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REVIEW

Brachial–ankle pulse wave velocity, cardio-ankle vascular index, and prognosis

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Background: Brachial–ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI) are indices of arterial stiffness, and several studies have used these indices. However, there is no comprehensive review of these parameters in the prognostic significance.

Methods: The aim of this study was to review the articles exploring the prognostic significance of these parameters. Articles demonstrating independent significance after multivariate analysis on the Cox proportional hazards model were defined as "successful." The success rate was compared using Fisher's exact test. In addition, multivariate logistic regression analysis was performed to explore the independent determinants of the success of prognostic prediction.

Results: The success rate of the baPWV articles (65.7% [46/70]) tended to be higher than that of the CAVI articles (40.0% [6/15]; *P*=0.083). Multivariate analysis demonstrated that log (number of patients) (OR 11.20, 95% CI 2.45–51.70, *P*=0.002) and dialysis population (OR 0.28, 95% CI 0.08–0.94, *P*=0.039) were positive and negative independent determinants of the success of prognostic prediction, respectively. In addition, after redefining two studies as the absence of arteriosclerosis obliterans (ASO) exclusion, baPWV (OR 3.36, 95% CI 0.86–13.20, *P*=0.083) and the existence of exclusion criteria of ASO (OR 3.08, 95% CI 0.96–9.93, *P*=0.060) exhibited statistical tendency in the multivariate analysis.

Conclusion: This study demonstrated that the number of study participants and dialysis population were the independent determinants of the success of prognostic prediction. This study also showed the importance of exclusion criteria of ASO when using these indices. In addition, a prospective large-scale study to confirm the superiority in the prognostic prediction of these indices is warranted.

Keywords: peripheral arterial disease, ankle–brachial index, diabetes, hemodialysis, cardiovascular events

Introduction

The burden of managing atherosclerotic diseases is increasing globally as economic development continues. Pulse wave velocity (PWV) and ankle–brachial index (ABI) have long been used to quantify arteriosclerosis and atherosclerosis,[1,2] and the clinical significance of each has been established.[3–5] Carotid–femoral PWV (cfPWV) is a representative marker of arterial stiffness, and several meta-analyses have demonstrated its independent prognostic predictability.[6–8] Vascular Profiler (VP; BP-203RPE, VP-1000, and VP-2000 series, Japanese product name "form") and VaSera (VS; VS-1000, VS-1500, VS-2000, and VS-3000 series) were first sold in Japan at the end of 1999[9,10] and in the first half of 2002,[11,12] respectively, which

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were new devices that can simultaneously measure brachial–ankle PWV (baPWV) and ABI. The specifications of VS changed to measure cardio-ankle vascular index (CAVI) and ABI in the first half of 2004, and it was continued to be sold.[13,14] Several English-language articles about both devices have been published. The first article discussing the prognostic predictability of the baPWV was published in 2005,[15] whereas the first article reporting that of the CAVI was published in 2009.[16] The number of articles detailing the prognostic predictability of baPWV rapidly increased after 2012, nearing 40 at the end of 2014.[17] Moreover, three meta-analyses and one rapid communication article using the data derived from one meta-analysis were also published.[18–21] As information accumulated, the baPWV threshold of 18 m/s was set as "high risk,"[3,22,23] whereas that of 14 m/s was set as "middle risk"[22] in the related guidelines. Five articles reported the prognostic significance of baPWV and CAVI in the same population.[24–28] However, no studies have comprehensively discussed the differences in prognostic predictability among those indices.[29] Therefore, this study aimed to identify articles that researched the prognostic predictability of both indices and compare the success rate wholly and in each category. Moreover, this review also aimed to explore the independent predictors of the success of prognostic prediction.

Methods

Identifying and defining articles

The concept and measurement method of baPWV and CAVI are available elsewhere.[10,14,22] The articles identified in this study were written in English (at least in the abstract) and indexed to PubMed or released publicly on the Internet. Each was obtained by the end of April 2018. Figure 1 shows the selection process of the objective studies. The PubMed search was performed using the related keywords such as "pulse wave velocity," "brachial–ankle pulse wave velocity," "cardio-ankle vascular index," "arterial stiffness," and "ankle–brachial index." Longitudinal studies that discussed the prognostic predictability of both indices were identified. End points included all-cause mortality (ACM), cerebrovascular–cardiovascular mortality (CCVM), cerebrovascular–cardiovascular events (CCVE), ischemic heart disease (IHD), major adverse cardiac events, and heart failure. When the other end points such as peripheral arterial disease (PAD) were included, they were explained additionally (Tables 1–3). Studies of functional prognosis such as a decline in cognitive function, kidney function, or activities of daily living were not included. Three meta-analyses and one rapid communication article detailing prognostic predictability of baPWV were excluded.[18–21] Longitudinal studies that did not include baPWV or CAVI as a prognostic variable were also excluded.[30–37]

Moreover, among the interventional studies in which those indices were measured, those that did not research their prognostic significance were also excluded because of the discrepancy in the research purpose.[38,39] One study reporting perioperative adverse events was also excluded.[40] Furthermore, one study that demonstrated the significance of baPWV using a Kaplan–Meier analysis (log-rank test, *P*<0.0001) was excluded because of considerable difficulty in adopting the Cox proportional hazards model, as the

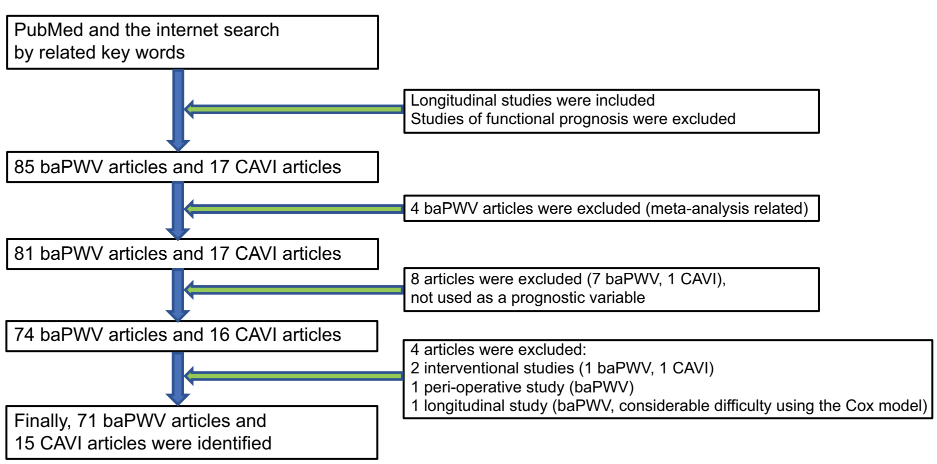

Figure 1 A flowchart of identifying prognostic studies of baPWV and CAVI articles.
Abbreviations: baPWV, brachial–ankle pulse wave velocity; CAVI, cardio-ankle vascular index.

Kaplan–Meier curves apparently showed nonproportional changes in the event rates.[41] Finally, a total of 71 baPWV articles and 15 CAVI articles were identified. The identified studies were categorized according to patient characteristics and the presence or absence of the clarified exclusion criteria of lower extremity (LE)-arteriosclerosis obliterans (ASO)/PAD. Any criteria such as "other vascular diseases" were not defined as the exclusion criteria of LE-ASO/PAD in this study. The studies demonstrating independent prognostic predictability of those indices on a multivariate Cox proportional hazards model or multivariate logistic regression model were defined as "successful." The studies showing significance on only Kaplan–Meier analysis (log-rank test) and/or not demonstrating statistical significance on a multivariate Cox proportional hazards model were defined as "failed." Comparisons between baPWV and CAVI were performed in all included articles, in the presence or absence of the clarified exclusion criteria of LE-ASO/PAD, in the population of dialysis (hemodialysis and peritoneal dialysis) or other than dialysis, and in the articles discussing both indices in a same cohort. However, one article studying both baPWV and CAVI in the same patient cohort did not describe the prognostic significance of baPWV as a primary end point. As such, that study was excluded from the statistical analysis as a baPWV article because the independent prognostic significance of baPWV for the primary end point was not clarified.[28] Moreover, because of the relatively ample number of baPWV articles, the studies with or without the clarified exclusion criteria of LE-ASO/PAD only among baPWV articles were compared to confirm the effect on success rate. Furthermore, multivariate logistic regression analysis was performed to explore the independent factors of the success of prognostic prediction.

Statistical analyses

Statistical analyses were performed using EZR (EZR on R commander version 1.33, September 1, 2016).[42] All comparisons between groups were performed using Fisher's exact test. However, a statistical analysis was not performed among the five articles that simultaneously studied baPWV and CAVI because of the too small sample and of the heterogeneity in the condition.[24–28] Moreover, logistic regression analysis was performed to explore the independent determinants of the success of prognostic prediction (success =1, failure =0). The following covariates were analyzed in the univariate analysis: baPWV or CAVI (baPWV =1, CAVI =0), presence of the clarified exclusion criteria of LE-ASO/PAD (yes =1, no =0), dialysis population (yes =1, no =0), follow-up period (years), age (years), male gender (%) in the study cohort, and log-transformed number of patients (log NoP). The number of patients was log transformed because of skewed distribution. In this analysis, the mean values of the patients' age and follow-up years were primarily used, and if not available, median values were used. The value of the mean/median patient age was missing in two studies.[43,44] The proportion of gender was also missing in one study.[44] Nevertheless, the analysis was performed without these missing data. The covariates whose P-value was ≤0.2 in the univariate analysis were entered into the multivariate model. Furthermore, reanalysis was performed by redefining two studies as the absence of LE-ASO/PAD exclusion,[27,45] because these studies were considered to insufficiently exclude LE-ASO/PAD patients (symptomatic PAD only). P-values of ≤0.05 were considered statistically significant, whereas P-values of $0.05<P\leq0.10$ were considered to have a statistical tendency.

