [47]
	↓	Miyoshi T. Clin Med Res 2017 [48]
	↓	Kiuchi S. Clin Pharmacol 2015 [49]
Mineralocorticoid receptor blocker	↓	Shibata T. Intern Med 2015 [51]
Direct renin inhibitor	↓	Miyoshi T. Open Heart 2017 [53]
	↓	Bokuda K. Hypertens Res 2018 [52]
Lipid control		
Statins	↓	Miyashita Y. J Atheroscler Thromb 2009 [70]
Eicosapentaenoic acid	↓	Satoh N. Hypertens Res 2009 [71]
Fibrates	↓	Yamaguchi T. J Atheroscler Thromb 2018 [72]
Nitroglycerin	↓	Shimizu K. Vasc Health Risk Manag 2016 [120]
	↓	Shimizu K. J Atheroscler Thromb 2017 [121]
Sarpogrelate hydrochloride	↓	Nagayama D. Int Heart J 2014 [122]
Anti-vascular endothelial growth factor inhibits	↓	Shiba T. Ophthalmologica 2016 [123]
Chemotherapy	↑	Shimizu N. J Clin Med Res 2017 [124]
Antiaging Supplements		
Resveratrol	↓	Imamura H. Int Heart J 2017 [24]
S-equol	↓	Usui T. Clin Endocrinol 2013 [25]
Smoking cessation	↓	Noike H. J Atheroscler Thromb 2010 [81]
Small amount of alcohol	↓	Nishiwaki M. Physiol Rep 2017 [127]
Exercise	↓	Alonso-Domínguez R. BMC Cardiovasc Disord 2019 [125]
Continuous positive airway pressure	↓	Kasai T. Am J Hypertens 2011 [80]

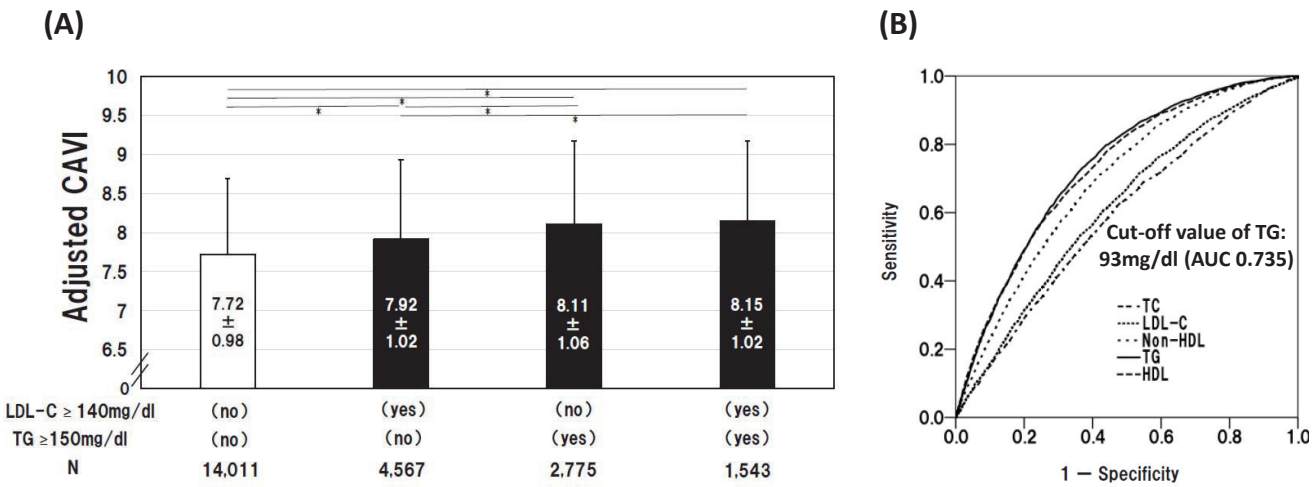

Fig. 1. Relationship of Adjusted CAVI with Types of Dyslipidemia and Lipid Parameters

