Review Article

Brachial-Ankle Pulse Wave Velocity, Mortality, and Cardiovascular Events

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Abstract

Pulse Wave Velocity (PWV) is used as an index of arterial stiffness worldwide. One standard PWV is the carotid-femoral PWV (cfPWV). Articles reporting the usefulness of brachial-ankle PWV (baPWV), which is measured at the brachium and ankle, are rapidly increasing.And the number of prognosis follow-up studies is approaching 40. Observing these reports, baPWV shows a prognostic predictability independent from classic atherosclerotic risk factors that are considered to improve upon the exclusion of patients with Peripheral Arterial Disease (PAD). On the other hand, it is difficult to exclude PAD only by the ordinal cut-off of ABI 0.9, especially in populations of patients with diabetes or those on hemodialysis. In this review, we summarize previously reported articles, identify the efficacy of baPWV in the various reports, consider why the predictability of baPWV is decreased in those populations, suggest possible solutions to avoid the use of inaccurate baPWV measurements, and present future perspectives.

Keywords: Brachial-Ankle Pulse Wave Velocity; Ankle-Brachial Index; Prognostic Predictability; Arterial Stiffness; Peripheral Arterial Disease; Cardiovascular Disease

Introduction

The prevention of atherosclerotic disease is an important issue in developed and developing countries. The prevention of this disease is based on controlling classical risk factors such as hypertension and Diabetes Mellitus (DM), but since it is impossible to perfectly predict future events by combining these factors, confirming arterial damage is important. CfPWV is an index vascular test with proven prognostic predictability, and many related studies have been performed in Europe [1,2].
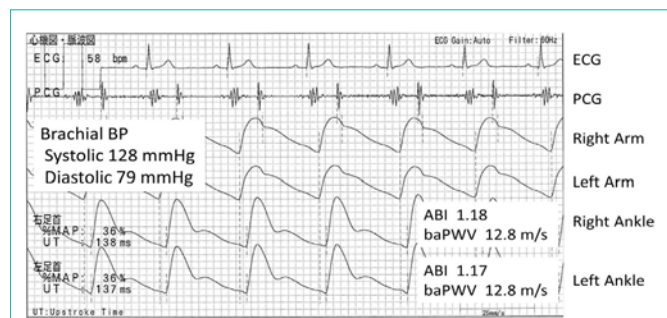
An apparatus that simultaneously measures Ankle-Brachial Index (ABI) and PWV became available in December 1999 in Japan. This machine continuously measures PWV between the brachium and the ankle (baPWV) after the ABI. With its procedural convenience, this machine first became rapidly popular in Japan and East Asian countries. The clinical use of baPWV was first started in Japan, so Japan is virtually the origin of this biomarker. The product name of this machine is "form" and it means "let us watch the 'form' of the pulse wave." Abroad, the name of "VP-1000" or "VP-2000" (Vascular Profiler) has essentially the same intent. Fifteen years have passed since its debut, and to date, more than 1000 English-language articles have reported the use of this device, not only the ABI tested by this device indicated prognostic predictability like as many preceding studies worldwide, the number of the studies of the prognostic significance of baPWV has reached nearly 40. Moreover, in early 2014, the cut-off value of 18 m/s was announced in the Japanese Circulation Society (JCS) and Japanese Society of Hypertension (JSH) guidelines [3,4]. In this review, we summarize articles focusing on the current prognostic value of baPWV and suggest possible solutions to avoid the use of inaccurate baPWV measurements as well as future perspectives.
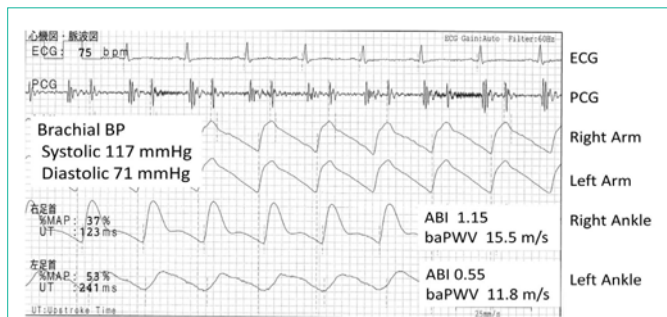
Researched Articles

Until the end of November 2014, 38 articles that mainly or additively researched the prognostic predictability of baPWV measured almost by VP in terms of all-cause mortality, cardiovascular mortality, and cardiovascular events were included. Cardiovascular events that were variously defined in different articles focusing on the events in these organs were considered in this review. The follow-up studies focusing on the progression to chronic kidney disease (>CKD3) or PAD were excluded. We summarized these articles by study population and checked the baPWV cut-off value and PAD exclusion criteria in each document because baPWV is underestimated in the limbs of patients with PAD [5]. We also included articles which provide the product name when the baPWV was measured by other apparatuses. The additive value to classical atherosclerotic risk factors is a crucial point in the consideration of the prognostic predictability of vascular function tests [6], so we classified the articles in which baPWV showed effectiveness as an independent prognostic biomarker after adjustment on Cox Multiple Regression Analysis (CMRA).

