Brachial-Ankle PWV: Current Status and Future Directions as a Useful Marker in the Management of Cardiovascular Disease and/or Cardiovascular Risk Factors

Hirofumi Tomiyama, Chisa Matsumoto, Kazuki Shiina and Akira Yamashina

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Since 2001, brachial-ankle pulse wave velocity (brachial-ankle PWV) measurement has been applied for risk stratification of patients with atherosclerotic cardiovascular disease and/or its risk factors in Japan. Measurement of the brachial-ankle PWV is simple and well standardized, and its reproducibility and accuracy are acceptable. Several cross-sectional studies have demonstrated a significant correlation between the brachial-ankle PWV and known risk factors for cardiovascular disease; the correlation is stronger in subjects with cardiovascular disease than in those without cardiovascular disease. We conducted a meta-analysis, which demonstrated that the brachial-ankle PWV is an independent predictor of future cardiovascular events. Furthermore, the treatment of cardiovascular risk factors and lifestyle modifications have been shown to improve the brachial-ankle PWV. Thus, at present, brachial-ankle PWV is close to being considered as a useful marker in the management of atherosclerotic cardiovascular disease and/or its risk factors.


Key words: Brachial-ankle pulse wave velocity, Arterial stiffness, Cardiovascular disease, Prevention

Introduction

Conventionally, anthropometric and biochemical data were used to assess the risk for cardiovascular disease1, 2). The Framingham risk score and NIPPON DATA 80 risk chart are standard tools for such risk assessment1, 2). However, several studies have indicated that risk assessment by these traditional tools fails to detect 30%–50% of subjects at high risk for cardiovascular disease3, 4). Furthermore, use of the recently proposed contemporary biomarkers, such as serum CRP, serum BNP, and serum homocysteine, can only add moderately to the assessment using the aforementioned standard risk assessment tools4, 5).

Under these circumstances, there was a need for the development of new physiological/imaging biomarkers for assessing the risk of cardiovascular disease3-5). Recently, markers of arterial stiffness have gained much attention in this regard6, 7), and of these, the brachial-ankle pulse wave velocity (brachial-ankle PWV) was identified as a simple-to-assess marker of the stiffness of the large- to middle-sized arteries6, 8). We have proposed some criteria for the establishment of a parameter as a useful marker in the management of cardiovascular disease and/or its risk factors (Table 1: modified Table 7 in reference 9). In this review, we discuss whether brachial-ankle PWV satisfies these criteria.

What is Brachial-Ankle PWV? How is Brachial-Ankle PWV Measured? [Methodological Considerations (Standardization, Reproducibility, and Accuracy)]

1. Standardization

Pulse wave velocity (PWV) reflects segmental arterial elasticity10). Contraction of the left ventricle generates a pulse wave, which is propagated throughout the arterial tree. PWV is calculated as the distance
The characteristic points of the waveforms are determined automatically according to this phase velocity theory. Components over 5 Hz are stored using a pass filter and the wavefront is determined. The time interval between the wavefront of the brachial waveform and that of the ankle waveform is defined as the time interval between the brachium and ankle (deltaTba).

The path lengths from the suprasternal notch to the brachium (Lb) and from the suprasternal notch to the ankle (La) are determined by an equation according to the height of the subject8). Then, the brachial-ankle PWV is calculated according to the following equation: 

\[ \text{brachial-ankle PWV} = \frac{Lb - Lb}{\text{deltaTba}}. \]

The standardization of the measurement, including the measurement conditions and recommendations on the user procedures, is described elsewhere11, 13). It has been demonstrated that the reliability of the brachial-ankle PWV measurement is diminished in subjects with atrial fibrillation, frequent arrhythmias, or inaccurate pulse wave recordings because of arterial stenosis (e.g., ankle brachial pressure index \( \beta 0.95 \))8, 13, 14).

The absolute values of the brachial-ankle PWV have been reported to be substantially higher than other measures of PWV15). There are some limitations in determining the path length traveled by the pulse wave, not only while measuring the carotid-femoral PWV7, 11), but also while measuring the brachial-ankle PWV8). This equipment simultaneously records PWV, blood pressure in the four extremities (i.e., the ankle-brachial pressure index is also obtained), electrocardiogram, and heart sounds8). The subjects are examined in the supine position, with the electrocardiographic electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped around both the brachium and ankles. The cuffs are connected to a plethysmographic sensor that determines the volume pulse form and an oscillometric pressure sensor that measures the blood pressure. The pulse volume waveforms are recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV is set at 1,200 Hz). Volume waveforms for the brachium and ankle are stored, and the sampling time is 10 s, with automatic gain analysis and quality adjustment. Thus, sufficient waveform data are obtained from samples stored. McDonald reported that the mean value of the phase velocity over 2~2.5 Hz is very close to the wavefront velocity12).