(A) Adjusted CAVI for three types of dyslipidemia were compared. CAVI was adjusted by gender, age, SBP or BMI. Data are presented as mean ± SD. *$P < 0.01$, one-way ANOVA followed by Bonferroni multiple comparison test. (B) Discriminatory powers of lipid parameters for high CAVI (≥ 90th percentile). Curves represent ROC analyses for discriminating the probability of high CAVI. CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; ROC, receiver-operating-characteristics; SD, standard deviation[67].

body mass index (BMI) is 25 or higher. Furthermore, CAVI is reduced by continuous positive airway pressure therapy[80].

(f) Smoking

CAVI is higher in smokers than in non-smokers[81, 82]. Brinkman index correlates with CAVI[20]. CAVI increases significantly after smoking one cigarette[82], and improves after cessation of smoking[81].

4. Obesity and Leanness

The obesity paradox is observed in the relationship between CAVI and BMI. In studies of relatively healthy people, CAVI is negatively related to BMI[83, 84]. Young females with anorexia nervosa show signs of early arteriosclerotic damage indicated by CAVI[85]. On the other hand, patients with visceral fat accumulation and concurrent metabolic disorders have high CAVI, as described below.

(a) Metabolic Syndrome

Several studies have reported that CAVI is high in metabolic syndrome[84, 86]. Kawada *et al.* found[87] a trend of positive association between CAVI and BMI < 25, high blood pressure or hypertriglyceridemia. Park *et al.*[32] reported that visceral and epicardial fat, but not subcutaneous fat, show a positive association with CAVI.

Body weight reduction improves CAVI and many risk factors in patients with metabolic syndrome[84]. Nagayama *et al.*[88] observed that weight reduction using a calorie restriction diet decreases CAVI in obese patients with type 2 diabetes, and that change in visceral fat area is a significant independent predictor for change in CAVI. These findings suggest that subcutaneous fat may have a protective effect on blood vessels, whereas visceral fat may cause metabolic disorders, resulting in increased arterial stiffness. Further investigation is required.

(b) Sarcopenia

Kirkham *et al.*[89] reported that CAVI is high in sarcopenic persons and CAVI is a significant predictor of skeletal mass index in women. Im *et al.*[90] observed a positive association of muscle mass deficits with arterial stiffness in middle-aged men. Xue *et al.*[91] showed that CAVI is associated with frailty in older patients. These findings suggest that skeletal muscle loss not only promotes vascular aging, but atherosclerosis may also promote sarcopenia.

5. Cognitive Decline

Patients with lower Mini Mental State Examination (MMSE) scores have higher CAVI[92], and the annual decreases in MMSE score are significantly larger in patients with high CAVI[93]. CAVI ≥ 10.0 is associated with future cognitive dysfunction[93]. Elderly people with high CAVI may be at greater risk of cognitive decline.

6. Autonomic Nervous System

CAVI reflects not only organic stiffness but also functional stiffness. Therefore, CAVI may be affected by the activity of the autonomic nervous system.

(a) Mental Stress and Sleep Disturbance

CAVI is significantly higher in shift workers[94] and workers working long overtime hours[95]. There is an inverse relationship between sleep duration and CAVI in children[96]. Interestingly, Shimizu *et al.*[97] reported that people had higher CAVI shortly after experiencing a huge earthquake, even though they were in a hospital situated about 300 km from the epicenter of the earthquake. These findings suggest that mental stress also increases CAVI.

(b) Septic Shock

Nagayama *et al.* studied patients with sepsis and found that their CAVI increased after 1-week treatment without increase in blood pressure[98]. This finding suggests that CAVI may reflect sepsis-induced vascular alteration which is not indicated by blood pressure change.

7. Collagen Diseases

Spinelli *et al.*[99] reported that rheumatoid arthritis patients have significantly higher CAVI, and that CAVI is associated with anti-carbamylated proteins antibodies in a multivariate regression analysis. Carlucci *et al.*[100] found increases in CAVI, noncalcified plaque burden and vascular inflammation quantified by 18F-fluorodeoxyglucose-PET/CT in patients with systemic lupus erythematosus. CAVI may be useful in the diagnosis and quantification of vascular inflammation in patients with collagen disease.