Measurement of baPWV and ABI

The method of measuring these indices by this apparatus was previously reported [7]. Briefly, after at least a 5-minute rest, four oscillometric cuffs are placed in both brachia and ankles, Electrocardiography (ECG) sensors are placed on both wrists, and a Phonocardiography (PCG) sensoris placed on the spine position. In the Hemodialysis (HD) population, the arm cuff is placed on the arm opposite the arteriovenous fistula. The original structure of the ankle cuff is composed of two parts, one that senses the pulse and another that occludes the artery. After automatically measuring the Blood Pressures (BP) of the four limbs, a plethysmogram is simultaneously

Figure 1: A typical normal case, 65 y.o. male. Both ABIs are normal and the pulse wave forms of the both ankles are also normal. These ankle pulse wave forms also show clear dicrotic wave in the early diastole. So these pulse wave forms are ideal for the ankle and PAD is hardly suspected, therefore use of baPWV is appropriate. 12.8 m/s is normal. So this male has an ideal result of this vascular physiological examination for his age.

Figure 2: A typical PAD case, 49 y.o. male. The left ankle pulse wave form is triangular and the height of this pulse wave is apparently lower than the right ankle. The left UT and %MAP are also much higher. The left baPWV is much lower than the right, but this is underestimated comparing to the right baPWV because of the stenosis, and cannot be used. The right ankle wave form is normal, but use of this baPWV 15.5 m/s is not appropriate as a prognostic biomarker because these patients are already at high risk with PAD.

measured for about 10 seconds. The pulse volume recording is performed on four limbs and the cuff pressure is kept at 55 mmHg. The Pulse-Transit Time (PTT) is calculated by the time difference between the up-stroke of the right brachium and both ankles as pulse transit Time brachial-ankle (Tba). The travel path of the pulse is defined as follows: Lba (cm) = 0.59 × height (cm) + 14.4 [8]. As such, baPWV is Lba/Tba. The baPWV value is reportedly significantly correlated with aortic PWV and the Pearson correlation coefficient is approximately 0.8 [7,9,10]. Its reproducibility is also reportedly good. The inter-observer coefficient is 0.98 [7] and the intra-observer coefficient is 0.89 [11].

In the evaluation of baPWV, the first step is to confirm whether there is decline of ABI to exclude baPWV underestimation [5] because PTT decreases when there is any significant stenosis in the pulse pathway. The ankle BP and ABI accuracy measured by this machine is also valid compared to the Doppler method [12-15], for example, the Pearson correlation coefficient of the ankle systolic BP is 0.95 [14]. Moreover, in this machine, Upstroke Time (UT), and percent mean arterial pressure (%MAP) are provided as quantitative indices of the pulse wave form. These parameters are supportively used to judge the existence of PAD in the clinical setting. Nevertheless, the studies included in this review did not add these supportive parameters to define PAD, so we only focused on whether they describe ABI/PAD exclusion criteria for baPWV analysis in this review. To easily image

this point, we provided two examples of the printed results of this apparatus to demonstrate the change of the ankle pulse wave form from normal to PAD (Figures 1,2).

Whole Reports

The first study of the prognostic value of baPWV was published in 2005. To date, 38 articles including the reports by the other apparatuses have been published [16-53]. By the end of 2009, there were only five reports, and its number increased rapidly after 2012. Table 1 lists all of the articles, most of which came from Japan, several came from East-Asia and one each came from Greece and Russia. Of the 37 reports excluding the meta-analysis [28], 29 were effective and eight were ineffective. The ineffective studies were most common in the HD cohorts. The summaries and speculations in various cohorts are described below.

Local Residents

Four articles were found in the general examination cohorts [21,31,32,34] (Table 2). The difference of the baPWV cut-off of the each report is the smallest in this population. Approximately 1000 people were followed up more than 6.5 years. The mean age at enrollment was 60 years and the cut-off baPWV was very similar. Therefore, the baPWV cut-off could be summarized at 17–18 m/s in this population.

Community-Dwelling Elderly

Four articles were found; with the exception of the Sheng study, the average age at enrollment was >75 years [18,20,42,45] (Table 3). The baPWV cut-off was in the range of 18.6–25 m/s. The Matsuoka study stated only that a value ≥25 m/s is an abnormally high value. If it was subjected to Receiver Operating Characteristic (ROC) curve analysis, it might be lower. Sheng reported a cut-off value of 23.3 m/s, but this analysis was done by comparison of the top decile to that of all patients. As such, similar to Matsuoka's study, the value might be lower if analyzed by another method such as ROC. The population in these cohorts is about 10 years older than that of the local resident mentioned above, so it is reasonable that the cut-off would increase. Nevertheless, the further accumulation of reports on the baPWV cut-off in the elderly is eagerly awaited.

Hypertensives, Outpatients, Chronic Kidney Disease

By summarizing these populations, we identified seven reports [25,26,29,30,33,35,37] (Table 4), all of which found baPWV effective. The cut-off values were in the range of 15.7–19.6 m/s. Yoon et al. reported that 15.7 m/s was the cut-off, but the younger mean patient age might be related. Chen et al. reported a 19.6 m/s cut-off, but the mean age at enrollment in that study was 69, which might affect this result. Moreover, these two reports did not mention the ABI/PAD exclusion criteria, so this might also be a factor. Nagai et al. reported a cut-off of 19.1 m/s, but the older mean age of 71 years is considered a reason. In the other four articles, mean age was near 60 and the cut-off was 17–18.9 m/s. As such, the baPWV cut-off could be summarized as 17–19 m/s in 60–70-year-old patients in these populations.

Coronary Artery Disease, Acute Coronary Syndrome, Heart Failure

There are eight articles in the heart disease cohort

Table 1: Lists of articles researching prognostic predictability of baPWV.