Results

All articles

A total of 70 articles on baPWV[15,24–27,43–107] and 15 articles on CAVI[16,24–28,108–116] were identified. Table 1 presents a summary of these articles. The success rate of independent prognostic predictability of the baPWV articles (65.7% [46/70]) tended to be higher than that of the CAVI articles (40.0% [6/15]; P=0.083; Figure 2).

Articles clarifying the exclusion criteria of LE-ASO/PAD

Table 2 presents the detailed information about the articles in this category. In this category, the success rates of baPWV and CAVI articles were 75.9% (22/29) and 57.1% (4/7), respectively (P=0.37). After excluding two studies that insufficiently excluded LE-ASO/PAD patients,[27,45] the success rates of baPWV and CAVI articles were 81.5% (22/27) and 66.7% (4/6), respectively (P=0.58).

Articles lacking or not clarifying the exclusion criteria of LE-ASO/PAD

In this category, the success rates of baPWV articles and CAVI articles were 58.5% (24/41) and 25% (2/8), respectively (P=0.12). After adding two studies that insufficiently excluded LE-ASO/PAD patients[27,45], the success rates of baPWV articles and CAVI articles were 55.8% (24/43) and 22.2% (2/9), respectively (P=0.14).

Table 1 A summary of the prognostic predictability of all examined baPWV and CAVI articles

Articles	Index	Result	Exclusion of ASO/PAD in the LE	Device	Population	Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Comments
Tomiyama et al[15]	baPWV	Successful	No	VP	ACS	215	63	77.7	2.2	CCVM	
Yamamoto et al[16]	CAVI	Failed	Yes	VS	Community-dwelling elderly	117	80	31.1	4	ACM	The mortality rate did not differ between those with CAVI ≥10 and CAVI <10
Kato et al[24]	baPWV, CAVI	baPWV Kaplan–Meier, CAVI failed	No	VS	Hemodialysis	194	64	65.5	3.3	ACM, nonfatal CCVE	ABI succeeded significantly
Kato et al[25]	baPWV, CAVI	baPWV successful, CAVI failed	Yes	VS	Hemodialysis	135	60	67.4	5.3	CCVM	
Otsuka et al[26]	baPWV, CAVI	baPWV failed, CAVI successful	Yes	baPWV not described, CAVI VS	IHD with impaired CAVI	211	65	55.9	2.9	CCVE	CAVI at the first occasion did not succeed
Kusunose et al[27]	baPWV, CAVI	baPWV Kaplan–Meier, CAVI failed	Yes	baPWV VP, CAVI VS	Outpatients with two or more risk factors	114	69	78.1	4.3	MACE	ABI=1.01±0.17 (SD)
Gohbara et al[28]	CAVI	Successful	Yes	VS	IHD, ACS	288	65	82.3	1.3 (median)	CCVE	
Yoshida et al[43]	baPWV	Failed	Not clarified	VP	Diabetes	783	30–75	66.6	5.5	CCVE	
Tokitsu et al[44]	baPWV	Failed	No	VP	IHD	401			2.9	CCVE	
Lau et al[45]	baPWV	Failed	Yes	VP	Diabetes	151	61	40.4	5.1	CCVE	
Kitahara et al[46]	baPWV	Successful	Yes	VP	Hemodialysis	671	59	64.9	2.8	ACM, CCVM	
Ninomiya et al[47]	baPWV	Successful	Yes	VP	General population	2,916	60	42.7	7.1	CCVE	
Maeda et al[48]	baPWV	Successful	Yes	VP	Diabetes	3,628	61	59.7	3.2	ACM, coronary events, cerebrovascular events	For the CCVEs, adjusted by modified FRS
Kuroiwa et al[49]	baPWV	Successful	Yes	VP	Community-dwelling elderly	450	77	67.3	3	ACM	A multivariate logistic regression analysis was performed
Seo et al[50]	baPWV	Successful	No	VP	IHD	372	65	63.2	2.2	MACE	
Chang et al[51]	baPWV	Successful	No	VP	Diabetes	452	68	54.2	5.8	ACM, CCVE	
Sheng et al[52]	baPWV	Successful	Yes	VP	Community-dwelling elderly	3,876	68	44.2	5.9	ACM, death of non-cerebrovascular–cardiovascular cause	Cox regression: the top decile vs whole population

(*Continued*)

Table 1 (*Continued*)

Article	Index	Result	Exclusion of ASO/PAD in the LE	Device	Population	Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Comments
Katakami et al[53]	baPWV	Successful	Yes	VP	Diabetes	1,040	59	65.0	7.5 (median)	CCVE + PAD (ABI <0.9)	
Ki et al[54]	baPWV	Successful	No	VP	IHD	372	65	63.2	2.2	MACE	
Kim et al[55]	baPWV	Successful	No	VP	Stroke	1,765	65	62.2	3.3	ACM, CCVM	
Kawai et al[56]	baPWV	Successful	Not clarified	VP	Hypertension	338	61	54.7	6.5	CCVE	An existence of ASO defined by ABI of <0.9 is unlikely because of the ABI value (1.13±0.00 [SE]). 118 subjects with past history of CVD and/or stroke were excluded
Nagai et al[57]	baPWV	Successful	Not clarified	VP	Outpatients	274	71	41.6	3.4	CCVE	
Takashima et al[58]	baPWV	Successful	Yes	VP	General population	4,164	59	37.2	6.5 (median)	CCVE	
Yoon et al[59]	baPWV	Successful	Not clarified	VP	CKD	117	54	61.5	1.0 (median)	CCVE	
Ishisone et al[60]	baPWV	Successful	Yes	VP	General population	973	59	46.9	7.8	CCVE	
Kawai et al[61]	baPWV	Successful	Yes	FCP-4731 (Fukuda Denshi)	Hypertension	440	61	56.1	6.3	CCVE	
Han et al[62]	baPWV	Successful	No	VP	Outpatients	185	62	56.2	1.7	CCVE	
Munakata et al[63]	baPWV	Successful	Yes	VP	Hypertension	662	60	45.4	3	CCVE	Nontreated hypertension at the recruitment
Chen et al[64]	baPWV	Successful	Not clarified	VP	CKD	145	69	68.3	1.2	ACM + commencement of dialysis	baPWV is adjusted by mean arterial pressure
Inoue et al[65]	baPWV	Successful	Yes	VP	Hemodialysis	197	66	61.9	5.8	CCVE	
Orlova et al[66]	baPWV	Successful	Not clarified	VS (considered)	IHD (male only)	224	56	100.0	3.5	MACE	
Nakamura et al[67]	baPWV	Successful	Yes	VP	IHD	564	64	80.9	2.1 (median)	CCVE	
Turin et al[68]	baPWV	Successful	Not clarified	VP	General population	2,642	58	33.8	6.5	ACM	Participants with a history of CVD were excluded
Miyano et al[69]	baPWV	Successful	Yes	VP	Community-dwelling elderly	530	76	39.1	3	ACM, CCVM	
Meguro et al[70]	baPWV	Successful	Yes	VP	HF	72	68	56.9	1.2	Readmission of HF exacerbation	

(*Continued*)

Table 1 (*Continued*)

Article	Index	Result	Exclusion of ASO/PAD in the LE	Device	Population	Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Comments
Matsuoka et al[71]	baPWV	Successful	Yes	VP	Community-dwelling elderly	298	80	40.3	3.4	CCVM	
Wang and Dang[72]	baPWV	Successful	Not clarified	VP	IHD with Kawasaki disease	48	45	25.0	2.1	MACE + in-stent restenosis of DES	
Chen et al[73]	baPWV	Successful	No	VP	Atrial fibrillation	167	69	68.3	2.2 (median)	CCVE	
Park et al[74]	baPWV	Failed	Yes	VP	IHD	203	57	52.7	4.2	CCVE	
Kuwahara et al[75]	baPWV	Failed	No	VP	Hemodialysis	300	61	61.0	7	ACM	
Orlova et al[76]	baPWV	Successful	Not clarified	VS	IHD	161	57	100.0	3.5	MACE	
Tanaka et al[77]	baPWV	Failed	No	VP	Hemodialysis	445	63	59.3	3.6	ACM, CCVE	
Amemiya et al[78]	baPWV	Failed	Not clarified	VP	Hemodialysis	186	61	61.8	4	ACM	
Chen et al[79]	baPWV	Failed	No	VP	Hemodialysis	212	59	44.8	2.4	ACM, CCVM	
Morimoto et al[80]	baPWV	Kaplan–Meier	Yes	VP	Hemodialysis	176	61	56.3	3.6	ACM, CCVM	
Nagata et al[81]	baPWV	Successful	No	VP	IHD	398	68	74.6	0.8	MACE	Succeeded only in patients with DES
Lee et al[82]	baPWV	Successful	Yes	VP	IHD	350	66	53.4	1.2 (median)	CCVE	
Chen et al[83]	baPWV	Failed	Yes	VP	CKD	227	65	43.0	1.8	CCVE	
Wei et al[84]	baPWV	Successful	No	VP	Hemodialysis	205	59	44.9	4.4	ACM, CCVE	
Iino et al[85]	baPWV	Failed	Not clarified	VP	IHD, outpatients	77	65	63.6	2	MACE	
Li et al[86]	baPWV	Failed	Yes	VP	Outpatients	238	69	42.9	1.7 (median)	ACM	
Sugamata et al[87]	baPWV	Successful	Not clarified	VP	IHD	923	65	71.5	5.3	MACE	
Song et al[88]	baPWV	Successful	No	VP	Hypertension	3,310	60	44.0	4.5 (median)	Stroke	
Ikura et al[89]	baPWV	Successful	No	VP	Diabetes with LE amputation	102	63	78.4	3.3	ACM	
Kawai et al[90]	baPWV	Failed	No	VP	Hypertension	353	63	57.2	7.9	Stroke	
Chen et al[91]	baPWV	Failed	No	VP	Hemodialysis	210	59	44.3	4.4	ACM, CCVE	
Mimura et al[92]	baPWV	Failed	No	VP	CKD	75	57	69.3	4	ACM	
Ahn et al[93]	baPWV	Successful	Not clarified	VP	Acute stroke	1,557	68	59.3	2.5 (median)	CCVM	
Kim et al[94]	baPWV	Failed	No	VP	Hemodialysis	77	53	51.9	5	ACM, CCVE	
Tabata et al[95]	baPWV	Failed	No	VP	IHD	149	71	67.1	1.9 (mean), 1.3 (median)	CCVE	
Saji et al[96]	baPWV	Failed	Not clarified	VP	Acute lacunar infarction	156	69	60.9	5.9 (median)	Ischemic stroke	
Ueki et al[97]	baPWV	Successful	Yes	VP	Outpatients, CVD	2,554	66	70.2	5	MACE	The cutoff of 16.44 m/s is significant only in patients aged 30–59 years
Aisu et al[98]	baPWV	Successful	Yes	VP	Outpatients	456	71 (median)	67.8	4.9 (median)	HF	