CAVI as a Predictor of Cardiovascular Events

Several studies have investigated the association between CAVI and future CV events **(Table 4)**. The participants in all the studies were at high risk for CVD, such as having hypertension, diabetes, obesity, CKD, and a history of CVD. Nine studies were from Japan[8-16], and the other two were from Taiwan[17] and Lithuania[18]. In most studies, baseline CAVI was a predictor of future CV events. However, CAVI did not predict CV events in hemodialysis patients in one study[9]. In the metanalysis of Matsushita *et al.*[101], the pooled hazard ratio for composite CVD events per 1 standard deviation increment in CAVI was 1.20 (95% confidence interval 1.05-1.36) in four prospective studies[11, 12, 14, 18]. Otsuka *et al.*[10] reported that the incidence of CV events after 2.9 years was significantly higher in the group with no improvement in CAVI at 6 months than in the group with improvement. This seems to be an interesting report that clarifies the relationship between change in CAVI over time and the occurrence of CV events.

Many of the above studies in Asian countries determined the CAVI cut-off values for CVD events[8, 13-17], and they are summarized in **Fig. 2**. In patients with type 2 diabetes, metabolic disorders, CKD and past history of CAD, the cut-off values for CVD events were 9.0-9.7 [8, 14, 15, 17]. Chung *et al.*[17] reported that patients with CAVI ≥ 9.0 had greater risk of CV events than those with CAVI < 9.0 (odds ratio 1.23). Therefore, CAVI ≥ 9.0 seems to indicate increased cardiovascular risk. On the other hand, the cut-off values for CVD events were 8.325-8.35 in patients with acute coronary syndrome[13, 16]. Gohbara *et al.*[13] reported that CAVI > 8.325 was an independent predictor of CV events (hazard ratio 18.0). Kirigaya *et al.*[16] reported that CAVI was an independent predictor of major adverse cardiovascular events, but baPWV was not. Therefore, an optimal CAVI cut-off value of 8 may be recommended for secondary prevention of CV events.

In several cross-sectional studies, the cut-off CAVI value for the presence of CAD defined as coronary artery stenosis ≥ 50% was 8.0, as described before[31, 32]. In addition, a few studies reported that coronary artery stenosis or calcification occurred as CAVI increased above 8.0 [17, 21, 28-30]. These findings suggest that CAVI ≥ 8.0 may be associated with subclinical or asymptomatic atherosclerosis.

The Physiological Diagnosis Criteria for Vascular Failure Committee propose cut-off CAVI values of 8.0 and 9.0 (< 8 for normal, ≥ 8 and < 9 for borderline, ≥ 9 for abnormal) **(Fig. 3)**[102]. We also agree with this definition. In Japan, two large multicenter longitudinal studies, CAVI-J and Coupling Registry, registering 3000-50000 high-risk patients are ongoing[103, 104]. These studies may reveal whether adding CAVI to the cardiovascular risk scoring systems improves the accuracy of CV risk prediction.

The Possible Role of CAVI in Cardio-Vascular Interaction

The proximal large vessels such as the aorta store the LV stroke volume during systole, and the elastic forces of the aortic wall forward part of this volume to the peripheral circulation during diastole, resulting in a nearly continuous peripheral blood flow. This systolic-diastolic interplay is defined as the Windkessel function. The Windkessel function influences not only the peripheral circulation but also the reduction of

Table 4. Summary on Association of CAVI with Cardiovascular Outcomes in Prospective Studies