	No.	Article	Population	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off	Notice
Effective (*)	30	Kuroiwa 2014 [45]	CDE	VP	450	76.6	3	All cause mortality	18.6 m/s	Multiple logistic regresion analysis
	29	Seo 2014 [44]	CAD	VP	372	65	2.2	Cardiac death, Major adverse cardiac events	16.7 m/s	The lower baPWV is applied, include ABI < 0.9
	28	Chang 2014 [43]	DM	VP	452	68	5.8	All cause mortality, Fatal and non-fatal cardiovascular events	≧17 m/s with ABI < 0.9	Include ABI < 0.9
	27	Sheng 2014 [42]	CDE	VP	3876	68.1	5.9	All cause mortality, non-cardiovascular mortality	23.3 m/s	Top decile versus whole population
	26	Katakami 2014 [41]	DM	VP	1040	59	7.5 (median)	Fatal and non-fatal cardiovascular events	15.5 m/s	
	25	Ki 2014 [40]	CAD	VP	372	65	2.2	Cardiac death, Major adverse cardiac events	16.7 m/s	The lower baPWV is applied, include ABI < 0.9
	24	Maeda 2014 [39]	DM	VP	3628	61	3.2	All cause mortality, Cerebrovascular events	24 m/s 14 m/s	
	23	Kim 2014 [38]	Stroke	VP	1765	65	3.3	All cause mortality, cardiovascular mortality	22.6 m/s	The higher baPWV is applied, include PAD
	22	Kawai 2014 [37]	HT	VP	338	61	6.5	Fatal and non-fatal cardiovascular events	18.9 m/s	
	21	Sugamata 2014 [36]	CAD	VP	923	65	5.3	Major adverse cardiac events	1SD increase	(***)
	20	Nagai 2013 [35]	Outpatients	VP	274	71	3.4	Fatal and non-fatal cardiovascular events	19.1 m/s	(***)
	19	Takashima 2014 [34]	LR	VP	4164	58.9	6.5 (median)	Fatal and non-fatal cardiovascular events	18 m/s	
	18	Yoon 2013 [33]	CKD	VP	117	54	1.0 (median)	Fatal and non-fatal cardiovascular events	15.7 m/s	eGFR <90, the higher baPWV is applied (***)
	17	Ishisone 2013 [32]	LR	VP	973	59	7.8	Fatal and non-fatal cardiovascular events	16.7 m/s (top quartile)	Cox multivariate analysis was performed for baPWV above 90th percentile
	16	Ninomiya 2013 [31]	LR	VP	2916	60	7.1	Fatal and non-fatal cardiovascular events	17.6 m/s	Hisayama-Study
	15	Kawai 2013 [30]	HT	Other	440	61	6.3	Fatal and non-fatal cardiovascular events	17.5 m/s	
	14	Han 2013 [29]	Outpatients	VP	185	62	1.7	Fatal and non-fatal cardiovascular events	17 m/s	Include ABI < 0.9
	13	Vlachopoulos 2012 [28]	Meta-Analysis, combined	Almost VP				All cause mortality, cardiovascular mortality, Fatal and non-fatal cardiovascular events	lowest group vs highest group, 1 m/s increase	Meta-Analysis, including data of abstracts obtained from a few conference, several studies Include ABI < 0.9
	12	Kato 2012 [27]	HD	Other	135	60	5.3	Cardiovascular mortality	16.6 m/s	
	11	Munakata 2012 [26]	HT	VP	662	60	3	Fatal and non-fatal cardiovascular events	17.5 m/s	J-TOPP Study
	10	Chen 2011 [25]	CKD	VP	145	69	1.2	Death or progression to commencement of dialysis	19.6 m/s	The higher baPWV is applied, baPWV is adjusted by mean BP for the analysis (***)
	9	Inoue 2012 [24]	HD	VP	197	66	5.8	Fatal and non-fatal cardiovascular events	1cm/s increase	
	8	Orlova 2010 [23]	CAD	Other	161	57	3.5	Major adverse cardiac events	positive ΔbaPWV	Russia (***)
	7	Nakamura 2010 [22]	CAD	VP	564	64	2.1 (median)	Fatal and non-fatal cardiac events	17.3 m/s	Effective in only DM patients
	6	Turin 2010 [21]	LR	VP	2642	58.4	6.5	All cause mortality	17 m/s	
	5	Miyano 2010 [20]	CDE	VP	530	76	3	All cause mortality, cardiovascular mortality	19.6 m/s	
	4	Meguro 2009 [19]	HF	VP	72	68	1.2	Re-admittion because of HF exacerbation	17.5 m/s	

	3	Matsuoka 2005 [18]	CDE	VP	298	79.6	3.4	Cardiovascular mortality	25 m/s	
	2	Kitahara 2005 [17]	HD	VP	671	59	2.8	All cause mortality, Cardiovascular mortality	19.6 m/s 23 m/s	
	1	Tomiyama 2005 [16]	ACS	VP	215	63	2.2	Fatal and non-fatal cardiovascular events	17 m/s	Include ABI < 0.9
Not Effective (**)	8	Park 2014 [53]	CAD	VP	203	57	4.2	Fatal and non-fatal cardiovascular events		Exclude ABI < 0.9
	7	Kuwahara 2014 [52]	HD	VP	300	61	7	All cause mortality		Include ABI < 0.9
	6	Yoshida 2012 [51]	DM	VP	783	No average (30-75)	5.5	Fatal and non-fatal cardiovascular events		(***)
	5	Tanaka 2011 [50]	HD	VP	445	63	3.6	All cause mortality, Cardiovascular mortality		Include ABI < 0.9
	4	Amemiya 2011 [49]	HD	VP	186	61	4	All cause mortality		(***)
	3	Chen 2010 [48]	HD	VP	212	59	2.4	All cause mortality, Cardiovascular mortality		Include ABI < 0.9
	2	Kato 2010 [47]	HD	Other	194	64	3.3	All cause mortality, Fatal and non-fatal cardiovascular events		Include ABI < 0.9
	1	Morimoto 2009 [46]	HD	VP	176	61	3.6	All cause mortality, Cardiovascular mortality		(****)

Table 2: Lists of articles researching local resident.