(*Continued*)

Table 1 (*Continued*)

Article	Index	Result	Exclusion of ASO/PAD in the LE	Device	Population	Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Comments
Kuo et al[99]	baPWV	Failed	Not clarified	VP	CKD	149	62	64.4	4.3	CCVE + renal function decline	
Kajimoto et al[100]	baPWV	Failed	No	VP	Diabetes	337	68	58.2	5	IHD	
Woo et al[101]	baPWV	Failed	No	VP	IHD	91	57	63.7	1.4	a denovo lesion + PCI	
Park et al[102]	baPWV	Successful	No	VP	Myocardial infarction	411	64	75.2	1	CCVE	
Lu et al[103]	baPWV	Successful	Yes	VP	General population	4,251	52	45.9	4.4 (median)	CCVE	baPWV is adjusted by heart rate such as 75 beats per minute
Tokitsu et al[104]	baPWV	Successful	Yes	VP	HF with preserved ejection function	426	71	55.3	2.8	CCVE	
Hwang et al[105]	baPWV	Successful	Yes	VP	Suspected IHD	523	58	60.6	3.7	CCVE	
Wang et al[106]	baPWV	Successful	Not clarified	VP	Peritoneal dialysis	254	61	61.4	2.6	ACM	
Taniguchi et al[107]	baPWV	Successful	Not clarified	VP	Community-dwelling elderly	1,744	71	43.0	7.0 (median)	ACM	Trajectories of baPWV were used
Yamaguchi et al[108]	CAVI	Failed	No	VS	Hemodialysis	270	63	56.3	4.5	CCVM, CCVE + revascularization for PAD	
Sato et al[109]	CAVI	Successful	Yes	VS	Outpatients	1,003	63	51.2	6.7	IHD + coronary artery events confirmed by coronary angiography	
Laucevičius et al[110]	CAVI	Kaplan–Meier	Not clarified	VS	Metabolic syndromes	2,106	54	37.9	3.8	CCVE	Middle-aged women and men without the history of CVD were included
Satoh-Asahara et al[111]	CAVI	Successful	Not clarified	VS	Obese patients (after excluding subjects with success in weight loss)	300	49	44.5	5	CCVE + PAD	End point: IHD 15, stroke 7, PAD 6, (exclusion criteria: history of IHD, stroke, other vascular diseases)
Chung et al[112]	CAVI	Successful	No	VS	Diabetes	626	64	46.0	4.1	CCVE	
Kubota et al[113]	CAVI	Successful	Yes	VS	Outpatients	400	69	63.0	2.3	CCVE	

(*Continued*)

Table 1 (*Continued*)

Article	Index	Result	Exclusion of ASO/PAD in the LE	Device	Population	Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Comments
Yoshihisa et al[114]	CAVI	Failed	No	VS	HF	378	67	65.1	1.4	ACM, cardiac death, noncardiac death, cardiac death + admission of HF	
Sawai et al[115]	CAVI	Failed	No	VS	CKD	139	71	74.8	2.7 (median)	CCVE	
Harada et al[116]	CAVI	Failed	No	VS	Hemodialysis	110	69	70.0	2.1 (median)	CCVE	

Abbreviations: ABI, ankle–brachial index; ACM, all-cause mortality; ACS, acute coronary syndrome; ASO, arteriosclerosis obliterans; baPWV, brachia–ankle pulse wave velocity; CAVI, cardio-ankle vascular index; CCVE, cerebrovascular–cardiovascular event; CCVM, cerebrovascular–cardiovascular mortality; CKD, chronic kidney disease; CVD, cardiovascular disease; DES, drug-eluting stent; FRS, Framingham risk score; HF, heart failure; IHD, ischemic heart disease; LE, lower extremity; MACE, major adverse cardiac event; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SE, standard error; VP, Vascular Profiler; VS, VaSera.

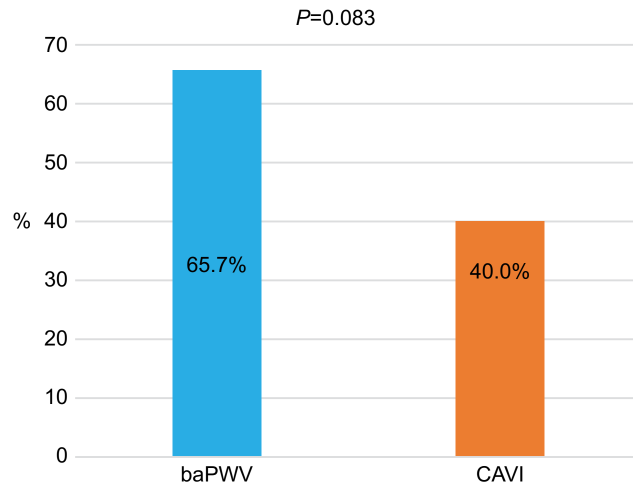

Figure 2 The success rate of baPWV and CAVI articles.
Abbreviations: baPWV, brachial–ankle pulse wave velocity; CAVI, cardio-ankle vascular index.

Population other than dialysis (hemodialysis and peritoneal dialysis)

In this category, the success rate of baPWV articles was 71.43% (41/57) which was similar to that of CAVI articles (54.5% [6/11]; *P*=0.30).

Studies of dialysis population only

In this category, the success rate of baPWV articles was 38.5% (5/13) which was similar to that of CAVI articles (0% [0/4]; *P*=0.26).

Studies comparing baPWV and CAVI in the same cohort

Table 3 presents the detailed information of the five articles in this category. Among the baPWV articles, the result was one success, two studies with statistical significance in the log-rank test, one failure, and one without a clarified result of the primary end point. Among the CAVI articles, the result was two successes and three failures. In the study that presented the success of baPWV, CAVI showed a statistical tendency in the Kaplan–Meier analysis (log-rank test, *P*=0.06). However, the trend disappeared after the adjustment for age, gender, and diabetes on the multivariate Cox proportional hazards model (*P*=0.49).[25] The two studies that showed a statistical significance of baPWV in the Kaplan–Meier analysis (log-rank test) did not reveal significance for CAVI.[24,27] In the study that demonstrated the success of CAVI and failure of baPWV, CAVI was analyzed with respect to the presence or absence of improvement for ≥6 months (persistently impaired CAVI).

However, the baPWV's raw value at the second occasion of the measurement was analyzed.[26] In a study in which the baPWV result was defined as "not clarified," the prognostic significance of baPWV in the multivariate Cox proportional hazards model analysis on the primary end point was not described. However, the prognostic significance of CAVI (not baPWV) on the secondary end point of nonfatal stroke was presented.[28]

Comparison of baPWV articles according to the presence or absence of the clarified exclusion criteria of LE-ASO/PAD

The success rate of the articles in the presence of these criteria (75.9% [22/29]) was similar to that in their absence (58.5% [24/41]; *P*=0.20; Figure 3A). However, after redefining two studies as the absence of LE-ASO/PAD exclusion,[27,45] the success rate of the articles in the presence of these criteria (81.5% [22/27]) was significantly higher than that of the articles in the absence (55.8% [24/43]; *P*=0.039; Figure 3B).

Multivariate logistic regression analysis to identify the independent determinants for the success of prognostic prediction

Table 4 presents this result. In the univariate analysis, log NoP (*P*=0.0006) and dialysis population (*P*=0.005) were significantly associated with the success of prognostic prediction, whereas baPWV and exclusion of LE-ASO/PAD showed a statistical tendency (*P*=0.071, *P*=0.076, respectively). In the multivariate analysis, log NoP (OR 11.20, 95% CI 2.45–51.70, *P*=0.002) and dialysis population (OR 0.28, 95% CI 0.08–0.94, *P*=0.039) were identified as the independent determinants of the success of prognostic prediction.

