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 19999,10 and in the first half of 2002,11,12 respectively, which
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,”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. 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. 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). 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. 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. The proportion of gender was also missing in one study. 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, because these studies were considered to insufficiently exclude LE-ASO/PAD patients (symptomatic P AD only). P-values of ≤0.05 were considered statistically significant, whereas P-values of 0.05<P≤0.10 were considered to have a statistical tendency.

Results
All articles
A total of 70 articles on baPWV and 15 articles on CAVI 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, 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, 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 al15  | baPWV   | Successful      | No                            | VP     | ACS                      | 215                | 63               | 77.7            | 2.2              |                  |                                         |
| Yamamoto et al16  | CAVI    | Failed          | Yes                           | VS     | Community-dwelling elderly | 117                | 80               | 31.1            | 4                |                  | The mortality rate did not differ between those with CAVI ≥10 and CAVI <10 |
| Kato et al24      | baPWV,  | baPWV successful, CAVI failed | No                           | VS     | Hemodialysis             | 194                | 64               | 65.5            | 3.3              | ACM              |                                |
|                   | CAVI    |                 |                               |        |                          |                    |                  |                 |                  |                  |                                |
| Kato et al25      | baPWV,  | baPWV successful, CAVI failed | Yes                          | VS     | Hemodialysis             | 135                | 60               | 67.4            | 5.3              | CCVM             |                                |
|                   | CAVI    |                 |                               |        |                          |                    |                  |                 |                  |                  |                                |
| Otsuka et al26    | baPWV,  | baPWV not described, CAVI | Yes                          | VS     | IHD with impaired CAVI   | 211                | 65               | 55.9            | 2.9              | CCVE             |                                |
|                   | CAVI    |                 |                               |        |                          |                    |                  |                 |                  |                  |                                |
| Kusunose et al27  | baPWV,  | baPWV Kaplan–Meier, CAVI | Yes                          | VS     | Outpatients with two or more risk factors | 114                | 69               | 78.1            | 4.3              | MACE             |                                |
|                   | CAVI    |                 |                               |        |                          |                    |                  |                 |                  |                  |                                |
| Gohbara et al28   | CAVI    | Successful      | Yes                           | VS     | IHD, ACS                 | 288                | 65               | 82.3            | 1.3 (median)    | CCVE             |                                |
| Yoshida et al23   | baPWV   | Failed          | Not clarified                 | VP     | Diabetes                 | 783                | 30–75            | 66.6            | 5.5              | CCVE             |                                |
| Tokitsu et al23   | baPWV   | Failed          | No                            | VP     | IHD                      | 401                |                  |                 |                  |                  |                                |
| Lau et al23       | baPWV   | Failed          | Yes                           | VP     | Diabetes                 | 151                | 61               | 40.4            | 5.1              | CCVE             |                                |
| Kitahara et al26  | baPWV   | Successful      | Yes                           | VS     | Hemodialysis             | 671                | 59               | 64.9            | 2.8              | ACM, CCVM         |                                |
| Ninomiya et al27  | baPWV   | Successful      | Yes                           | VP     | General population       | 2,916              | 60               | 42.7            | 7.1              | CCVE             |                                |
| Maeda et al28     | 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 al29   | baPWV   | Successful      | Yes                           | VP     | Community-dwelling elderly | 450                | 77               | 67.3            | 3                | ACM              | A multivariate logistic regression analysis was performed |
| Seo et al30       | baPWV   | Successful      | No                            | VP     | IHD                      | 372                | 65               | 63.2            | 2.2              | MACE             |                                |
| Chang et al31     | baPWV   | Successful      | No                            | VP     | Diabetes                 | 452                | 68               | 54.2            | 5.8              | ACM, CCVE         |                                |
| Sheng et al32     | 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<sup>3</sup> | baPWV | Successful | Yes | VP | Diabetes | 1,040 | 59 | 65.0 | 7.5 (median) | CCVE + PAD (ABI <0.9) |
| Ki et al<sup>4</sup> | baPWV | Successful | No | VP | IHD | 372 | 65 | 63.2 | 2.2 | MACE |
| Kim et al<sup>5</sup> | baPWV | Successful | No | VP | Stroke | 1,765 | 65 | 62.2 | 3.3 | ACM, CCVM |
| Kawai et al<sup>6</sup> | baPWV | Successful | Not clarified | VP | Hypertension | 338 | 61 | 54.7 | 6.5 | CCVE |
| Kawai et al<sup>7</sup> | baPWV | Successful | Not clarified | VP | Outpatients | 274 | 71 | 41.6 | 3.4 | CCVE |
| Takashima et al<sup>8</sup> | baPWV | Successful | Yes | VP | General population | 4,164 | 59 | 37.2 | 6.5 (median) | CCVE |
| Yoon et al<sup>9</sup> | baPWV | Successful | Not clarified | VP | CKD | 117 | 54 | 61.5 | 1.0 (median) | CCVE |
| Ishihara et al<sup>10</sup> | baPWV | Successful | Yes | VP | General population | 973 | 59 | 46.9 | 7.8 | CCVE |
| Han et al<sup>11</sup> | baPWV | Successful | No | VP | Outpatients | 185 | 62 | 56.2 | 1.7 | CCVE |
| Munakata et al<sup>12</sup> | baPWV | Successful | Yes | VP | Hypertension | 662 | 60 | 45.4 | 3 | CCVE |
| Chen et al<sup>13</sup> | baPWV | Successful | Not clarified | VP | CKD | 145 | 69 | 68.3 | 1.2 | ACM + commencement of dialysis |
| Inoue et al<sup>14</sup> | baPWV | Successful | Yes | VP | Hemodialysis | 197 | 66 | 61.9 | 5.8 | CCVE |
| Orlova et al<sup>15</sup> | baPWV | Successful | Not clarified | VS (considered) | IHD (male only) | 224 | 56 | 100.0 | 3.5 | MACE |
| Nakamura et al<sup>16</sup> | baPWV | Successful | Yes | VP | IHD | 564 | 64 | 80.9 | 2.1 (median) | CCVE |
| Turin et al<sup>17</sup> | baPWV | Successful | Not clarified | VP | General population | 2,642 | 58 | 33.8 | 6.5 | ACM |
| Miyano et al<sup>18</sup> | baPWV | Successful | Yes | VP | Community-dwelling elderly | 530 | 76 | 39.1 | 3 | ACM, CCVM |
| Meguro et al<sup>19</sup> | baPWV | Successful | Yes | VP | HF | 72 | 68 | 56.9 | 1.2 | Readmission of HF exacerbation |