Article	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Takashima 2014 [34]	VP	4164	58.9	6.5 (median)	Fatal and non-fatal cardiovascular events	18 m/s
Ishisone 2013 [32]	VP	973	59	7.8	Fatal and non-fatal cardiovascular events	16.7 m/s (top quartile)
Ninomiya 2013 [31]	VP	2916	60	7.1	Fatal and non-fatal cardiovascular events	17.6 m/s
Turin 2010 [21]	VP	2642	58.4	6.5	All cause mortality	17 m/s

Abbreviations; VP: Vascular Profiler In Ishisone 2013, Cox multivariate analysis was performed for baPWV above 90th percentile.

Table 3: Lists of articles researching community dwelling elderly.

Article	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Kuroiwa 2014 [45]	VP	450	76.6	3	All cause mortality	18.6 m/s
Sheng 2014 [42]	VP	3876	68.1	5.9	All cause mortality, non- cardiovascular mortality	23.3 m/s
Miyano 2010 [20]	VP	530	76	3	All cause mortality, cardiovascular mortality	19.6 m/s
Matsuoka 2005 [18]	VP	298	79.6	3.4	Cardiovascular mortality	25 m/s

Abbreviations; VP: Vascular Profiler In Kuroiwa 2014, multiple logistic regression analysis was performed.

Table 4: Lists of articles researching hypertensives, outpatients, chronic kidney disease.

Article	Population	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Kawai 2014 [37]	HT	VP	338	61	6.5	Fatal and non-fatal cardiovascular events	18.9 m/s
Nagai 2013 [35]	Outpatients	VP	274	71	3.4	Fatal and non-fatal cardiovascular events	19.1 m/s (***)
Yoon 2013 [33]	CKD	VP	117	54	1 (median)	Fatal and non-fatal cardiovascular events	15.7 m/s (***)
Kawai 2013 [30]	HT	Other	440	61	6.3	Fatal and non-fatal cardiovascular events	17.5 m/s
Han 2013 [29]	Outpatients	VP	185	62	1.7	Fatal and non-fatal cardiovascular events	17 m/s
Munakata 2012 [26]	HT	VP	662	60	3	Fatal and non-fatal cardiovascular events	17.5 m/s
Chen 2011 [25]	CKD	VP	145	69	1.2	Death or progression to commencement of dialysis	19.6 m/s (***)

Abbreviations; VP: Vascular Profiler; HT: Hypertension; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate (***) Not mentioned about ABI exclusion criteria nor described about ABI value itself In Yoon 2013, effective only in the group of eGFR <90, the higher baPWV is applied. In Han 2013, patients with ABI < 0.9 are included. In Chen 2011, the higher baPWV is applied and baPWV is adjusted by mean BP for the analysis.

Table 5: Lists of articles researching heart diseases.

Article	Population	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Seo 2014 [44]	CAD	VP	372	65	2.2	Cardiac death, Major adverse cardiac events	16.7 m/s
Ki 2014 [40]	CAD	VP	372	65	2.2	Cardiac death, Major adverse cardiac events	16.7 m/s
Sugamata 2014 [36]	CAD	VP	923	65	5.3	Major adverse cardiac events	1 SD increase (***)
Orlova 2010 [23]	CAD	Other	161	57	3.5	Major adverse cardiac events	positive ΔbaPWV (***)
Nakamura 2010 [22]	CAD	VP	564	64	2.1 (median)	Fatal and non-fatal cardiac events	17.3 m/s
Meguro 2009 [19]	HF	VP	72	68	1.2	Re-admission because of HF exacerbation	17.5 m/s
Tomiyama 2005 [16]	ACS	VP	215	63	2.2	Fatal and non-fatal cardiovascular events	17 m/s
Park 2014 [53]	CAD	VP	203	57	4.2	Fatal and non-fatal cardiovascular events	

Abbreviations; VP: Vascular Profiler; CAD: Coronary Artery Disease; HF: Heart Failure; ACS: Acute Coronary Syndrome; SD: Standard Deviation (***) Not mentioned about ABI exclusion criteria nor described about ABI value itself. In Seo 2014 and Ki 2014, the lower baPWV is applied, include ABI <0.9. In Nakamura 2010, effective only in only DM patients. In Tomiyama 2005, ABI <0.9 is included. In Park 2014, ABI <0.9 is excluded.

Table 6: Lists of articles researching diabetes mellitus.

Article	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Chang 2014 [43]	VP	452	68	5.8	All cause mortality, Fatal and non-fatal cardiovascular events	≥17 m/s with ABI < 0.9
Katakami 2014 [41]	VP	1040	59	7.5 (median)	Fatal and non-fatal cardiovascular events	15.5 m/s
Maeda 2014 [39]	VP	3628	61	3.2	All cause Mortality, Cerevrovascular events	24 m/s 14 m/s
Yoshida 2012 [51]	VP	783	No average (30-75)	5.5	Fatal and non-fatal cardiovascular events	(***)

Abbreviations; VP: Vascular Profiler (***) Not mentioned about ABI exclusion criteria nor described about ABI value itself. In Chang 2014, ABI < 0.9 is included.