Table 5 summarizes the result after redefining two studies as the absence of LE-ASO/PAD exclusion.[27,45] In the univariate analysis, exclusion of LE-ASO/PAD (*P*=0.01), dialysis population (*P*=0.005), and log NoP (*P*=0.0006) were significantly associated with the success of prognostic prediction, whereas baPWV showed statistical tendency (*P*=0.071). In the multivariate analysis, log NoP and dialysis population were the statistically significant factors (for log NoP: OR 9.04, 95% CI 1.90–43.00, *P*=0.006; for dialysis population: OR 0.27, 95% CI 0.07–0.96, *P*=0.043). However, baPWV and the exclusion of LE-ASO/PAD showed statistical tendency in the success of prognostic prediction (for baPWV: OR 3.36, 95% CI 0.86–13.20, *P*=0.083; for the exclusion of LE-ASO/PAD: OR 3.08, 95% CI 0.96–9.93, *P*=0.060).

Discussion

Overview

To the best of our knowledge, this study is the first to comprehensively review the prognostic predictability of baPWV and CAVI. The current number of English articles using the indices of VP and VS is approximately 1,800 and 550, respectively.[117] The ratio of articles studying the prognostic significance of these parameters did not differ significantly (baPWV 70/1,800; CAVI 15/550, *P*=0.24). There were five articles that simultaneously studied prognostic significance of baPWV and CAVI in a same patient population. The success rate of baPWV articles tended to be higher than that of CAVI articles (65.7% vs 40.0%, *P*=0.083). Dialysis population and log NoP were the independent determinants for the success in the multivariate logistic regression analysis (Table 4). Moreover, after redefining two studies as the absence of exclusion of LE-ASO/PAD,[27,45] the success rate in the presence of these criteria was significantly higher than that in the absence of these criteria among the baPWV articles only (81.5% vs 55.8%, *P*=0.039). Furthermore, multivariate logistic analysis showed that baPWV and exclusion of LE-ASO/PAD had a statistical trend on the success of prognostic prediction (*P*=0.083, *P*=0.060, respectively). The multivariate analysis also showed that the effects of dialysis population and log NoP were attenuated, although these parameters were still significant (*P*=0.043, *P*=0.006, respectively; Table 5). Therefore, log NoP had the strongest power on the success of prognostic prediction among the articles investigated in this study. Actually, the most studies involving >1,000 participants were successful in the prognostic prediction.[47,48,52,53,55,58,68,88,93,97,103,107,109] These studies mostly used baPWV, and one study used CAVI.[109] However, the largest study of CAVI involving >2,000 participants failed.[110] Moreover, this review confirmed that the dialysis population (mostly hemodialysis) was a negative determinant of the success of prognostic prediction of the baPWV and CAVI. This is not surprising because the incidence of having false-negative LE-ASO/PAD is high even if the exclusion criteria are defined as ABI of ≤0.9 in the hemodialysis population. Age, proportion of male gender, and follow-up period in the study population had no effect on the success of baPWV and CAVI in the prognostic prediction. In general, age and gender affect

Table 2 Detailed information about baPWV and CAVI articles in which ASO and/or PAD was excluded from the analysis

Articles	Index	Result	Criteria of ASO/PAD exclusion	Device	Population	Number of patients	Age (mean; years)	Male gender (%)
Yamamoto et al[16]	CAVI	Failed	ASO	VS	Community-dwelling elderly	117	80	31.1
Kato et al[25]	baPWV	Successful	ABI <0.9	VS	Hemodialysis	135	60	67.4
Kato et al[25]	CAVI	Failed	ABI <0.9	VS	Hemodialysis	135	60	67.4
Otsuka et al[26]	baPWV	Failed	PAD	Not described	IHD with impaired CAVI	211	65	55.9
Otsuka et al[26]	CAVI	Successful	PAD	VS	IHD with impaired CAVI	211	65	55.9
Kusunose et al[27]	baPWV	Failed	Symptomatic PAD	VP	Outpatients with two or more risk factors	114	69	78.1
Kusunose et al[27]	CAVI	Failed	Symptomatic PAD	VS	Outpatients with two or more risk factors	114	69	78.1
Gohbara et al[28]	CAVI	Successful	PAD	VS	IHD, ACS	288	65	82.3
Lau et al[45]	baPWV	Failed	Symptomatic PAD	VP	Diabetes	151	61	40.4
Kitahara et al[46]	baPWV	Successful	ABI <0.9	VP	Hemodialysis	671	59	64.9
Ninomiya et al[47]	baPWV	Successful	ABI <0.9	VP	General population	2,916	60	42.7
Maeda et al[48]	baPWV	Successful	ABI <0.9	VP	Diabetes	3,628	61	59.7

Follow-up (years)	Primary end point	Number of events	Cutoff	HR (adjusted)	HR as a continuous variable (adjusted)	Comments
4	ACM	14	10	Not provided	Not provided	The mortality rate did not differ between patients with CAVI ≥10 and CAVI <10
5.3	CCVM	22	16.6 m/s (the top tertile)	16.9 (95% CI 1.1–251.8, *P*=0.04)	Not provided	
5.3	CCVM	22	9.9 (the top tertile)	Failed	Not provided	
2.9	CCVE	28	baPWV at the second occasion	Failed	Not provided	
2.9	CCVE	28	Persistently impaired CAVI in 6 months	Persistently impaired CAVI: 3.3 (95% CI 1.47–8.59, *P*<0.01)	Not provided	CAVI at the first occasion did not succeed
4.3	MACE	35	17.03 m/s	Not provided	Failed	ABI=1.01±0.17 (SD)
4.3	MACE	35	9.2	Not provided	Failed	ABI=1.01±0.17 (SD)
1.3 (median)	CCVE	19	8.325	18 (95% CI 2.369–136.8, *P*=0.005)	Not provided	In the secondary end point (nonfatal ischemic stroke), CAVI succeeded, baPWV failed
5.1	CCVE	16	14.67 m/s	Not provided	Failed	
2.8	ACM, CCVM	86, 55	19.6 m/s (the third quartile), 23 m/s (the top quartile)	ACM, the third quartile: 3.32 (95% CI 1.22–9.02, *P*=0.019), the top quartile: 4.08 (95% CI 1.46–11.43, *P*=0.007)/ cardiovascular mortality, the top quartile: 7.03 (95% CI 1.49–33.08, *P*=0.014)	Not provided	
7.1	CCVE	126	17.6 m/s	The third quintile: 7.17 (95% CI 1.66–31.03, *P*=0.008), the fourth quintile: 8.77 (95% CI 1.99–38.71, *P*=0.004), the top quintile: 12.20 (95% CI 2.68–55.64, *P*=0.001)	Per 20% of baPWV, 1.31 (95% CI 1.11–1.54, *P*=0.002)	
3.2	ACM, coronary events, cerebrovascular events	Not provided	24 m/s, 14 m/s, 14 m/s	1.84 (95% CI 1.13–2.88, *P*=0.016), 1.69 (95% CI 1.06–2.84, *P*=0.025), 1.63 (95% CI 1.01–2.76, *P*=0.046)	Not provided	For the CCVEs, adjusted by modified FRS

(*Continued*)

Table 2 (*Continued*)

Article	Index	Result	Criteria of ASO/PAD exclusion	Device	Population	Number of patients	Age (mean; years)	Male gender (%)
Kuroiwa et al[49]	baPWV	Successful	History of ASO, ABI<0.9	VP	Community-dwelling elderly	450	77	67.3
Sheng et al[52]	baPWV	Successful	ABI<0.9	VP	Community-dwelling elderly	3,876	68	44.2
Katakami et al[53]	baPWV	Successful	PAD	VP	Diabetes	1,040	59	65.0
Takashima et al[58]	baPWV	Successful	ABI<0.9	VP	General population	4,164	59	37.2
Ishisone et al[60]	baPWV	Successful	ABI ≤0.9	VP	General population	973	59	46.9
Kawai et al[61]	baPWV	Successful	ABI<0.9	FCP-4731 (Fukuda Denshi)	Hypertension	440	61	56.1
Munakata et al[63]	baPWV	Successful	PAD	VP	Hypertension	662	60	45.4
Inoue et al[65]	baPWV	Successful	PAD	VP	Hemodialysis	197	66	61.9
Nakamura et al[67]	baPWV	Successful	ABI<0.9	VP	IHD	564	64	80.9
Miyano et al[69]	baPWV	Successful	ABI<0.9	VP	Community-dwelling elderly	530	76	39.1
Meguro et al[70]	baPWV	Successful	PAD	VP	HF	72	68	56.9
Matsuoka et al[71]	baPWV	Successful	ABI ≤0.9	VP	Community-dwelling elderly	298	80	40.3
Park et al[74]	baPWV	Failed	ABI<0.9	VP	IHD	203	57	52.7
Morimoto et al[80]	baPWV	Failed	ABI<0.9	VP	Hemodialysis	176	61	56.3
Lee et al [82]	baPWV	Successful	ABI<0.9	VP	IHD	350	66	53.4
Chen et al [83]	baPWV	Failed	ABI<0.9	VP	CKD	227	65	43.0
Li et al [86]	baPWV	Failed	ABI≤0.9	VP	Outpatients	238	69	42.9
Ueki et al [97]	baPWV	Successful	ABI≤0.9, ABI>1.4	VP	Outpatients, CVDs	2,554	66	70.2