Table 1. Criteria for the establishment of a parameter as a useful marker in the management of atherosclerotic cardiovascular disease and/or its risk factors

<table>
<thead>
<tr>
<th>Criteria for the establishment of a parameter as a useful marker in the management of atherosclerotic cardiovascular disease and/or its risk factors</th>
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<tbody>
<tr>
<td># Methodological considerations (standardization, reproducibility, accuracy)</td>
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<tr>
<td># Correlations with known risk factors for cardiovascular disease</td>
</tr>
<tr>
<td># Value distribution (reference limits and discrimination limits)</td>
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<tr>
<td># Mechanisms of initiation and progression of cardiovascular disease</td>
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<tr>
<td># Value as a predictor of the prognosis independent of other established markers</td>
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<tr>
<td># Therapeutic regression and its relation to improvement of the prognosis</td>
</tr>
<tr>
<td># Clinical applications (screening, diagnosis, prognostication, and treatment)</td>
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</tbody>
</table>

2. Accuracy and Reproducibility

Central arterial stiffness is more relevant to CV.
Table 2. References to examine the usefulness of the brachial-ankle pulse wave velocity to predict the prognosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Age &amp; Gender</th>
<th>Follow-up duration</th>
<th>Outcome and number of events</th>
<th>Results of analysis</th>
<th>Exclude ABI &lt; 0.90</th>
<th>Remarks</th>
<th>Significance of baPWV measurement</th>
<th>Adjustment for age &amp; BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>Chen SC, et al. Clin J Am Soc Nephrol. 2011; 6: 724-32.</td>
<td>145 patients with CKD stage 3-5 (20% patients had CVD)</td>
<td>69 ± 12 years old M/F (99/46)</td>
<td>15 ± 3 months</td>
<td>17 patients started on dialysis and 8 patients died (including 4 CV deaths)</td>
<td>HR for initiation of hemodialysis or death associated with 1 cm/sec increase of the baPWV = 1.001 (1.000-1.001) (after adjustments for eGFR, history of CVD).</td>
<td>No</td>
<td>Yes</td>
<td>No (BP was not included as a variable, but adjustment was made for the prevalence of hypertension).</td>
</tr>
<tr>
<td>69</td>
<td>Sheng CS Hypertension 2014; 64: 1124-30.</td>
<td>3876 elderly subjects (59% had hypertension)</td>
<td>68 ± 7 years old M/F (1713/2163)</td>
<td>5.9 years</td>
<td>316 all-cause deaths, 148 cardiac deaths, and 46 stroke deaths</td>
<td>HR associated with baPWV in the top decile (top 10% baPWV)=baPWV &gt; 2330 cm/sec=1.56 (1.16-2.08) for all-cause death,=1.46 (0.90-2.05) for CV death, and=1.49 (0.69-3.20) for stroke death (after adjustments for age, gender, BMI, smoking habit, drinking habit, history of treatment for risk factors, MBP, serum creatinine, and TC).</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>70</td>
<td>Kim J et al. Hypertension 2014; 64: 240-6</td>
<td>1765 patients with acute stroke</td>
<td>65 ± 12 years old M/F (1097/668)</td>
<td>3.3 ± 1.6 years</td>
<td>228 deaths (143 vascular deaths: heart disease cerebrovascular disease artery disease)</td>
<td>HRs associated with baPWV &gt; 2263 vs. baPWV &lt; 1779 cm/sec=1.97 (1.25-3.08) for all-cause death and=2.39 (1.33-4.29) for cardiovascular death (baPWV tertile= &lt; 1779, 1779-2263, &gt; 2263). HR associated with baPWV ≥ 1000 cm/sec=1.54 (1.27-1.87) for all-cause death=2.41 (1.57-3.70) for cardiovascular death (after adjustments for age, gender, history of hypertension, history of DM, smoking habit, LDL, TG, BS, and DBP).</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>71</td>
<td>Kawai T, et al. J Atheroscler Thromb. 2013; 20: 391-400.</td>
<td>440 patients with hypertension (40 patients had a history of CVD)</td>
<td>61 ± 0.6 (SE) years old M/F (247/193)</td>
<td>6.3 ± 0.1 (SE) years</td>
<td>62 stroke + CVD (coronary artery disease, heart failure, rupture of aortic aneurysm).</td>
<td>HR associated with baPWV &gt; 1750 cm/sec=2.048 (1.176-3.616) for stroke + CVD (after adjustments for age, gender, DM, smoking habit, presence/absence of dyslipidemia, and positive/negative history of medication for hypertension).</td>
<td>Yes</td>
<td>Yes</td>
<td>No (adjustment was made for the history of antihypertensive medication but not for the SBP values).</td>
</tr>
<tr>
<td>72</td>
<td>Matsuoka O et al. Biomed Pharmacother. 2005 59 Suppl 1: S40-4.</td>
<td>298 elderly subjects (age &gt;75 years)</td>
<td>79 ± 5 years old M/F (120/178)</td>
<td>1227 days</td>
<td>9 CV deaths (5 myocardial infarction deaths and 4 stroke deaths)</td>
<td>OR associated with 200 cm/sec increase of the baPWV = 1.302 (1.110-1.525) for CV death (after adjustments for age and the hasegawa dementia scale).</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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(Cont Table 2)