[16,19,22,23,36,40,44,53]; of them, seven found baPWV effective (Table 5). However, only three of the eight studies clearly described their ABI/PAD exclusion criteria. The baPWV effective studies that did not exclude PAD found a higher baPWV or did not use baPWV in the limbs with an ABI < 0.9, and these methods are considered the reason for the effective outcome. On the contrary, Park et al. reported that baPWV was not effectiveness even after excluding those with an ABI <0.9. Nakamura et al. reports that baPWV does not have predictability in groups of patients without DM, so it is not unnatural for similar results to be found among different study populations. Orlova et al. presented the only study from the Caucasian population. However, this result would have to be carefully applied to Asian populations, especially Japanese, since this study included only male patients, the average life expectancy of Russian men differs from that of Japanese men by >10 years, and the prevalence of disease differs between Caucasian and Japanese men. Review of these eight reports in the heart disease population revealed that 17–18 m/s could be set as a baPWV cut-off with some limitations depending on condition. Otsuka et al. reported results in a similar category [54]; as such, we did not add this paper to the list because it did not specify which device was used to measure baPWV.

Stroke

The subject of this cohort had acute ischemic stroke [38]. The measurement of baPWV is usually performed on the third admission day, so we must consider that this condition would differ from the general elective condition. The baPWV cut-off of 22.6 m/s is much higher for the cohort of this age than those in other studies,

which must be considered in its application to other populations. Furthermore, sub-group analysis after excluding the patients with atrial fibrillation and a borderline ABI < 0.95 showed a higher Hazard Ratio (HR) of 0.5–0.6 with each 10 m/s increase. This stresses the importance of PAD exclusion criteria for baPWV evaluations.

Diabetes

Vlachopolous et al. already mentioned that the prognostic value of baPWV was lower among the DM population in a 2012 meta-analysis [28]. There are four studies and some difference of the results exists among these papers [39,41,43,51] (Table 6). Yoshida et al. reported no explanation about PAD exclusion criteria and that ABI was not an anthropometric parameter itself (it cannot be asserted that this subgroup is not excluded). In this study, the highest quartile of baPWV showed a significantly lower event-free survival rate on Kaplan-Meier analysis, so the predictability of baPWV was lost after CMRA adjustment including Framingham Risk Score as a covariate. Chang et al. included patients with an ABI < 0.9, but their stratification method combined values of baPWV ≥ 17 m/s and ABI < 0.9. In other words, in the patients who have at least one limb with an ABI < 0.9, they reclassified patients by a baPWV > 17 m/s, which might be effective.

Maeda et al. and Katakami et al. both reported baPWV efficacy. However, the cut-off baPWV differed extensively even though they excluded patients with ABI < 0.9 and the average patient age was very close. Furthermore, 24 m/s for total mortality and 14 m/s for cardiovascular events were reported by Maeda et al., so we speculate that this is the reason for the finding. Natsuaki et al. simultaneously

Table 7: Lists of articles researching hemodialysis patients.

Article	Apparatus	Number of patients	Age (average)	Follow-up period (years)	End point	baPWV cut-off
Kato 2012 [27]	Other	135	60	5.3	Cardiovascular mortality	16.6 m/s
Inoue 2012 [24]	VP	197	66	5.8	Fatal and non-fatal cardiovascular events	lcm/s increase
Kitahara 2005 [17]	VP	671	59	2.8	All cause mortality, Cardiovascular mortality	19.6 m/s 23 m/s
Kuwahara 2014 [52]	VP	300	61	7	All cause mortality	
Tanaka 2011 [50]	VP	445	63	3.6	All cause mortality, Cardiovascular mortality	
Amemiya 2011 [49]	VP	186	61	4	All cause mortality	(***)
Chen 2010 [48]	VP	212	59	2.4	All cause mortality, Cardiovascular mortality	
Kato 2010 [47]	Other	194	64	3.3	All cause mortality, Fatal and non-fatal cardiovascular events	
Morimoto 2009 [46]	VP	176	61	3.6	All cause mortality, Cardiovascular mortality	(****)

Abbreviations; VP: Vascular Profiler (***) Not mentioned about ABI exclusion criteria nor described about ABI value itself (****) Excluded ABI<0.9, and ABI is included in the cox regression analysis. In Kuwahara 2014, Tanaka 2011, Chen 2010, Kato 2010, ABI < 0.9 is included.

reported on the prognostic predictability of ABI in the same study cohort [55]. In this report, patients with an abnormal (≤0.9) or borderline (0.91–0.99) ABI were found to equally have a significant two-fold HR for total mortality and cardiovascular mortality compared to those with a normal (1.0–1.4) ABI. Furthermore, the risk of progression to the abnormal ABI was also significantly higher in patients with a borderline ABI than those with an ABI> 1.0. These results strongly imply that especially in patients with DM, a borderline ABI may indicate progression of systemic atherosclerosis, especially in other arteries. There is one case in which ABI is borderline or pseudo normal even when there is a significant stenosis in the arteries of the lower limbs that was considered to be caused by calcification, the so-called Moenckeberg's arteriosclerosis, which is common in DM and HD [56,57]. As a result of these conditions, baPWV may have been already underestimated in patients with a borderline ABI, which then caused the discrepancy in baPWV cut-off values. On the other hand, Maeda et al. reported that the hazards of mortality and cardiovascular events increase linearly with baPWV but that the raw ratios of the mortality and coronary events differ by only about two-fold between the lowest (<14.4 m/s) and highest (>19.8 m/s) quartiles. This ratio is much lower compared to those of general populations. Therefore, in the Maeda study, a number of high-risk patients with a borderline ABI whose risks were virtually the same as patients with an ABI ≤ 0.9 were included in the lowest and the two middle quartiles of baPWV, which is considered the reason for the smaller difference in the occurrence of death and cardiovascular events between the lowest and the highest quartiles of baPWV. The same phenomenon likely exists in Katakami study, in which it could not be denied that there was an influence that decreased the baPWV values. Therefore, in the DM cohort, an ABI < 1.0 should be considered high-risk. And if the pulse wave form of the ankle is not normal, the use of baPWV as a prognostic biomarker should be pended.