Follow-up (years)	Primary end point	Number of events	Cutoff	HR (adjusted)	HR as a continuous variable (adjusted)	Comments
3	ACM	28	18.61 m/s	OR 3.22 (95% CI 1.26–8.22, P=0.014)	Per 1 m/s, OR 1.10 (95% CI 1.00–1.21, P=0.047)	A multivariate logistic regression analysis was performed
5.9	ACM, death of non-cerebrovascular–cardiovascular cause	316, 168	23.3 m/s	1.56 (95% CI 1.16–2.08, P=0.003), 1.60 (95% CI 1.18–2.75, P=0.006)	Failed	Cox regression: the top decile vs whole population
7.5 (median)	CCVE + PAD (ABI <0.9)	113	15.5 m/s	Not provided	Per 1 SD, 1.33 (95% CI 1.09–1.62, P=0.004) the SD is not provided	
6.5 (median)	CCVE	40	18 m/s	2.70 (95% CI 1.18–6.19)/vs <14 m/s, 6.94 (95% CI 1.43–33.73)	Failed	
7.8	CCVE	37	The top decile	2.58 (95% CI 1.24–5.37, P=0.012)	Per 1 SD, 1.47 (95% CI 1.09–1.98, P=0.011)	
6.3	CCVE	62	17.5 m/s	2.048 (95% CI 1.176–3.616, P=0.0113)	Not provided	
3	CCVE	24	17.5 m/s	2.97 (95% CI 1.006–9.380)	Not provided	Nontreated hypertension at the recruitment
5.8	CCVE	89	Not provided	Not provided	Per 1 cm/s, 1.046 (95% CI 1.006–1.086, P=0.0220)	In reality, the unit is considered to be meter per second
2.1 (median)	CCVE	122	17.3 m/s for the diabetes patients only	1.97 (95% CI 1.01–3.84, P=0.046)	Not provided	
3	ACM, CCVM	30, 11	19.63 m/s, 19.63 m/s	5.3 (95% CI 2.2–12.7), 18.7 (95% CI 2.2–157.6)	Per 1 m/s, 1.09 (95% CI 1.00–1.18), 1.12 (95% CI 1.01–1.25)	
1.2	Readmission of HF exacerbation	7	17.5 m/s	5.101 (95% CI 1,034–25.166, P=0.045)	Not provided	
3.4	CCVM	9	25 m/s	Not provided	Per 2 m/s, 1.302 (95% CI 1.110–1.525, P=0.0011)/per 5 m/s, 1.933 (95% CI 1.300–2.874, P=0.0011)	
4.2	CCVE	36	Not provided	Not provided	Failed	
3.6	ACM, CCVM	17, 9	18 m/s	Not provided	Failed	
1.2 (median)	CCVE	21	17.9 m/s	2.03 (95% CI 1.08–6.38, P=0.007)	Not provided	
1.8	CCVE	28	Not provided	Not provided	Failed	
1.7 (median)	ACM	15	16 m/s	Failed	Not provided	
5	MACE	133	16.44 m/s	Not provided	Per 1 m/s, 1.17 (95% CI 1.04–1.32, P=0.011)	The cutoff of 16.44 m/s is significant only in patients aged 30–59 years

(*Continued*)

Table 2 (*Continued*)

Article	Index	Result	Criteria of ASO/PAD exclusion	Device	Population	Number of patients	Age (mean; years)	Male gender (%)
Aisu et al[98]	baPWV	Successful	ABI<0.9	VP	Outpatients	456	71 (median)	67.8
Lu et al[103]	baPWV	Successful	ABI<0.9	VP	General population	4,251	52	45.9
Tokitsu et al[104]	baPWV	Successful	ABI ≤0.9	VP	HF with preserved ejection function	426	71	55.3
Hwang et al[105]	baPWV	Successful	ABI<0.9	VP	Suspected IHD	523	58	60.6
Sato et al[109]	CAVI	Successful	ABI<0.9	VS	Outpatients	1,003	63	51.2
Kubota et al[113]	CAVI	Successful	ABI<0.9	VS	Outpatients	400	69	63.0

Abbreviations: ABI, ankle–brachial index; ACM, all-cause mortality; ACS, acute coronary syndrome; ASO, arteriosclerosis obliterans; baPWV, brachia–ankle pulse wave velocity; CAVI, cardio-ankle vascular index; CCVE, cerebrovascular–cardiovascular events; CCVM, cerebrovascular–cardiovascular mortality; CKD, chronic kidney disease; CVD, cardiovascular disease; FRS, Framingham risk score; HF, heart failure; IHD, ischemic heart disease; LE, lower extremity; MACE, major adverse cardiac events; PAD, peripheral arterial disease; VP, Vascular Profiler; VS, VaSera.

the progression of arterial stiffness and thus prognosis.[118] However, the result of this study is plausible because this study explored the key factors for the success of prognostic prediction of baPWV and CAVI, not investigating the factors affecting arterial stiffness. This study also confirmed that more than half of the articles did not clarify the exclusion criteria of LE-ASO/PAD or did not exclude patients with LE-ASO/PAD when using baPWV and CAVI in the prognostic studies.

baPWV

Main findings

The success rate of baPWV articles (65.7%) tended to be higher than that of CAVI articles (40.0%) (*P*=0.083). This difference may be partly caused by the number of the study population. The success rate of baPWV articles (75.9%) was similar to that of CAVI articles (57.1%) in the studies clarifying the exclusion criteria of LE-ASO/PAD. Among the 29 baPWV articles that had the patient exclusion criteria of LE-ASO/PAD, seven articles failed to prove prognostic significance of baPWV. Among the seven articles, two excluded those patients only with symptomatic PAD.[27,45]

The former study consisted of patients with multiple risk factors for cardiovascular disease (CVD), and the mean ABI in this cohort was 1.01±0.17 (SD). Therefore, patients with an ABI of ≤0.9 existed at high probability. In this study, baPWV, but not CAVI, showed statistical significance in the Kaplan–Meier analysis. Nevertheless, its significance was lost after multivariate adjustment by the Cox model including ABI as a covariate, and the cutoff ABI of 1.04 was selected as an independent predictor.[27] Moreover, the mean baPWV and CAVI values of both sides were used in the analysis. This condition meant that the decreased baPWV or CAVI

Follow-up (years)	Primary end point	Number of events	Cutoff	HR (adjusted)	HR as a continuous variable (adjusted)	Comments
4.9 (median)	HF	30	Not provided	Not provided	Per 1 m/s,1.21 (95% CI 1.11–1.33, *P*<0.01), per ΔbaPWV 10%, 1.51 (95% CI 1.23–1.86, *P*<0.01)	
4.4 (median)	CCVE	74	16.7 m/s (Youden's index)	Unadjusted, 11.2 (95% CI 6.59–19.1, *P*<0.0001)	Per 3.23 m/s (1 SD), 1.50 (95% CI 1.26–1.78, *P*≤0.0001)	baPWV is adjusted by heart rate such as 75 beats per minute
2.8	CCVE	91	<13 m/s (the first quintile), 19 m/s ≤<22 m/s (the fourth quintile), 22 m/s < (the top quintile)	2.88 (95% CI 1.12–7.38, *P*=0.03), 2.20 (95% CI 1.14–4.25, *P*=0.02), 2.56 (95% CI 1.28–5.14, *P*=0.01)	Not provided	
3.7	CCVE	66	16.19 m/s	4.717 (95% CI 2.675–8.319, *P*<0.001)	Per 1 m/s, 1.129 (95% CI 1.074–1.187, *P*<0.001)	
6.7	IHD + coronary artery events confirmed by coronary angiography	90	10.09 (the top quartile)	Failed	Per CAVI =1, 1.126 (95% CI 1.006–1.259, *P*=0.039)	
2.3	CCVE	49	≥10 (the top tertile)	2.25 (95% CI 1.02–4.95, *P*=0.04)	Not provided	

on the side with asymptomatic PAD would lower the mean parameter. However, in reality, a patient was considered to have a high-risk prognosis.[5,22,117,119] Therefore, the risk of a patient with asymptomatic PAD who was considered at equivalently high risk as a patient with symptomatic PAD was considerably underestimated by the falsely lowered baPWV or CAVI.[27]

In the study by Lau et al,[45] the study cohort included patients with diabetes vintage of 15.2±7.5 years. Thus, the high probability of a falsely overestimated ABI due to arterial calcification in the lower limbs was considered.[5] The mean ABI of both sides, 1.1±0.1, was used in the analysis, and the high probability of asymptomatic LE-ASO/PAD was considered. Furthermore, the mean baPWV of both sides was also used; as such, a similar phenomenon observed in the study by Kusunose et al would be most likely.[27] As a result, no prognostic significance of baPWV was proven in this study.[45] Thus, at least when utilizing baPWV and CAVI as prognostic predictors that include the lower-limb arteries in the measuring path, these findings imply that the exclusion of symptomatic PAD is insufficient. Therefore, redefining of these two articles and the reanalysis were performed, and this change presented the statistically higher success rate in the presence of exclusion criteria of LE-ASO/PAD than that in the absence of the criteria among the baPWV articles. At the same time, baPWV and exclusion of LE-ASO/PAD showed a statistical tendency in the multivariate logistic model (Table 5).

However, within the articles that clarified the exclusion criteria using ABI (≤0.9) or an expression of LE-ASO/PAD exclusion, the other five studies did not prove an independent prognostic significance of baPWV. The cohorts of these studies were as follows: two patients with IHD,[26,74] of the patients receiving hemodialysis,[80] one of the patients

Table 3 Details of the articles in which the prognostic predictability of baPWV and CAVI was analyzed in the same cohort

Articles	Index	Result	Exclusion of ASO/PAD in the LE	Criteria of ASO/PAD exclusion	Other exclusion criteria	Usage of baPWV–CAVI	Device	Population
Kato et al[24]	baPWV, CAVI	baPWV Kaplan–Meier, CAVI failed	No			Average	VS	Hemodialysis
Kato et al[25]	baPWV, CAVI	baPWV successful, CAVI failed	Yes	ABI <0.9	Over 76 years old	Higher	VS	Hemodialysis
Otsuka et al[26]	baPWV, CAVI	baPWV failed, CAVI successful	Yes	PAD	AF, other various criteria		baPWV not described, CAVI VS	IHD with impaired CAVI
Kusunose et al[27]	baPWV, CAVI	baPWV Kaplan–Meier, CAVI failed	Yes	Symptomatic PAD	End-stage neoplasm, etc.	Average	baPWV VP, CAVI VS	Outpatients with two or more risk factors
Gohbara et al[28]	baPWV, CAVI	baPWV not described, CAVI successful	Yes	PAD	AF, aortic diseases, etc.	Average	baPWV VP, CAVI VS	IHD, ACS

Abbreviations: ABI, ankle–brachial index; ACM, all-cause mortality; ACS, acute coronary syndrome; AF, atrial fibrillation; ASO, arteriosclerosis obliterans; baPWV, brachial–ankle pulse wave velocity; CAVI, cardio-ankle vascular index; CCVE, cerebrovascular–cardiovascular event; CCVM, cerebrovascular–cardiovascular mortality; IHD, ischemic heart disease; MACE, major adverse cardiac event; PAD, peripheral arterial disease; VP, Vascular Profiler; VS, VaSera.