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</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>Inoue T et al. Heart Vessels. 2012; 27: 135-42.</td>
<td>197 patients under hemodialysis</td>
<td>66 ± 12 years old M/F (122/75)</td>
<td>69 ± 45 months</td>
<td>89 CV events (12 stroke events, 54 CAD events, 6 heart failure events, and 17 PAD events)</td>
<td>HR associated with 1 cm/sec increase of the baPWV = 1.046 (1.006-1.086) for CV events (after adjustments for age, gender, TC, HDL, SBP, BMI, PS, hemoglobin, and serum Ca/P).</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>Takashima N, et al. J Hum Hypertens. 2014; 28: 323-7</td>
<td>4164 subjects without CVD from the general population</td>
<td>59 ± 13 years old M/F (2615/1549)</td>
<td>6.5 years</td>
<td>40 CV events (29 stroke events + 11 acute myocardial infarction events)</td>
<td>HR associated with baPWV &gt; 1800 cm/sec = 2.70 (1.18-6.19) for CV events, and = 3.12 (1.18-8.26) for stroke (after adjustments for age, gender, smoking habit, drinking habit, BMI, HDL, LDL, TG, HbA1c, treatment history for risk factors, and mean BP).</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Ishisone T et al. Int Heart J. 2013; 54: 160-5.</td>
<td>973 subjects from the general population</td>
<td>59 ± 11 years old M/F (456/517)</td>
<td>7.8 years</td>
<td>37 CV events (stroke events, heart failure events, myocardial infarction events, CV deaths)</td>
<td>HR associated with baPWV /SD (not mentioned) increase = 1.47 (1.09-1.98) for CV events. HR associated with baPWV over 90th percentile = 2.58 (1.24-5.37) for CV events (value not mentioned) (after adjustments for age, gender, history of DM, dyslipidemia and obesity, smoking habit, and history of antihypertensive medication).</td>
<td>Yes</td>
<td>Yes</td>
<td>No (adjustments were made for the prevalence of hypertension and history of antihypertensive medication, but not for the SBP values).</td>
</tr>
<tr>
<td>76</td>
<td>Ninomiya T, et al. J Hypertens. 2013; 31: 477-83;</td>
<td>2916 subjects from the general population</td>
<td>60 ± 11 years old M/F (1662/1254)</td>
<td>7.1 years</td>
<td>126 CV events (82 stroke events and 48 CAD events)</td>
<td>HR associated with baPWV &gt; 1705 = 8.77 (1.99-38.71) for CV events; HR associated with baPWV &gt; 2042 = 12.20 (2.68-55.64) for CV events; HR associated with 20% increase of the baPWV = 1.31 (1.11-1.54) for CV events (baPWV, quintile = &lt; 1317, 1317-1501, 1502-1704, 1705-2042, &gt; 2042) (after adjustments for age, gender, history of hypertension and DM, TC, HDL, obesity, smoking habit, alcohol habit, and exercise habit).</td>
<td>Yes</td>
<td>Yes</td>
<td>No (adjustment was made for the prevalence of hypertension, but not for the BP values).</td>
</tr>
<tr>
<td>77</td>
<td>Tanaka M et al. Atherosclerosis. 2011; 219: 643-7.</td>
<td>445 patients under hemodialysis</td>
<td>63 ± 11 years old M/F (264/181)</td>
<td>43 ± 17 months</td>
<td>206 CV events (125 cardiac events, 39 cerebrovascular events, and 42 PAD events)</td>
<td>HR associated with baPWV &gt; 2310 cm/sec vs. baPWV &lt; 1850 = 1.51 (0.68-1.97) for all CV events = 2.63 (0.89-7.80) for death (baPWV tertile = &lt; 1850, 1850-2310, &gt;2310).</td>
<td>No</td>
<td>ABI &lt; 0.90 was a significant predictor of the for the prognosis.</td>
<td>No</td>
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<td>80 Kaneko H, et al.</td>
<td>236 patients with coronary artery disease</td>
<td>67 ± 10 years old M/F (198/38)</td>
<td>267 ± 55 days</td>
<td>33 patients developed new coronary lesions.</td>