Hemodialysis

Nine articles in our search results focused on the HD population [17,24,27,46-50,52]; of them, only three reported that baPWV was an effective prognostic marker (Table 7). Nevertheless, there are very important lessons of baPWV evaluation, especially in these studies. The four of six studies that did not show baPWV effectiveness did not exclude patients with PAD or an ABI < 0.9. Another paper did not

mention ABI/PAD exclusion criteria. Therefore, only the Morimoto et al. study certainlyexcluded patients with an ABI < 0.9 among these six papers. On the contrary, the three studies that showed baPWV effectiveness all excluded those with an ABI < 0.9.

Kitahara et al. reported that CMRA analysis of all 785 patients with an ABI < 0.9 revealed that baPWV lost its prognostic value and that ABI was the most powerful prognostic predictor (p < 0.0001). Next, they re-analyzed 671 patients after excluding those with an ABI < 0.9 by CMRA, baPWV was independently effective from other confounding factors even including ABI as an adjustment. It should be considered that an ABI that is borderline (0.90–0.99) or >1.3 was also independent prognostic factor in this 671-patient analysis.

Two reports of Kato et al. are also interesting. In their 2010 article [47], they analyzed baPWV and PAD and found that baPWV lost its effectiveness after CMRA. They also reported that an ABI < 1.0 is an independent prognostic predictor. On the other hand, in their 2012 report [27], upon reanalyzing the population after excluding those with an ABI < 0.9 and adding a 2-year follow-up extension, they found that baPWV was effective as an independent predictor of cardiovascular death. In addition, ABI was not included in the CMRA model in this report since it did not differ significantly between the deceased and surviving patients. More interestingly, in this article, BP-adjusted PWV showed a statistical tendency for cardiovascular death on Kaplan-Meier analysis, but this trend disappeared after adjustment for age, sex, and DM by CMRA. This implies that BP-adjusted PWV cannot always necessarily provide better results as a prognostic biomarker. In this study, the average baPWV was 16.0 m/s, median baPWV was 15.2 m/s, and highest tertile was ≥16.6 m/s, all of which were lower than those of other HD studies, and the differences in device use is thought to have greater influence than excluding patients ≥ 75 years.

Next, the reports of Amemiya et al. [49] and Inoue et al. [24] were from the same institution, and it is important that Inoue et al. demonstrate baPWV effectiveness by certainlyexcluding ABI < 0.9 even though the cohorts differed between these two studies. In addition to these reports that indicate baPWV effectiveness excluding apparent PAD, Morimoto et al. did not demonstrate this [46], so we speculate that this is the reason. As we have shown, Kitahara

Figure 3: A hemodialysis case of upper limb PAD of the non-HA side, 72 y.o. male. The brachial BP is able to be measured only on the left arm because the right arm has a HA. This brachial BP is very low and the pulse wave form of the left arm is triangular and blunt. So this apparently shows the existence of PAD. As a result, the ABIs are abnormally high. And these pulse wave forms are also apparently triangle on the both side. So PADs of both legs are also strongly suspected. Therefore, both ABI and baPWV are not reliable at all.

et al. proved that not only higher baPWV also borderline ABI are independent prognostic predictors even after the exclusion of ABI < 0.9. In this study, even an ABI of 1.0–1.09 also shows a tendency or close value (p = 0.113 for total mortality, p = 0.086 for cardiovascular mortality after CMRA). On the other hand, Ono et al., one of the co-authors of the Kitahara article, previously reported on ABI prognostic values in 1010 HD patients [12] but did not measure or describe baPWV. In this 2003 report, needless to say, in addition to patients with an ABI < 0.9 or 0.90–0.99, those with an ABI of 1.0–1.09 showed worse prognosis than those with a normal ABI of 1.1–1.29 (HR, 1.92 and 95% Confidence Interval [CI], 1.02–3.59 for total mortality; HR, 2.82 and 95% CI, 1.22–6.54 for cardiovascular mortality after CMRA). Actually, Ono mentions that an ABI < 1.1 should already be noted from the view of prognosis. Furthermore, one study described that the best cut-off ABI was 1.1 for predicting total morality in patients with HD by ROC analysis, on which the Area Under the Curve (AUC) was 0.79, sensitivity was 0.9, and specificity was 0.62 [58]. This report comes from the same institute of Amemiya and Inoue. Therefore, in the HD population, it is implied that even an ABI < 1.1 can indicate a worse prognosis depending on the cohort.