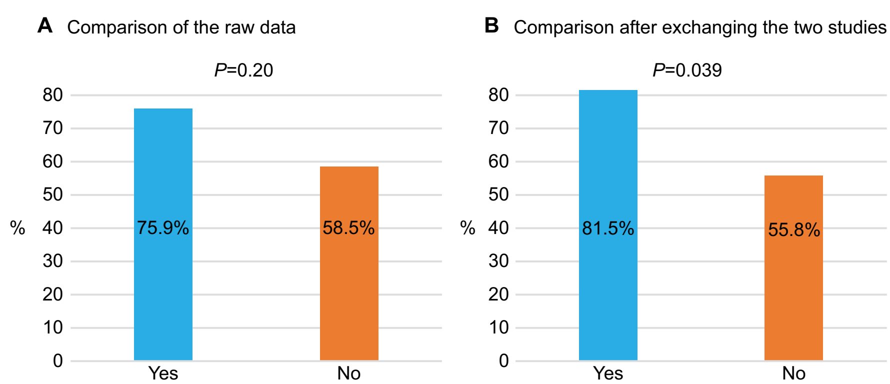

Figure 3 The success rate of baPWV articles according to the presence of exclusion criteria of LE-ASO/PAD. (**A**) Comparison of the raw data. (**B**) Comparison after exchanging the two studies.
Abbreviations: baPWV, brachial–ankle pulse wave velocity; LE-ASO/PAD, lower extremity-arteriosclerosis obliterans/peripheral arterial disease.

Number of patients	Age (mean; years)	Male gender (%)	Follow-up (years)	Primary end point	Number of events	Cutoff	HR (adjusted)	HR as a continuous variable (adjusted)	Comments
194	64	65.5	3.3	ACM, nonfatal CCVE	39, 15	baPWV 17.5 m/s (the top tertile), CAVI 10.7 (the top tertile)	Failed	Not provided	ABI succeeded significantly
135	60	67.4	5.3	CCVM	22	baPWV 16.6 m/s (the top tertile), CAVI 9.9 (the top tertile)	16.9 (95% CI 1.1–251.8, P=0.04)	Not provided	
211	65	55.9	2.9	CCVE	28	baPWV at the second occasion, persistently impaired, CAVI in 6 months	baPWV failed, persistently impaired CAVI 3.3 (95% CI 1.47–8.59, P<0.01)	Not provided	CAVI at the first occasion did not succeed
114	69	78.1	4.3	MACE	35	baPWV =17.03 m/s, CAVI =9.2	Not provided	Failed	ABI=1.01±0.17 (SD)
288	65	82.3	1.3 (median)	CCVE	19	baPWV, not provided, CAVI 8.325	baPWV not provided, CAVI 18 (95% CI 2.369–136.8, P=0.005)	Not provided	In the secondary end point (nonfatal ischemic stroke), CAVI succeeded, baPWV failed

Table 4 Logistic regression analysis exploring the independent determinants of the success of prognostic prediction

	Univariate		Multivariate	
Covariates	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
baPWV (yes =1)	2.87 (0.92–9.03)	0.071		
Exclusion of ASO/PAD (yes =1)	2.30 (0.92–5.77)	0.076		
Dialysis population (yes =1)	0.19 (0.06–0.60)	0.005	0.28 (0.08–0.94)	0.039
Age (years)	0.99 (0.93–1.07)	0.87		
Male gender (%)	1.00 (0.97–1.03)	0.97		
Follow-up period (years)	1.00 (0.78–1.27)	0.97		
Log (number of patients)	14.00 (3.13–62.80)	0.0006	11.20 (2.45–51.70)	0.002

Notes: baPWV =1 or CAVI =0 is used as a binary variate. The "success or failure" in the studies simultaneously comparing baPWV and CAVI was defined for each index. Thus, the total number of the included studies is 85.
Abbreviations: ASO, arteriosclerosis obliterans; baPWV, brachial–ankle pulse wave velocity; CAVI, cardio-ankle vascular index; PAD, peripheral arterial disease.

with chronic kidney disease stage 3–5,[83] and one of an outpatient population with a 78% incidence of diabetes.[86] Thus, these studies were conducted in population that were still very likely to include patients with LE-ASO/PAD (false-negative LE-ASO/PAD), even if the exclusion criterion was set at ABI ≤0.9. Therefore, the reason for failure in these five studies is considerably similar to that in the two studies.[27,45] The reason why ABI and/or (false-

Table 5 Logistic regression analysis exploring the independent determinants of the success of prognostic prediction after exchanging the studies excluding patients with only symptomatic PAD

	Univariate		Multivariate	
Covariates	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
baPWV (yes =1)	2.87 (0.92–9.03)	0.071	3.36 (0.86–13.20)	0.083
Exclusion of ASO/PAD (yes =1)	3.71 (1.37–10.10)	0.01	3.08 (0.96–9.93)	0.060
Dialysis population (yes =1)	0.19 (0.06–0.60)	0.005	0.27 (0.07–0.96)	0.043
Age (years)	0.99 (0.93–1.07)	0.87		
Male gender (%)	1.00 (0.97–1.03)	0.97		
Follow-up period (years)	1.00 (0.78–1.27)	0.97		
Log (number of patients)	14.00 (3.13–62.80)	0.0006	9.04 (1.90–43.00)	0.006

Notes: baPWV =1 or CAVI =0 is used as a binary variate. The "success or failure" in the studies simultaneously comparing baPWV and CAVI was defined for each index. Thus, the total number of the included studies is 85.
Abbreviations: ASO, arteriosclerosis obliterans; baPWV, brachia–ankle pulse wave velocity; CAVI, cardio-ankle vascular index; PAD, peripheral arterial disease.

negative) LE-ASO/PAD is a stronger indicator of prognosis is given in the following section.

Prognostic significance of ABI is much stronger than that of baPWV without sufficient exclusion of LE-ASO/PAD

In the hemodialysis cohort that did not exclude patients with LE-ASO/PAD, it was already demonstrated that a high baPWV (the top quartile of baPWV ≥23.6 m/s) lost prognostic significance after multivariate adjustment including ABI as one of the covariates using the Cox model, even though a high baPWV showed significance in the Kaplan–Meier analysis.[46] This is because ABI, which assesses LE-ASO/PAD as a more severe disease, is a considerably stronger prognostic indicator than baPWV. In the same study, baPWV showed independent prognostic significance after the exclusion of patients with an ABI of <0.9. Nevertheless, patients with a borderline ABI of 0.90–0.99 and patients with a high ABI of ≥1.3 also showed independent prognostic significance. Furthermore, patients with a low normal ABI of 1.00–1.09 showed a statistical tendency or a close value as a prognostic indicator (*P*=0.113 for ACM, *P*=0.086 for CCVM after adjustment).[46]

In another study of hemodialysis patients evaluating the prognostic significance of ABI but not using baPWV,[120] patients with an abnormal ABI of <0.9 and those with a borderline ABI of 0.90–0.99 showed the worst prognosis. However, in the present study, those with a high ABI of ≥1.3 and even those with a low normal ABI of 1.00–1.09 showed significantly worse prognosis than those with a reference ABI of 1.10–1.29 (in those with a low normal ABI of 1.00–1.09, an HR of 1.92% and 95% CI of 1.02–3.59 for ACM and an HR of 2.82% and 95% CI of 1.22–6.54 for CCVM after multivariate adjustment using the Cox proportional hazards model). In the report published in 2003, Ono et al[120] mentioned that those with an ABI of 0.9–1.1 as well as those with an abnormal ABI should be carefully monitored in the hemodialysis population.