<td>OR associated with increase of the baPWV by 1 cm/sec = 1.002 (1.001-1.003) for the development of new coronary artery lesions (after adjustments for history of CKD, statin use, and HDL).</td>
<td>No</td>
<td>Cox regression model analysis was not applied, instead multivariate logistic regression was applied.</td>
<td>Yes</td>
<td>No (age and the prevalence of hypertension were not significant variables)</td>
</tr>
<tr>
<td>81 Nakamura M et al.</td>
<td>191 patients with coronary artery disease and DM</td>
<td>65 ± 9 years old M/F (157/34)</td>
<td>25 months</td>
<td>59 CV events (12 deaths + re-infarction, re-vascularization, and heart failure events)</td>
<td>HR associated with baPWV &gt; 1730 = 1.97 (1.01-3.84) for CV events (after adjustments for age, gender, history of acute myocardial infarction, BMI, eGFR, history of treatment for risk factors, history of heart failure). No direct adjustment was made for the BP values, however, adjustment was made for the history of hypertension.</td>
<td>No</td>
<td>In patients with CAD, baPWV was a significant predictor of the prognosis in cases with DM (n = 373), but not in cases without DM. The significance of ABI &lt; 0.9 as a predictor was not examined.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>82 Sugamata W, J Cardiol.</td>
<td>923 patients with coronary artery disease</td>
<td>65 ± 12 years old M/F (660/263)</td>
<td>64 ± 30 months</td>
<td>116 coronary events (29 cardiac deaths, 46 myocardial infarction events, and 41 angina events)</td>
<td>HR associated with 1-SD (381 cm/sec) increase of the baPWV = 1.52 (1.27-1.82) for coronary events (after adjustments for age, SBP , smoking habit, gender, history of DM, LDL, HDL, CRP , LVEF , and severity of coronary disease).</td>
<td>No</td>
<td>The baPWV was a significant predictor of the prognosis, independent of the IMT or FMD.</td>
<td>Yes</td>
<td>No (SBP was not a significant variable)</td>
</tr>
<tr>
<td>83 Nagai K, et al. Atherosclerosis.</td>
<td>274 elderly subjects (31 subjects had CVD)</td>
<td>71 ± 12 years old M/F (114/160)</td>
<td>41 ± 28 months</td>
<td>42 CV events (CAD, stroke, TIA, heart failure, renal failure, PAD, or dissection of aorta)</td>
<td>HR associated with baPWV tertile increase &gt; 2110 vs. baPWV &lt; 1600 cm/sec = 2.582 (1.445-4.614) for CV events; HR associated with increase by 1 m/sec = 1.060 (1.001-1.111) for CV events (after adjustment for the Framingham risk score).</td>
<td>No</td>
<td>The baPWV was a significant predictor of the prognosis, independent of the carotid IMT.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>84 Yoshida M, et al. Diabetes Care.</td>
<td>783 patients with DM</td>
<td>Not described</td>
<td>5.5 ± 0.4 years</td>
<td>85 CV events (50 coronary events and 35 stroke events)</td>
<td>HR associated with baPWV in the 4th quartile (after adjustments for age, gender, BMI, SBP, HbA1c, TC, HDL, TG, and smoking habit) (the HR was not depicted).</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>85 Maeda Y et al. Diabetes Care. 2014; 37:2383-90.</td>
<td>3268 patients with DM</td>
<td>61 years old M/F (2166/1462)</td>
<td>3.2 ± 2.2 years</td>
<td>All-cause death, coronary events, and cerebrovascular events (The number of events was not described).</td>
<td>OR associated with baPWV &gt; 2400 cm/sec = 1.84 (1.13-2.88) for all-cause death</td>
<td>Yes</td>
<td>Yes (BP was not a significant variable for the prognosis)</td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td>86 Yoon HE et al. Int J Med Sci. 2013; 10:1430-6.</td>
<td>117 subjects with eGFR &lt; 90 ml/min/1.73</td>
<td>54 ± 10 years old M/F (72/45)</td>
<td>367 days</td>