An existence of ASO defined by ABI of <0.9 is unlikely because of the ABI value (1.1±0.00 [SE]). 118 subjects with past history of CVD and/or stroke were excluded.
| 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        | baPWV | Successful | Yes                        | VP     | Community-dwelling elderly  | 298                | 80                | 40.3            | 3.4              | CCVM             |                                                |
| Wang and Dang         | baPWV | Successful | Not clarified                | VP     | IHD with Kawasaki disease   | 48                 | 45                | 25.0            | 2.1              | MACE + in-stent restenosis of DES |                                                |
| Chen et al            | baPWV | Successful | No                           | VP     | Atrial fibrillation         | 167                | 69                | 68.3            | 2.2 (median)    | CCVE             |                                                |
| Park et al            | baPWV | Failed    | Yes                          | VP     | IHD                         | 203                | 57                | 52.7            | 4.2              | CCVE             |                                                |
| Kuwahara et al        | baPWV | Failed    | No                           | VP     | Hemodialysis                | 300                | 61                | 61.0            | 7                | ACM              |                                                |
| Orlova et al          | baPWV | Successful | Not clarified                | VP     | Hemodialysis                | 161                | 57                | 100.0           | 3.5              | MACE             |                                                |
| Tanaka et al          | baPWV | Failed    | No                           | VP     | Hemodialysis                | 445                | 63                | 59.3            | 3.6              | ACM, CCVE        |                                                |
| Amemiya et al         | baPWV | Failed    | Not clarified                | VP     | Hemodialysis                | 186                | 61                | 61.8            | 4                | ACM              |                                                |
| Chen et al            | baPWV | Failed    | No                           | VP     | Hemodialysis                | 212                | 59                | 44.8            | 2.4              | ACM, CCVM        |                                                |
| Morimoto et al        | baPWV | Successful | Yes                          | VP     | Hemodialysis                | 176                | 61                | 56.3            | 3.6              | ACM, CCVM        |                                                |
| Nagata et al          | baPWV | Successful | No                           | VP     | Methemodialysis             | 398                | 68                | 74.6            | 0.8              | MACE             | Succeeded only in patients with DES          |
| Lee et al             | baPWV | Successful | Yes                          | VP     | IHD                         | 350                | 66                | 53.4            | 1.2 (median)    | CCVE             |                                                |
| Chen et al            | baPWV | Failed    | Yes                          | VP     | CKD                         | 227                | 65                | 43.0            | 1.8              | CCVE             |                                                |
| Wei et al             | baPWV | Successful | No                           | VP     | Hemodialysis                | 205                | 59                | 44.9            | 4.4              | ACM, CCVE        |                                                |
| Iino et al            | baPWV | Failed    | Not clarified                | VP     | IHD, outpatients            | 77                 | 65                | 63.6            | 2                | MACE             |                                                |
| Li et al              | baPWV | Failed    | Yes                          | VP     | Outpatients                 | 238                | 69                | 42.9            | 1.7 (median)    | ACM              |                                                |
| Sugamata et al        | baPWV | Successful | Not clarified                | VP     | IHD                         | 923                | 65                | 71.5            | 5.3              | MACE             |                                                |
| Song et al            | baPWV | Successful | No                           | VP     | Hypertension                | 3,310              | 60                | 44.0            | 4.5 (median)    | Stroke           |                                                |
| Ikura et al           | baPWV | Successful | No                           | VP     | Diabetes with LE amputation | 102                | 63                | 78.4            | 3.3              | ACM              |                                                |