Moreover, in a study of a hemodialysis cohort that evaluated the prognostic predictability of ABI in ACM, the best cutoff ABI of 1.1 was demonstrated by a receiver operating characteristic (ROC) curve analysis (area under the ROC curve to predict mortality, 0.79; sensitivity, 0.90; specificity, 0.62).[121] This significance was maintained after multivariate analysis using the Cox model. In the studies that evaluated the diagnostic ability of ABI compared to imaging modalities or clinical symptoms in patients on hemodialysis, an ABI threshold of 1.01–1.10 was mainly reported.[122–124] Ohtake et al[123] suggested raising the ABI cutoff to 1.1 in patients on hemodialysis. In a cohort of patients with diabetes, significant HRs and *P*-values in prognostic predictability (ACM and CCVM) were reportedly similar between those with an abnormal ABI of ≤0.9 and those with a borderline ABI of 0.91–0.99 (both HRs of about 2.0, significant) compared to those with normal ABI of 1.00–1.4.[125] Moreover, in a study of a cohort with multiple cardiovascular risk factors and a history of CVDs, those with a borderline ABI of 0.91–0.99 showed significantly higher HRs in ACM (HR 2.27, *P*=0.005) and CCVM (HR 3.47, *P*=0.003) than those with a normal ABI of 1.00–1.4.[126]

Among the studies of patients with IHD, one report showed the independent prognostic predictability of a borderline ABI of 0.91–0.99,[127] whereas another study demonstrated the best cutoff ABI of 1.057 as an independent prognostic predictor.[128] In contrast, in the Hisayama study involving a general population, those with abnormal ABI of ≤0.9 clearly showed independent prognostic predictability in CCVE (HR 2.40, *P*=0.02). However, those with a borderline ABI of 0.91–0.99 did not show any difference compared to those with a normal ABI of 1.0–1.4, and the result was virtually the same even in the Kaplan–Meier analysis.[129] All the ABI values in the study mentioned earlier were measured using VP. The information described earlier indicated that there are frequent cases in which those with LE-ASO/PAD still exist after excluding those with an ABI of ≤0.9 and that a borderline or low normal ABI has stronger prognostic significance than baPWV depending on the cohort or at least has confounding power to weaken the prognostic significance of baPWV in the multivariate analysis. Moreover, it is also plausible that the existence of the patients with false-negative LE-ASO/PAD weakens the prognostic significance of baPWV even if ABI is not included in the multivariate model, because the prognostic risk of such a patient cannot be appropriately assessed by baPWV even if the higher baPWV is used.[117] Simply, in other words, the existence of the false-negative LE-ASO/PAD weakens the prognostic significance of baPWV (and also CAVI) anyway regardless of the ABI included in the multivariate model or not.

Appropriate settings when evaluating baPWV and CAVI

Therefore, to set the exclusion criteria of LE-ASO/PAD to appropriately assess baPWV as a prognostic indicator, the cutoff ABI of ≤0.9 is sometimes insufficient, or it would be necessary to increase the ABI value in such a case. This is one of the limitations when using baPWV (and also CAVI). As such, among the seven studies that failed to show the prognostic significance of baPWV,[26,27,45,74,80,83,86] if the exclusion criteria of LE-ASO/PAD were defined to include the upstroke time (UT)[130] and/or percent mean arterial pressure (%MAP),[131] the baPWV success rate would be higher. This might be the same for CAVI. In contrast, several studies showed the independent prognostic significance of baPWV and CAVI without the clarified exclusion criteria of LE-ASO/PAD or without LE-ASO/PAD exclusion. For this reason, some studies might have excluded LE-ASO/PAD using the cutoff ABI of ≤0.9, but it might not be just precisely described in the articles (it is very likely in three articles of reference number of 56, 68, and 111 for some reasons). These studies might also be performed in the cohort with a low frequency of LE-ASO/PAD even if LE-ASO/PAD was not excluded. It is also plausible that the independent prognostic predictability of baPWV or CAVI was proven incidentally in the relationship of the covariates included in the multivariate model.

In reality, two baPWV[56,68] and one CAVI[111] studies, which were defined as not clarifying exclusion criteria of LE-ASO/PAD, were considered most likely to exclude those with LE-ASO/PAD and/or ABI of ≤0.9. It is almost certain according to the data of ABI (ABI=1.13±0.00 [standard error], the number of patients was 338),[56] the context of the patient exclusion criteria and the end point,[111] and the information of other studies of their institutions.[58,68] Therefore, reanalysis was performed. Among the baPWV articles, the success rate of the articles in the presence of these criteria (82.8% [24/29]) was significantly higher than that of the articles in the absence of these criteria (53.7% [22/41]; *P*=0.020). In the multivariate logistic regression analysis (Table S1), exclusion of LE-ASO/PAD emerged as an independent predictor of the successful prognostic prediction (*P*=0.022). The *P*-value of baPWV improved (from 0.083 to 0.059).

CAVI

Main findings

The success rate tended to be lower in studies of CAVI than in those of baPWV (40% vs 65.7%, *P*=0.083). Moreover, all four studies of a hemodialysis cohort failed to show prognostic significance.[24,25,108,116] In three of the four studies, LE-ASO/PAD was not excluded.[24,106,114] The prognostic significance of CAVI was also definitely weakened by uncertainty or absence of the exclusion criteria of LE-ASO/PAD. The relatively small number of the participants in the hemodialysis studies might also affect the outcome. However, among the studies clarifying the exclusion criteria of LE-ASO/PAD, the success rate was 57.1% (4/7), which was lower than that for studies of baPWV (75.9%), although this was not statistically significant. Moreover, four of the six studies that showed the independent prognostic significance of CAVI implied that the statistical power was not very strong from the aspect of *P*-values despite the studied cohorts not being very small (*P*=0.039 for 1,003 patients; *P*=0.029 for 300 patients; *P*=0.049 or<0.05 for 626 patients; *P*=0.04 for 400 patients).[109,111–113] Furthermore, the largest study of CAVI involving 2,106 Caucasian participants with metabolic syndromes failed. In this study, there were no clarified criteria of LE-ASO/PAD. Nevertheless, the subjects were middle aged (54±6 years), and those with the previous history of CVDs were excluded. Thus, the prevalence of LE-ASO/PAD was considered low in this cohort. In the present study, CAVI showed statistical significance in the Kaplan–Meier analysis and the univariate Cox model. However, in the multivariate analysis, this significance was lost, and age and gender were selected as the independent prognostic predictors.[110] These phenomena are similar to that of the hemodialysis study by Kato et al.[25] In Kato's study, the statistical tendency of CAVI was lost after the adjustment of age, gender, and diabetes in the multivariate Cox proportional hazards model.

Therefore, considering the whole information described earlier, the prognostic power of CAVI may be weaker than that of baPWV. The possible reasons are described in the following section.

Factors possibly affecting prognostic predictability of CAVI

CAVI is a product of PWV adjusted by blood pressure, and its concept is derived from the stiffness parameter β.[14] In adopting the concept of the stiffness parameter β on heart–ankle PWV (haPWV), the equation is as follows: $\beta = \text{CAVI} = 2\rho \cdot PP^{-1} \cdot \text{Ln}(SBP/DBP) \cdot haPWV^2$ where ρ is the blood density, PP is the pulse pressure, and Ln is a natural logarithm.[14] As a result of this method, CAVI is considered less dependent on blood pressure than baPWV or independent from blood pressure.[14,132] However, the appropriateness of using only brachial blood pressure as the representative of the haPWV measuring path, as well as the independence of blood pressure, has been controversial.[132–141] A few authors in these studies clearly denied the blood pressure independence of CAVI.[135,138,139] To calculate haPWV, the pulse transit times between the brachial–ankle and the heart–brachial are required. The equation of haPWV is as follows: $haPWV = Lha/Tha = Lha/(Tba + Thb)$, where Lha is the length between the heart and the ankle, Tha is the pulse transit time between the heart and the ankle, Tba is the pulse transit time between the brachium and the ankle, and Thb is the pulse transit time between the heart and the brachium.[14] However, measuring Tha or Thb is virtually impossible. Therefore, it is substituted with the time interval between the onset of the second heart sound and that of the dicrotic notch (DN) on the brachial pulse wave form ($Thb \fallingdotseq T'hb = TII–DN$). Nevertheless, one study reported that this method using volume plethysmography could induce a 50% reduction in CAVI.[142] The timings of the second sound and the DN themselves could be falsely determined depending on the patient's condition, especially in cases of valvular heart diseases. Furthermore, the blood density ρ is considered constant in the VS device, but this is not always constant in vivo. Kato et al[25] pointed out the change in blood density of patients on hemodialysis.[143] Moreover, we must recognize the risk of using the brachial blood pressure of the upper extremity (UE)-ASO in those on hemodialysis. Patients on hemodialysis reportedly have falsely elevated ABI to a certain extent because of UE-ASO on the contralateral side of the hemodialysis access, and its frequency was reportedly about 10% in the Japanese hemodialysis patients.[117,144] In all four hemodialysis cohort studies that failed to show the prognostic significance of CAVI, no difference in CAVI was found between those with and without the primary end point (before adjustment). This might be caused by the absence of exclusion criteria of LE-ASO/PAD in three of the studies. Nevertheless, a decreased brachial blood pressure due to UE-ASO and error in the pulse transit time (T′hb and Tba) might have partly affected the results. We must also recognize that a false measurement of ABI and baPWV in the cases of UE-ASO in patients on hemodialysis would affect the prognostic predictability of baPWV.[117]

With respect to blood pressure and ABI measurement, we must recognize that there are a few minor differences between VP and VS. VP synchronizes the timing of SBP determination to make it simultaneous. In contrast, a blood pressure measurement using VS is basically performed through the sequential method (from the right side to the left side). Thus, for determining SBPs in the arms and ankles, the difference in measurement time is considered more likely to occur with VS than with VP. In the statement document of the American Heart Association published in 2012 regarding the measurement and interpretation of ABI, two studies reported that the left ABI measured using the Doppler method was significantly lower (0.03) than the right ABI.[5] In a meta-analysis of the risks of inter-arm blood pressure differences, a significantly increased relative risk of inter-arm difference (ie, difference in SBP ≥10 mmHg) was demonstrated in the sequential method compared to the simultaneous method.[145] The difference in the risk of the inter-arm blood pressure difference mentioned earlier may affect the individual ABI and the prevalence of LE-ASO/PAD (it could also change the excluded patients) and may affect the brachial blood pressure to be used in the CAVI equation. Furthermore, as a fundamental issue, we may have to ensure that the blood pressure measured by the oscillometric method is used in the CAVI equation of VS. Blood pressures measured by the oscillometric method are reportedly lower than those measured by the invasive method (internal arterial pressure).[146–148] This implies that, even if it is theoretically correct to use the brachial blood pressure as a representative value of the systemic arteries in the CAVI equation, because it is an oscillometric method anyway, a discrepancy inevitably exists regardless of the device used. It should also be recognized that the invasive method is not always perfect.