Author	Country	Subjects	Mean Age	Baseline CAVI	Duration of Follow-up	CV Outcomes	Incidence (%) (1,000 person-years)	Prognostic Value	Cut-off Value	NRI
Kubota *et al.* 2011 [8]	Japan	400 patients with metabolic disorders or past history of CAD	63.2-73.9	Not described	27.2 months	Coronary artery disease, stroke and death	54.0	Hazard ratio of CVD was significantly higher in CAVI ≥ 10.0 group (HR 2.25).	9.0	Not described
Kato *et al.* 2012 [9]	Japan	135 hemodialysis patients	60	9.7	63 months	Primary outcome: All-cause and CV mortalities. Secondary outcome: Fatal and non-fatal CV events.	52.2	Not significant.	Not described	Not described
Otsuka *et al.* 2014 [10]	Japan	211 CAD patients	65	9.87-10.05	2.9 years	Cardiac death, non-fatal MI, unstable angina pectoris, recurrent angina pectoris 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	Not described
Laucevičius *et al.* 2015 [18]	Lithuania	2,106 metabolic syndrome 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 (p=0.045) and MI (p=0.027).	7.95	Not described
Satoh-Asahara *et al.* 2015 [11]	Japan	425 obese patients	51.5	7.6	5 years	Angina pectoris, myocardial infarction, stroke and arteriosclerosis obliterans.	15.8	CAVI was a significant predictor of CV events (HR 1.44 per 1 unit increase).	Not described	0.164 (p=0.066)
Sato *et al.* 2015 [12]	Japan	1,003 subjects with CV risk factor	62.5	9.25	6.7 years	Myocardial infarction and stable/unstable angina pectoris.	13.4	CAVI was independently associated with future CV event risk (HR 1.126 per 1 unit increase).	Not described	Not described
Chung *et al.* 2015 [17]	Taiwan	626 patients with type 2 diabetes	64	8.8	4.1 years	Death, ACS, ischemic stroke and any coronary revascularization for coronary artery disease.	38.2	Patients with CAVI ≥ 9.0 had greater CV events than those with CAVI < 9.0 (OR 1.23).	9.0	Not described
Gohbara *et al.* 2016 [13]	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	Not described
Kusunose *et al.* 2016 [14]	Japan	114 patients with at least 2 CV risk factors	69	8.5	4.25 years	Cardiac death, non-fatal myocardial infarction/ coronary revascularization, acute pulmonary edema and stroke.	72.2	CAVI was not a significant predictor of CV events. CAVI was associated with a 5% per year decline in kidney function (HR: 1.52 per 1 SD increase).	9.2	Not described
Hitsumoto *et al.* 2018 [15]	Japan	460 patients with chronic kidney disease	74	9.7	60.1 months	Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke and hospital admission for heart failure.	39.5	A MACE was significantly higher in group CAVI > 10 than in non-group CAVI < 10 (HR 2.04).	9.7	Not described
Kirigaya *et al.* 2019 [16]	Japan	387 patients with ACS	64	8.4-9.0	62 months	CV death, recurrence of ACS, heart failure requiring hospitalization, or stroke.	31.0	CAVI was an independent predictor of MACE (HR 1.496) and cardiovascular death (HR 2.204), but ba PWV was not. The addition of CAVI to GRACE score enhanced NRI (0.337).	8.35	0.337 (p=0.034)

CAVI, cardio-ankle vascular index; CV, cardiovascular; CAD, coronary artery disease; CVD, cardiovascular disease; NRI, net reclassification improvement; MI, myocardial infarction; HR, hazard ratio; ACS, acute coronary syndrome; OR, odds ratio; SD, standard deviation; MACE, major adverse cardiovascular events; GRACE, global registry for acute coronary events