| Kawai et al           | baPWV | Failed    | No                           | VP     | Hypertension                | 353                | 63                | 57.2            | 7.9              | Stroke           |                                                |
| Chen et al            | baPWV | Failed    | No                           | VP     | Hemodialysis                | 210                | 59                | 44.3            | 4.4              | ACM, CCVE        |                                                |
| Mimura et al          | baPWV | Failed    | No                           | VP     | CKD                         | 75                 | 57                | 69.3            | 4                | ACM              |                                                |
| Ahn et al             | baPWV | Successful | Not clarified                | VP     | Acute stroke                | 1,557              | 68                | 59.3            | 2.5 (median)    | CCVM             |                                                |
| Kim et al             | baPWV | Failed    | No                           | VP     | Hemodialysis                | 77                 | 53                | 51.9            | 5                | ACM, CCVE        |                                                |
| Tabata et al          | baPWV | Failed    | No                           | VP     | IHD                         | 149                | 71                | 67.1            | 1.9 (mean), 1.3 (median) | CCVE             |                                                |
| Saji et al            | baPWV | Failed    | Not clarified                | VP     | Acute lacunar infarction    | 156                | 69                | 60.9            | 5.9 (median)    | Ischemic stroke |                                                |
| Ueki et al            | 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            | 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.           | baPWV | Failed | Not clarified                 | VP     | CKD        | 149               | 62               | 64.4            | 4.3              | CCVE + renal function decline |
| Kajimoto et al.      | baPWV | Failed | No                            | VP     | Diabetes   | 337               | 68               | 58.2            | 5                | IHD               |
| Woo et al.           | baPWV | Failed | No                            | VP     | IHD        | 91                | 57               | 63.7            | 1.4              | a denovo lesion + PCI |
| Park et al.          | baPWV | Successful | No                           | VP     | Myocardial infarction | 411           | 64               | 75.2            | 1                | CCVE               |
| Lu et al.            | baPWV | Successful | Yes                          | VP     | General population | 4,251         | 52                | 45.9            | 4.4 (median) | CCVE               |
| Tokitsu et al.       | baPWV | Successful | Yes                          | VP     | HF with preserved ejection function | 426         | 71               | 55.3            | 2.8              | CCVE               |
| Hwang et al.         | baPWV | Successful | Yes                          | VP     | Suspected IHD | 523           | 58                | 60.6            | 3.7              | CCVE               |
| Wang et al.          | baPWV | Successful | Not clarified               | VP     | Peritoneal dialysis | 254         | 61                | 61.4            | 2.6              | ACM                |
| Taniguchi et al.     | baPWV | Successful | Not clarified               | VP     | Community-dwelling elderly | 1,744     | 71                | 43.0            | 7.0 (median) | ACM                |
| Yamaguchi et al.     | CAVI  | Failed  | No                            | VS     | Hemodialysis | 270          | 63                | 56.3            | 4.5              | CCVM, CCVE + revascularization for PAD |
| Sato et al.          | CAVI  | Successful | Yes                          | VS     | Outpatients | 1,003         | 63                | 51.2            | 6.7              | IHD + coronary artery events confirmed by coronary angiography |
| Laucevičius et al.   | CAVI  | Kaplan–Meier | Not clarified               | VS     | Metabolic syndromes | 2,106        | 54                | 37.9            | 3.8              | CCVE               |
| Satoh-Asahara et al. | CAVI  | Successful | Not clarified               | VS     | Obese patients (after excluding subjects with success in weight loss) | 300        | 49                | 44.5            | 5                | CCVE + PAD |
| Chung et al.         | CAVI  | Successful | No                            | VS     | Diabetes    | 626             | 64               | 46.0            | 4.1              | CCVE               |
| Kubota et al.        | CAVI  | Successful | Yes                          | VS     | Outpatients | 400           | 69               | 63.0            | 2.3              | CCVE               |