As described above, Kato et al. showed that an ABI < 1.0 indicated worse prognosis [47] and Natsuaki et al. proved worse prognosis in patients with DM and a borderline ABI [55]. Considering this knowledge, in the patients at higher risk of lower limb artery calcification such as those with DM and HD, a borderline ABI indicates the progression of systemic atherosclerosis in the arteries body wide. This also implies that even in patients with an ABI > 1.0, a pseudo-normal ABI and prognostic deterioration should be considered depending on the cohort. Actually, the best cut-off ABI for patients with PAD > 50% square stenosis by computed tomography angiography was 0.99 in the ordinal PAD cohort [59]. In addition, Okamoto et al. reported that the sensitivity of an ABI < 0.9 for PAD in the HD cohort was only 29.9% [60]. Furthermore, other reports have shown that even a difference in ABI or ankle BP can predict future prognosis independently from ABI itself [61,62]. The Morimoto study excluded patients with an ABI < 0.9, but CMRA was performed including ABI as an adjustment, so some patients whose ABI was 0.91–1 or slightly higher might have worse prognosis, meaning baPWV underestimation but higher risk at the same time.

As a result, the prognostic significance of baPWV is considered lost. In the HD studies, the prognostic value of baPWV was hardly proven, at least without the exclusion of patients with an ABI < 0.9.

Overestimation of ABI on Upper-Limb PAD

Above we discussed the overestimation of ABI that resulted from arterial calcification in the patients on HD, and there is a considerable pitfall of measuring ABI and baPWV in the HD population. As we know, ABI is calculated by dividing the ankle systolic BP by the higher brachial BP [56,57]. Measuring the brachial BP of the Hemodialysis Access (HA) side is generally contraindicated, so the brachial BP is mostly measured on the non-HA side. If PAD exists in the non-HA side (i.e. subclavian artery), its ABI is inevitably overestimated because the denominator used to calculate ABI is lower than when there is no upper-limb PAD (Figure 3). Furthermore, in this condition, baPWV is also likely overestimated. The PTT from the heart to the brachium possibly prolongs because of the stenosis, so the time difference of the brachium and the ankle shortens and the denominator for the baPWV calculation decreases. As a result, baPWV is overestimated (Figure 3).

Of the articles we reviewed, no report defined exclusion criteria that considered this phenomenon, at least in the methodology explanation. Actually, much data such as ABI > 1.5 and baPWV > 40 m/s were seen in the Kitahara report [17]. An abnormally high ABI is also caused by arterial calcification and aortic valve regurgitation, and it is unclear whether an abnormally high ABI is a product after exclusion of the upper-limb PAD pitfall. Of course, a patient with a pseudo-high baPWV will definitely be at high risk. The BP difference of the upper limb mostly caused by upper-limb PAD is reportedly a prognostic predictor, at least in non-HD cohorts [63,64]. We must interpret the results in HD patients in whom ABI and baPWV are tested in only one brachium much more carefully than those in other populations. For these reasons, when using baPWV as a clinical biomarker in HD, a concept may require discussion. That is, it should only be indicated when at least upper-limb PAD is definitely denied and ABI is normal (i.e. ≥1.0), ideally when the pulse wave form of the ankle is normal on both sides. Clinicians should consider stratifying the risk of HD patients by ABI only unless a patient is in the condition mentioned above. This concept should be also considered in the DM population, especially in terms of the ankle pulse wave form, although ABI overestimation by upper-limb PAD is deniable in most cases.

Perspective

Here we provided an outline of 38 articles that evaluated the prognostic predictability of baPWV. Except for a meta-analysis of 2012 [28], 29 found it effective and eight found it ineffective. In the 2012 meta-analysis article, publication bias was evaluated by funnel plot analysis. The authors concluded that it is unlikely that there would be number of the articles estimated necessary to lose baPWV effectiveness using the fail-safeNtest. This meta-analysis was published online in early summer 2012, and they utilized the data of 16 previously published studies (of the summarized studies, 13 were effective and three were not, and these numbers were derive from the efficacy in the original article, not about the data used in this meta-analysis, and we excluded the data of the abstracts of various conferences). Approximately 2.5-fold more studies are currently available, and the balance of effective and ineffective results did not
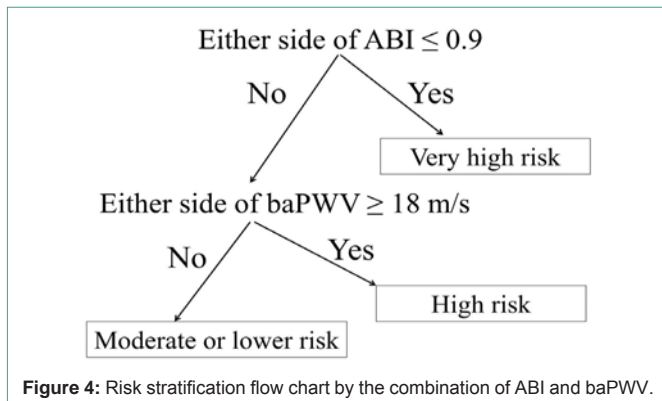
Figure 4: Risk stratification flow chart by the combination of ABI and baPWV.

Figure 5: Precise risk stratification by ABI, baPWV (modified for this review article).

change. The data including PAD was included in this meta-analysis. Therefore, at present, even if we consider publication bias, baPWV as a whole has additive value as a prognostic predictor independent from classical risk factors. As such, we consider why baPWV has prognostic predictability. Aortic PWV has proven prognostic predictability independent from classical risk factors [1,2], while baPWV has shown a strong correlation with aortic PWV [7,9,10]. This is the same by evaluating the artery lengths, which is based on magnetic resonance imaging measurements [10]. At the same time, among various PWV, aortic PWV is the strongest factor that regulates baPWV on multiple regression analysis [10]. Therefore, it is reasonable that baPWV shows similar characteristics like cfPWV regarding prognostic predictability.