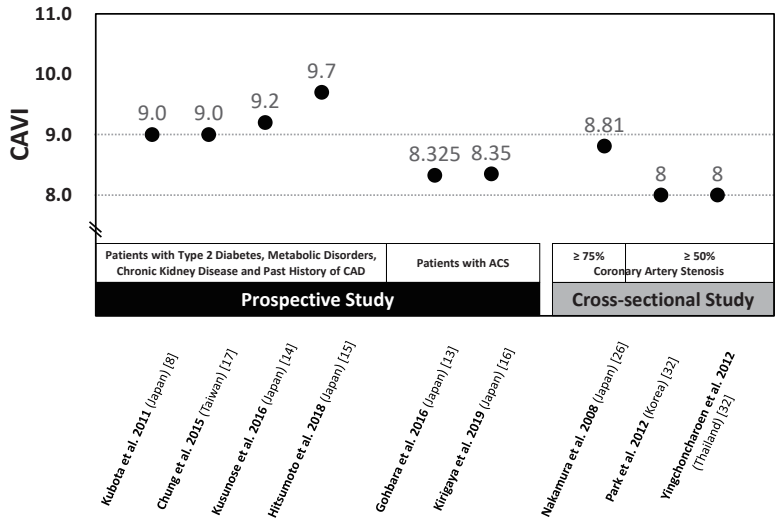

Fig. 2. Summary of Optimal Cut-off Values of CAVI for Coronary Artery Disease Reported by Prospective and Cross-sectional Studies

CAD, coronary artery disease; ACS, acute coronary syndrome.

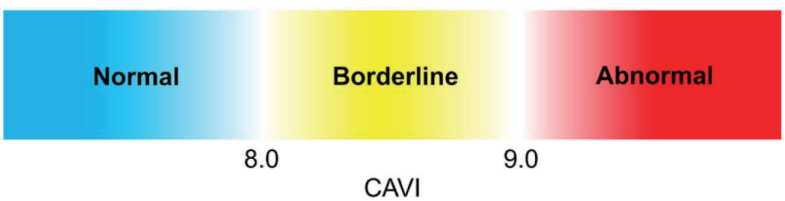

Fig. 3. Estimated Criteria for Medial Layer Dysfunction and its Border Zone of CAVI

CAVI cut-off values of 8.0 and 9.0 (<8 for normal, ≥ 8 and <9 for borderline, ≥ 9 for abnormal) are proposed by the Physiological Diagnosis Criteria for Vascular Failure Committee[102].

LV afterload. To assess the elastic properties of the aortic Windkessel, an index that theoretically indicate the "intrinsic" stiffness of the aortic wall is required. Therefore, CAVI, which is independent of blood pressure, may be a useful index reflecting this vascular function.

Schillaci *et al.*[105] reported that subjects with inappropriately high LV masses have higher CAVI values, but not higher PWV values. A few studies show a relationship between LV ejection fraction and CAVI[106]. These reports provide evidence that CAVI reflects afterload, and high CAVI leads to myocardial hypertrophy. Furthermore, Sakane *et al.*[107] reported that elevated CAVI is independently associated with LV diastolic dysfunction in patients with preserved systolic function. Other studies also found an association between high CAVI and LV diastolic dysfunction[106, 108]. These findings suggest that increased arterial stiffness may be a risk factor for LV diastolic heart failure, independent of blood pressure.

Since the LV function and morphology are closely related to arterial stiffness, treatments that improve CAVI may also improve LV function and prevent heart failure. Recently, Ogawa *et al.*[109] reported that CAVI and physical function assessed by 6-minute walk distance are complementary to each other in elderly heart failure patients. Development of new cardiac rehabilitation by monitoring CAVI is anticipated.

Difference in Blood Pressure Dependence between CAVI and Variant CAVI$_0$ and its Reason

CAVI represents blood pressure-independent arterial stiffness, as described above (eq, 1). In 2017, Spronck *et al.*[19] proposed a variant index termed CAVI$_0$, and the calculation formula is given in eq. 2.

$$CAVI_0 = 2\rho \times \frac{PWV^2}{Pd} - \ln\left(\frac{Pd}{P0}\right) \quad \text{(eq.2)}$$

P0: reference pressure (100 mmHg)

Spronck *et al.*[19] claimed that the conventional CAVI was blood pressure-dependent based on the following reasons. First, there is slight difference between