Difference between CAVI and baPWV

Various factors that would affect the prognostic significance of CAVI were discussed earlier. The correlation between baPWV and haPWV, which is a parameter in the CAVI equation, is reportedly very high in healthy male individuals of the general population (r=0.92 for baPWV and haPWV in the right side, n=135; mean, 59 years old).[149] In contrast, the blood pressure dependence of CAVI is reportedly weaker than that of baPWV.[14,132] Moreover, several studies have shown superior associations with other atherosclerotic parameters of CAVI to that of baPWV.[150,151] However, we may have to recognize that the characteristics of PWV, which is considered to natively possess prognostic significance,[6–8,18–21] might be affected by various factors in the measurement and the equation of CAVI as pointed out earlier. Furthermore, we suppose that CAVI is superior to baPWV as an index of arterial wall stiffness. Nevertheless, we may also have to recognize that the superiority for quantifying arterial wall stiffness itself is a different issue from superiority as a prognostic predictor. We may also have to recognize a study that showed the superiority of baPWV to CAVI in terms of reproducibility in the Caucasian population, although the statistical difference was not described.[152]

Perspective

Necessity of more prognostic studies of CAVI

Three meta-analyses of the prognostic significance of baPWV have already been published,[18–21] and the cutoff baPWV of 18 m/s is largely consistent.[3,21,22] No published meta-analysis has examined the prognostic significance of CAVI probably due to the shortage of reports. Thus, further studies are required. The large-scale CAVI-J study that aims to validate the prognostic significance of CAVI is currently in progress, and its results are pending.[153] A few large longitudinal studies in Western countries are also in progress. According to the MARK study in Spain, CAVI was significantly and positively associated with an index of physical functional quality of life (standardized physical component: the higher, the better), ABI was also significantly and positively associated (both after multivariate adjustment), and baPWV was not correlated.[154] Moreover, baPWV and CAVI showed similar correlations with carotid atherosclerosis indices.[155] This result is similar to that of the Japanese hemodialysis study.[143] In the comparison of cfPWV and CAVI according to the Advanced Approach to Arterial Stiffness study of 18 European countries, age–gender adjustment of cfPWV but not CAVI was higher in the patients with metabolic syndrome than those without.[141,156] A similar result was also reported in Japan. In the present study, baPWV but not CAVI was significantly higher in the patients with metabolic syndromes than those without among the middle-aged health checkup population.[157] It will be interesting to note whether the same difference in study results as that obtained in the Japanese cohorts is demonstrated.[136,154,156]

Necessity of rigorous patient exclusion criteria

When using baPWV and CAVI, especially in a study cohort consisting of patients with severe conditions, the patient exclusion criteria should be more rigorous; at least, LE-ASO/PAD definition of ABI ≤0.9 should be used. Arrhythmia and aortic valve disease should be used as well.[117] In addition, UE-ASO should be considered in patients receiving hemodialysis.[117,144] Especially, regarding the exclusion criteria of LE-ASO/PAD in the study of prognostic significance, as the first step, we can set the best ABI cutoff by ROC curve analysis in the prognostic prediction. The analysis of baPWV and CAVI can be permitted only in patients with an ABI that exceeds the best cutoff. When using a simple cutoff such as ABI ≤0.9 or ABI ≤0.99, the heart rate-adjusted UT[130] and %MAP[86,131] should also be included in the criteria.[158] Moreover, the use of a higher baPWV and CAVI on either side is favorable.[22,119] Especially, when using the mean or designated side of those indices, the masked LE-ASO/PAD must be thoroughly excluded.

Adopting the concept of stiffness parameter β and other methods of blood pressure adjustment

The concept of stiffness β and CAVI[14] can be applied to other devices that measure PWV and blood pressure if we neglect the “a” and “b” constants, which are used to convert the slope and the coordinate of the CAVI equation in VS. We can also use a general constant for the blood density ρ. In fact, a few studies have adopted this idea using VP.[159] However, this is not exactly the same as the CAVI measured by VS. Nevertheless, a baPWV-derived CAVI, the brachial–ankle vascular index, is comparable to the baPWV, and this conversion is quite easy to make. Therefore, a reanalysis comparing both indices in the previously published studies would be interesting. If necessary, haPWV can also be measured by changing the VP settings.[149] Regarding CAVI, Spronck et al[138] suggested a novel method of adjusting blood pressure. Steppan et al[135] also suggested “arterial stiffness index,” which is the product of PWV divided by PP (PWV/PP), as an effective method to adjust the influence of blood pressure on PWV. One study indicated a strong linear relationship between baPWV and the sum of four-limb PP.[160] Applying those concepts to these devices would also be easy.

Necessity of prospective large-scale study

Finally, this study discussed the independent prognostic predictability of baPWV and CAVI after adjustment by the multivariate Cox proportional hazards model. The more important ability is the additive predictive value on conventional risk factors (reclassification improvement in risk stratification), which was demonstrated in a few studies of baPWV and CAVI.[47,111] This was also demonstrated in the latest meta-analysis of baPWV using individual participant data.[20] Further studies are expected to confirm the superior index including this factor. Furthermore, no study to date directly compared prognostic predictability of baPWV and cfPWV in a same study population. Therefore, a prospective large-scale study is warranted to simultaneously investigate baPWV, CAVI, cfPWV, and other arterial stiffness indices in the prognostic significance.

Limitations

There are several limitations to the interpretation of the results. First, because the number of articles was insufficient, the multivariate logistic analysis showed only the statistical tendency for the significance of baPWV after redefining the studies. Moreover, the analysis also demonstrated the most powerful effect of the number of the participants in each study. This implies that the success of the prognostic prediction strongly relies upon the quality of the study itself. However, it should be recognized that the statistical tendency for baPWV and exclusion criteria of LE-ASO/PAD emerged in the number of currently available articles. The results also imply that the reproducibility of baPWV as a prognostic predictor is superior to that of CAVI in the various clinical conditions. Moreover, the fact that baPWV already showed results similar to those for cfPWV in the meta-analyses would be consistent with the results of this study as a whole. Furthermore, we should recognize that only 40% of the studies proved the prognostic significance of CAVI. Second, publication bias was not considered in this study. As such, denying the existence of unpublished studies that could affect the statistical results is difficult. Nevertheless, the ratio of articles that clarified the exclusion criteria of LE-ASO/PAD was similar in the baPWV and CAVI studies. The success rates of the baPWV and CAVI studies declined in the absence of clarified exclusion criteria of LE-ASO/PAD. Moreover, the ratio of the articles studying the prognostic significance of these parameters did not differ significantly (baPWV 70/1,800; CAVI 15/550). Therefore, the prognostic studies of baPWV and CAVI were published without strong bias. Third, this study did not consider other criteria of the patient exclusion such as arrhythmia and aortic valve diseases. However, the description and the definition of the patient exclusion criteria are diverse among each study and sometimes uncertain. Thus, it was impossible to quantitatively include these factors in the statistical analysis. Nevertheless, the major limitation when using baPWV and CAVI is the presence of LE-ASO/PAD. Therefore, this factor was representatively included in the analysis. Fourth, this study did not consider the difference of covariates entered into the Cox multivariate model in each study. It is possible that the success or failure of prognostic prediction of baPWV and CAVI are induced by missing covariates or inappropriate adjustment. However, most articles researched in this study were peer reviewed. Therefore, the incidence of the inappropriate multivariate analysis would be low. Fifth, this study considered seven parameters potentially included in the multivariate logistic analysis. There might be other important factors that should have been included. Nevertheless, the number of the successful studies in the prognostic prediction was 52. Therefore, it was difficult to increase the number of parameters anyway. Finally, PubMed was the only database used in this study. However, PubMed is a widely used database worldwide, so most of the English-written articles related to the theme of this study are included.

Conclusion

This study demonstrated that the number of study participants and dialysis population were the independent determinants of the successful prognostic prediction in the baPWV and CAVI articles. This study also showed that baPWV tended to be superior to CAVI in the prognostic prediction. Moreover, the exclusion criteria of LE-ASO/PAD also affected the prognostic predictive success of both indices. Therefore, for the appropriate use of these indices, thorough LE-ASO/PAD exclusion is essential. In addition, a large-scale prospective study to simultaneously research the prognostic significance of these indices is warranted.

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Disclosure

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(Article 23) and on the supreme law provided in Article 98 of the Constitution of Japan. Dai Ato reports no other conflicts of interest in this work.

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Supplementary material

Table S1 Logistic regression analysis after redefining three studies (five studies in total)

	Univariate		Multivariate	
Covariates	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
baPWV (yes =1)	2.87 (0.92–9.03)	0.071	3.91 (0.95–16.10)	0.059
Exclusion of ASO/PAD (yes =1)	4.68 (1.73–12.70)	0.003	4.01 (1.22–13.20)	0.022
Dialysis population (yes =1)	0.19 (0.06–0.60)	0.005	0.27 (0.07–1.00)	0.049
Age (years)	0.99 (0.93–1.07)	0.87		
Male gender (%)	1.00 (0.97–1.03)	0.97		
Follow-up period (years)	1.00 (0.78–1.27)	0.97		
Log (number of patients)	14.00 (3.13–62.80)	0.0006	8.42 (1.75–40.50)	0.008

Notes: baPWV =1 or CAVI =0 is used as a binary variate. The "success or failure" in the studies simultaneously comparing baPWV and CAVI was defined for each index. Thus, the total number of the included studies is 85.

Abbreviations: ASO, arteriosclerosis obliterans; baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; PAD, peripheral arterial disease.