<td>12 CV events (5 CAD events 6 CVD events and 1 arrhythmia event)</td>
<td>HR associated with a baPWV 1.0 m increase of the baPWV = 1.002 (1.000-1.004) for CV events (after adjustment for age).</td>
<td>No</td>
<td>Yes (BP was not a significant variable for the prognosis)</td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td>87 Katakami N et al., Cardiovasc Diabetol. 2014; 13:128.</td>
<td>1040 patients with DM</td>
<td>59 ± 10 years old M/F (676/364)</td>
<td>7.5 years</td>
<td>113 CV events (40 cardiac events, 56 cerebrovascular events, 14 PAD events, and 3 heart failure events)</td>
<td>HR associated with baPWV &gt; 1550 cm/sec = 1.21 (1.01-1.44) for CV events (after adjustments for age, gender, smoking habit, BMI, SBP, HDL, LDL, TG, serum creatinine, and treatment history for risk factors).</td>
<td>No</td>
<td>Yes (BP was not a significant variable for the prognosis)</td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td>88 Kato A. et al. Ther Apher Dial. 2012; 16:232-41</td>
<td>135 patients under hemodialysis</td>
<td>60 ± 11 years old M/F (91/44)</td>
<td>63 ± 4 months</td>
<td>32 deaths (including 22 CV deaths), 37 CV events (9 CAD events, 9 CVD events, 6 heart failure events, 6 sudden deaths, and 2 PAD events)</td>
<td>HR associated with baPWV in the 1430-1660 tertile or baPWV &gt; 1660 cm/sec vs. baPWV 1430 cm/sec = 16.9 (1.1-251.8) for CV death (after adjustments for age, gender, smoking habit, history of diabetes, mean BP, serum creatinine, serum calcium, serum phosphate, TC, hemoglobin, serum parathormone).</td>
<td>Yes</td>
<td>CAVI was not a significant predictor of the prognosis.</td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td>89 Munakata M et al. Hypertens Res. 2012; 35:839-42</td>
<td>662 patients with hypertension</td>
<td>60 ± 12 years old M/F (298/364)</td>
<td>3 years</td>
<td>24 CV events (11 cerebrovascular events, 12 cardiac events, and 1 AAA event)</td>
<td>HR associated with baPWV &gt; 1763 cm/sec = 2.97 (1.006-9.380) for CV events (after adjustments for age, gender, BMI, SBP, heart rate, blood glucose, TC, serum creatinine, smoking habit, and treatment history for risk factors).</td>
<td>Yes</td>
<td>Yes (BP was not a significant variable for the prognosis)</td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td>90 Morimoto S, et al. Am J Nephrol 2009; 30, 55-63.</td>
<td>199 patients under hemodialysis</td>
<td>61 ± 13 years old M/F (112/87)</td>
<td>43 ± 10 months</td>
<td>24 deaths (14 CV deaths and 10 non-CV deaths)</td>
<td>HR associated with 1 cm/sec increase of the the baPWV=1.000 (0.999-1.002) for death, and =1.001 for CV death (0.999-1.003).</td>
<td>Yes</td>
<td>Yes (BP was not a significant variable for the prognosis)</td>
<td>Yes</td>
<td>No No</td>
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<tr>
<td>91</td>
<td>Kitahara T et al. Am J Kid Dis 2005; 46, 688-696,</td>
<td>785 patients under hemodialysis</td>
<td>60 ± 13 years old M/F (506/279)</td>
<td>34 ± 11 months</td>
<td>131 deaths (including 85 CV deaths)</td>
<td>When ABI was excluded, HRs associated with baPWV &gt; 2380cm/sec vs. baPWV &lt; 1700 cm/sec = 1.96 (1.01-3.82) for all-cause death (baPWV quartiles &lt; 1700, 1700-2010, 2010-2380, &gt;2380). When ABI was included, the HR was 1.79 (0.93-3.48) (after adjustments for age, gender, history of DM, smoking habit, BMI, history of CVD, SBP, DBP, and serum TC).</td>
<td>No</td>
<td>When the ABI was also included, the baPWV was only a marginal predictor of the prognosis.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>92</td>
<td>Miyano I et al. Hypertens Res 2010: 33, 678-682</td>
<td>530 elderly subjects</td>