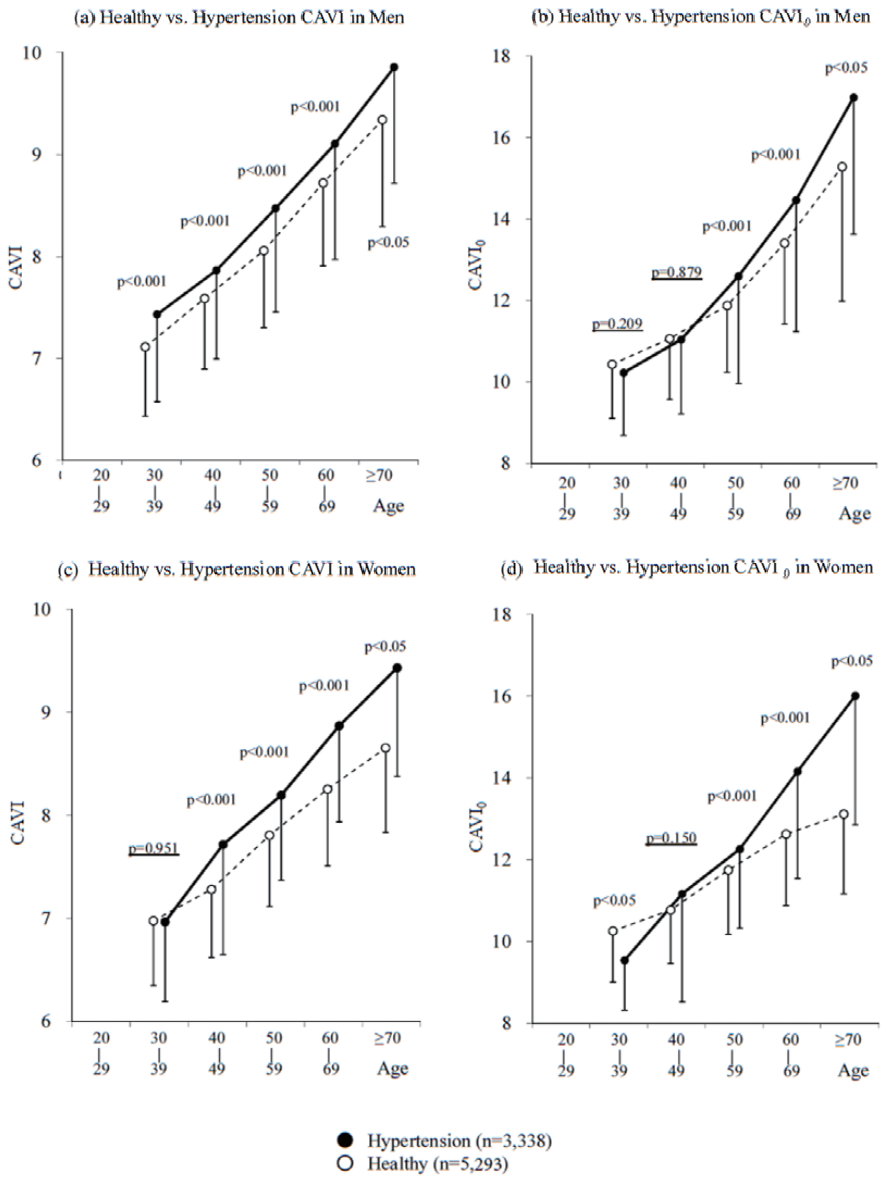

Fig. 4. Comparison of the Significant Differences of CAVI and CAVI0 between Healthy Group and Hypertensive Group Stratified by Age in Men (a and b) and Women (c and d)[112]