(Continued)
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. In a study in which the baPWV result was defined as “not clarified,” the prognostic significance of baPWV in the multivariate 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.

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, \( P = 0.006 \) 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. 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. 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 the 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, 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. These studies mostly used baPWV, and one study used CAVI. However, the largest study of CAVI involving >2,000 participants failed. 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 \( \leq 0.9 \) 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 al16                | CAVI  | Failed | ASO VS Community-dwelling elderly | VS     | 117        | 80                 | 31.1             |
| Kato et al25                    | baPWV | Successful | ABI <0.9 VS Hemodialysis | VS     | 135        | 60                 | 67.4             |
| Kato et al25                    | CAVI  | Failed | ABI <0.9 VS Hemodialysis | VS     | 135        | 60                 | 67.4             |
| Otsuka et al26                  | baPWV | Failed | PAD Not described | IHD with impaired CAVI | 211 | 65 | 55.9 |
| Otsuka et al26                  | CAVI  | Successful | PAD VS IHD with impaired CAVI | VS     | 211        | 65                 | 55.9             |
| Kusunose et al27                | baPWV | Failed | Symptomatic PAD VP | Outpatients with two or more risk factors | 114 | 69 | 78.1 |
| Kusunose et al27                | CAVI  | Failed | Symptomatic PAD VS | Outpatients with two or more risk factors | 114 | 69 | 78.1 |
| Gohbara et al28                 | CAVI  | Successful | PAD VS IHD, ACS | 288 | 65 | 82.3 |
| Lau et al11                     | baPWV | Failed | Symptomatic PAD VP | Diabetes | 151 | 61 | 40.4 |
| Kitahara et al46                | baPWV | Successful | ABI <0.9 VP | Hemodialysis | 671 | 59 | 64.9 |
| Ninomiya et al47                | baPWV | Successful | ABI <0.9 VP | General population | 2,916 | 60 | 42.7 |
| Maeda et al48                   | baPWV | Successful | ABI <0.9 VP | Diabetes | 3,628 | 61 | 59.7 |
Table 2
Detailed information about baPWV and CAVI articles in which ASO and/or PAD was excluded from the analysis