It is frequently noted that baPWV has the characteristic of being measured much higher than the real speed of the pulse wave. This is mainly caused by the condition in which heart-brachial PWV is smaller than heart-ankle PWV (haPWV) [10]. This means that the ratio of PTT heart-brachium for its distance is larger than the ratio of PTT heart-ankle for its distance, which makes Tba smaller for the defined length Lba (mentioned in the measurement paragraph) compared to Tha for its distance. Consequently, baPWV is higher than haPWV, and it increases almost parallel to aortic PWV with age [10]; in reality, this phenomenon does not cause serious issues in the clinical setting.

There were some contradicting studies among the articles reviewed, and some future subjects were proposed. It is known that baPWV tends to be effective in populations in which PAD can be effectively excluded by an ABI < 0.9; if we do this certainly, the effectiveness of baPWV is considered remarkably high. As such, it would be reasonable and easily stratify the risks for future mortality and cardiovascular events. First, a patient with an ABI ≤ 0.9 is considered at very high risk. Second, a patient with an ABI > 0.9 and a baPWV ≥ 18 m/s is considered at high risk. Third, a patient with an ABI > 0.9 and a baPWV 14–18 m/s is considered at middle risk. Finally, a patient with an ABI > 0.9 and a baPWV < 14 m/s is considered at lower risk (Figure 4). These baPWV cut-off values could be defined by age. This stratification method is applicable easily in the clinical setting and was recently named the Steno-Stiffness Index (SSI), which was recently introduced at the Artery Society 2014 [65]. On the other hand, in populations in which PAD is not efficiently excluded only by an ABI < 0.9, especially those with DM and HD, baPWV effectiveness is reduced. Thus, PAD exclusion criteria would have to be stricter in
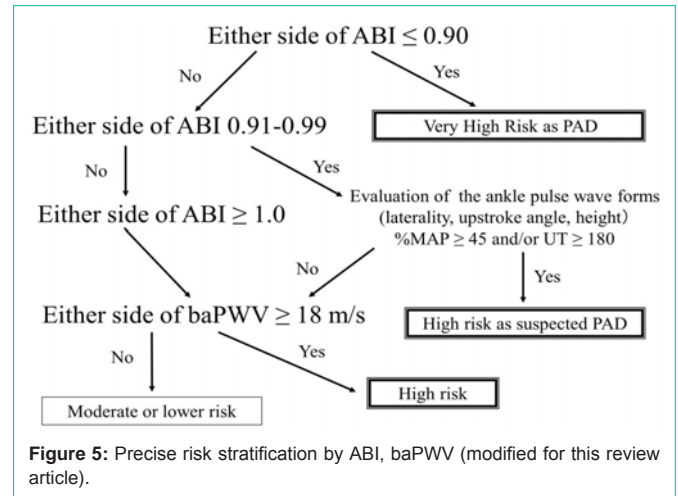
these patients, even though it will lose some degree of its simplicity. This precise SSI considers borderline ABI in combination with UT and %MAP to confirm the pulse wave form if necessary (Figure 5) [66]. To ensure a more precise SSI stratification, the best exclusion criteria of PAD for baPWV use as a prognostic biomarker is expected to be validated in the various cohorts as well as non-Asian populations. The use of a precise SSI would be more appropriate in western countries than in the Japanese general population. Because the prevalence of PAD morbidity in Japan is approximately 3% in the general elderly population approximately 70 years of age [67,68,69,70], it is expected to be much higher in the western countries [71,72]. The arterial path length is thought to differ between Asian and Caucasianpopulations, which might lead to the different baPWV cut-off values even upon PAD exclusion.

There are still a number of studies in which baPWV was evaluated without PAD exclusion, and some avoided the risk of poorer baPWV effectiveness, but this might have occurred by chance. Even if baPWV is accurate in the absence of PAD and ABI is <0.9 in the other side limb, we must recognize that this low ABI would be a stronger prognostic predictor depending on the population. Kitahara et al. reported that even the highest quartile of baPWV (≥23.8 m/s) loses its effectiveness as a predictor after CMRA adjustment to include patients with an ABI < 0.9, and ABI was the strongest predictor in this analysis [17]. Inter-study discrepancies are expected to persist if we continue to use baPWV without appropriate PAD exclusion. Therefore, in studies going forward, it is expected that baPWV should be standardized and not used as a prognostic predictor when PAD exists even only in one lower limb. Moreover, the higher, lower, right only, left only, or average baPWV can be used. According to the SSI concept, use of the higher baPWV is recommended.

Here we describe the expectation for knowledge accumulation of baPWV prognostic predictability. A larger meta-analysis conducted by the raw data in which patients with PAD patients are appropriately excluded according to the SSI concept is awaited in the future and should be repeated periodically. Improvements in the Net-Reclassification Index (NRI) as well as aortic PWV are also expected [2]. NRI improvement was demonstrated in the general population of the Hisayama study [31]. Moreover, to establish baPWV as a surrogate biomarker for the treatment of atherosclerotic diseases, a long-term intervention study targeting baPWV is desired.

Conclusion

Here we summarized available studies of baPWV prognostic predictability, which is independent from classical atherosclerotic risk factors. This efficacy is considered to improve when patients with PAD are appropriately excluded in the examination of various study populations.

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