the β formula of Hayashi *et al.*[4] and that of Kawasaki *et al.*[110]. Second, ln(Ps/Pd)/ΔP in the CAVI formula is not equal to 1/Pd. Furthermore, they pointed out that the arterial stiffness value should be corrected with a reference pressure[19], and added "– ln(Pd/P0)" in the CAVI0 equation. They showed that CAVI was dependent on blood pressure based on mathematical simulation and concluded that CAVI leads to an erroneous conclusion in clinical studies[19]. In response to this claim, Shirai *et al.* reconfirmed the independency of CAVI from blood pressure at the time of measurement using measurements by the VaSera system and explained the reason for the difference between CAVI and CAVI0, both theoretically and in actual clinical studies[111]. In addition, it is known that PWV measured at the foot-to-foot interval differs from that measured at the top-to-top interval of the pulse wave during the cardiac cycle. The pulse transition time of PWV measured in CAVI using the VaSera system is not just the foot-to-foot period of the pulse wave at the pressure level of Pd, but almost the mid-to-mid period. Therefore, there was a concern that calculation of CAVI0 using only 1/Pd may yield unexplainable results. This concern was demonstrated in a cross-sectional study of a large population comparing CAVI with CAVI0, as shown in **Fig. 4** [112]. CAVI was higher in the hypertensive group than in the healthy group in both men and women, whereas CAVI0 was signifi-

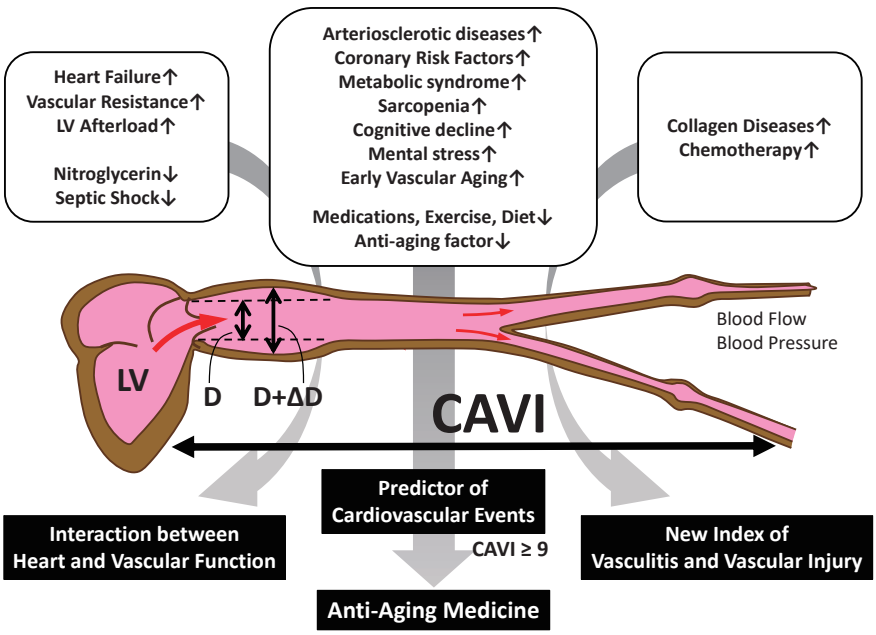

Fig. 5. CAVI not only Predicts Cardiovascular Events, but may also be Developed as a New Index of Vascular Functions

cantly lower in women aged 30-39 years in the hypertensive group compared to the corresponding healthy control group. This unexplainable result was thought to be due to the strong dependence of $CAVI_0$ on Pd. Incidentally, ln(Pd/P0) is actually negligible in clinical study.

Conclusions

CAVI is an index reflecting arterial stiffness without being influenced by blood pressure. Since its development in 2004, a large volume of evidence has validated CAVI as a parameter for clinical evaluation of arterial stiffness. In recent years, an increasing number of studies have investigated the association between CAVI and future CV events, and CAVI of 9 has been proposed to be the optimal cut-off value for predicting CVD in Asian patients. Apart from the conventional role of being a marker of cardiovascular events, recent research has shed light on the clinical use of CAVI as an index of arterial stiffness for evaluation of a wide range of cardiovascular disorders including vasculitis in collagen diseases, septic conditions and heart failure, as well monitoring of interventions for controlling cardiovascular risk factors, as shown in Fig. 5. This research trend may open up new horizons of vascular function index using CAVI.

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