| 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 1.1–25.1, 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                         |
| 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 | 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)
| Article               | Index | Result   | Criteria of ASO/PAD exclusion | Device | Population                | Number of patients | Age (mean; years) | Male gender (%) |
|----------------------|-------|----------|-------------------------------|--------|---------------------------|--------------------|------------------|-----------------|
| Kuroiwa et al²⁴      | baPWV | Successful | History of ASO, ABI<0.9     | VP     | Community-dwelling elderly | 450                | 77               | 67.3            |
| Sheng et al²²        | baPWV | Successful | ABI<0.9                      | VP     | Community-dwelling elderly | 3,876              | 68               | 44.2            |
| Katakami et al³³     | baPWV | Successful | PAD                          | VP     | Diabetes                  | 1,040              | 59               | 65.0            |
| Takashima et al³⁸    | baPWV | Successful | ABI<0.9                      | VP     | General population        | 4,164              | 59               | 37.2            |
| Ishisone et al⁴⁰     | baPWV | Successful | ABI ≤0.9                     | VP     | General population        | 973                | 59               | 46.9            |
| Kawai et al⁴⁷        | baPWV | Successful | ABI<0.9                      | FCP-4731 (Fukuda Denshi) | Hypertension       | 440                | 61               | 56.1            |
| Munakata et al⁴⁵     | baPWV | Successful | PAD                          | VP     | Hypertension              | 662                | 60               | 45.4            |
| Inoue et al⁴⁵        | baPWV | Successful | PAD                          | VP     | Hemodialysis              | 197                | 66               | 61.9            |
| Nakamura et al⁴⁷     | baPWV | Successful | ABI<0.9                      | VP     | IHD                       | 564                | 64               | 80.9            |
| Miyano et al⁴⁹       | baPWV | Successful | ABI<0.9                      | VP     | Community-dwelling elderly | 530                | 76               | 39.1            |
| Meguro et al⁵⁰       | baPWV | Successful | PAD                          | VP     | HF                        | 72                 | 68               | 56.9            |
| Matsuoka et al⁵³     | baPWV | Successful | ABI ≤0.9                     | VP     | Community-dwelling elderly | 298                | 80               | 40.3            |
| Park et al⁵⁴         | baPWV | Failed    | ABI<0.9                      | VP     | IHD                       | 203                | 57               | 52.7            |
| Morimoto et al⁵⁰     | baPWV | Failed    | ABI<0.9                      | VP     | Hemodialysis              | 176                | 61               | 56.3            |
| Lee et al⁵²          | baPWV | Successful | ABI<0.9                      | VP     | IHD                       | 350                | 66               | 53.4            |
| Chen et al⁵³         | baPWV | Failed    | ABI<0.9                      | VP     | CKD                       | 227                | 65               | 43.0            |
| Li et al⁵⁶           | baPWV | Failed    | ABI<0.9                      | VP     | Outpatients               | 238                | 69               | 42.9            |
| Ueki et al⁵⁷         | 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 | Non-treated hypertension at the recruitment |
| 5.8              | CCVE              | 89               | Not provided | Not provided | Per 1 cm/s, 1.04 (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 1.10–1.525,  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)
the progression of arterial stiffness and thus prognosis. 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. 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.

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. Moreover, the mean baPWV and CAVI values of both sides were used in the analysis. This condition meant that the decreased baPWV or CAVI

### Table 2 (Continued)

| Article       | Index | Result | Criteria of ASO/PAD exclusion | Device | Population | Number of patients | Age (mean; years) | Male gender (%) |
|---------------|-------|--------|-------------------------------|--------|------------|--------------------|-------------------|-----------------|
| Aisu et al108 | baPWV | Successful | ABI<0.9                      | VP     | Outpatients | 456                | 71 (median)      | 67.8            |
| Lu et al109   | baPWV | Successful | ABI<0.9                      | VP     | General population | 4,251              | 52               | 45.9            |
| Tokitsu et al124 | baPWV | Successful | ABI ≤0.9                     | VP     | HF with preserved ejection function | 426                | 71               | 55.3            |
| Hwang et al106 | baPWV | Successful | ABI<0.9                      | VP     | Suspected IHD | 523                | 58               | 60.6            |
| Sato et al109 | CAVI  | Successful | ABI<0.9                      | VS     | Outpatients | 1,003              | 63               | 51.2            |
| Kubota et al113 | 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.
Table 2

| 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 ≥baPWV 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 3.3 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 |          |

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 al24     | baPWV, CAVI      | baPWV Kaplan–Meier, CAVI failed             | No                            |                               |                          | Average              | VS     | Hemodialysis            |
| Kato et al25     | baPWV, CAVI      | baPWV successful, CAVI failed               | Yes                           | ABI <0.9                      | Over 76 years old        | Higher               | VS     | Hemodialysis            |
| Otsuka et al26   | baPWV, CAVI      | baPWV failed, CAVI successful               | Yes                           | PAD                           | AF, other various criteria | baPWV not described, CAVI |       | IHD with impaired CAVI  |
| Kusunose et al27 | baPWV, CAVI      | baPWV Kaplan–Meier, CAVI failed             | Yes                           | Symptomatic PAD               | End-stage neoplasm, etc. | Average              | baPWV VP, CAVI VS | IHD with two or more risk factors |
| Gohbara et al28  | 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.
with chronic kidney disease stage 3–5, and one of an outpatient population with a 78% incidence of diabetes. 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. The reason why ABI and/or (false-
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 al120 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 al122 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

### 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

| Covariates                      | Univariate OR (95% CI) | P-value | Multivariate 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.
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 \(\leq 0.9\) 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 \(\leq 0.9\) 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 \(\leq 0.9\), 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\(^ {76,68}\) 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 \(\leq 0.9\). 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.\(^ {58,60}\) 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. These phenomena are similar to that of the hemodialysis study by Kato et al. 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 $\beta$. In adopting the concept of the stiffness parameter $\beta$ on heart–ankle PWV (haPWV), the equation is as follows: $\beta = \frac{\text{haPWV}}{2\rho \cdot \text{PP} \cdot \ln(\text{SBP/}DBP)}$, where $\rho$ is the blood density, PP is the pulse pressure, and Ln is a natural logarithm. As a result of this method, CAVI is considered less dependent on blood pressure than baPWV or independent from blood pressure. 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.

To calculate haPWV, the pulse transit times between the brachial–ankle and the heart–brachial are required. The equation of haPWV is as follows: $\text{haPWV} = \frac{L_{ha}}{T_{ha}} = \frac{L_{ha}}{T_{ba} + T_{hb}}$, where $L_{ha}$ is the length between the heart and the ankle, $T_{ba}$ is the pulse transit time between the heart and the ankle, $T_{hb}$ is the pulse transit time between the brachium and the ankle, and $T_{hb}$ is the pulse transit time between the heart and the brachium. However, measuring $T_{ha}$ or $T_{hb}$ 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 ($T_{hb} \approx T_{hb} = T_{II} - DN$). Nevertheless, one study reported that this method using volume plethysmography could induce a 50% reduction in CAVI. 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 $\rho$ is considered constant in the VS device, but this is not always constant in vivo. Kato et al pointed out the change in blood density of patients on hemodialysis. 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. 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 $T_{ba}$) 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.

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. 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. 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). 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). In contrast, the blood pressure dependence of CAVI is reportedly weaker than that of baPWV. Moreover, several studies have shown superior associations with other atherosclerotic parameters of CAVI to that of baPWV. However, we may have to recognize that the characteristics of PWV, which is considered to natively possess prognostic significance, 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.

Perspective
Necessity of more prognostic studies of CAVI
Three meta-analyses of the prognostic significance of baPWV have already been published, and the cutoff baPWV of 18 m/s is largely consistent. 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. 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. Moreover, baPWV and CAVI showed similar correlations with carotid atherosclerosis indices. This result is similar to that of the Japanese hemodialysis study. 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. 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. It will be interesting to note whether the same difference in study results as that obtained in the Japanese cohorts is demonstrated.

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. In addition, UE-ASO should be considered in patients receiving hemodialysis. 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 and %MAP should also be included in the criteria. Moreover, the use of a higher baPWV and CAVI on either side is favorable. 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 $\beta$ and other methods of blood pressure adjustment
The concept of stiffness $\beta$ and CAVI 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 $\rho$. In fact, a few studies have adopted this idea using VP. 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. Regarding CAVI, Spronck et al suggested a novel method of adjusting blood pressure. Steppan et al 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. 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.\(^{39}\) 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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baPWV and CAVI as prognostic predictors
343
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## Supplementary material

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

| Covariates                          | Univariate | P-value | Multivariate | P-value |
|-------------------------------------|------------|---------|--------------|---------|
|                                     | OR (95% CI)|         | OR (95% CI)  |         |
| 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.