<td>76 ± 5 years old M/F (207/323)</td>
<td>3 years</td>
<td>30 deaths (including 11 CV deaths)</td>
<td>HR associated with baPWV &gt; 1963 cm/sec = 5.3 (2.2-12.7) for all-cause death, 18.7 (2.2-157.6) for CV death (after adjustments for age, gender, and SBP). For the case of baPWV &gt; 1868 cm/sec: HR for all-cause death was 2.98 (1.25-7.07) and that for CV death was 10.01 (1.21-82.49).</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>93</td>
<td>Meguro T Circ J 2009; 73, 673-680</td>
<td>72 patients with heart failure</td>
<td>68 ± 14 years old M/F (41/31)</td>
<td>14 months</td>
<td>17 patients re-admitted for heart failure.</td>
<td>HR associated with baPWV &gt; 1750 cm/sec = 5.101 (1.034-25.166) for re-admission for heart failure (after adjustments for age, SBP, gender, serum BNP, and heart rate).</td>
<td>No</td>
<td>Mean LVEF 53%; therefore, most of the study patients might have had heart failure with preserved systolic function.</td>
<td>Yes</td>
</tr>
<tr>
<td>94</td>
<td>Kuwahara M et al. Ther Apher Dial. 2014; 18: 9-18.</td>
<td>300 patients under hemodialysis (19.3% patients had CVD)</td>
<td>61 ± 10 years old M/F (183/117)</td>
<td>7 years</td>
<td>124 cardio-vascular events and 43 cerebrovascular events. 164 CV events (cardiac &amp; cerebrovascular events + PAD)</td>
<td>HR associated with 0.1 unit increase of the ABI = 0.794 (0.687-0.917) for CV events (after adjustments for age and baPWV). The adjusted HR of the baPWV was not described.</td>
<td>No</td>
<td>No (BP was not a significant variable for the prognosis).</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ABI=ankle brachial pressure index; Exclude ABI <0.90=subjects with ABI <0.90 were excluded from the analysis; BP=blood pressure; baPWV=brachial-ankle pulse wave velocity; Significance of baPWV=value of the baPWV to predict future cardiovascular events; CVD=cardiovascular disease; M=male; F=female; CV death=cardiovascular death; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; CABG=coronary artery bypass graft surgery; LVEF=left ventricular ejection fraction; HR=hazard ratio; BMI=body mass index; CAD=coronary artery disease; TIA=transient ischemic attack; PAD=peripheral arterial disease; IMT=intima-media thickness; TC=serum total cholesterol; HDL=serum high-density lipoprotein cholesterol; TG=serum triglycerides; ROC=receiver-operating characteristic curve; LDL=serum low-density lipoprotein cholesterol; RO=odds ratio; HD=hemodialysis; CAVI=cardio-ankle vascular index; AAA=abdominal aortic aneurysm; CKD=chronic kidney disease; CRP=serum C-reactive protein; FMD=flow-mediated vasodilation; BS=blood sugar
risk stratification than peripheral arterial stiffness. The brachial-ankle PWV reflects not only the stiffness of the elastic arteries but also that of the muscular arteries. Even so, the brachial-ankle PWV has been demonstrated to be closely correlated with the markers of central arterial stiffness (i.e., aortic PWV measured by an invasive method and the carotid-femoral PWV).

The reproducibility of measurement of the brachial-ankle PWV has been reported to be acceptable (i.e., Pearson’s correlation coefficients of inter-observer and intra-observer reproducibility \( r \) at 0.98 and 0.87, respectively. The corresponding coefficients of inter-observer and intra-observer variations were 8.4\% and 10.0\%, respectively).

**Factors Affecting the Value of the Brachial-Ankle PWV (Correlations with known Risk Factors for Cardiovascular Disease)**

The functional/structural stiffness of the arteries can increase via several mechanisms.

1. **Age and Blood Pressure**
   Age is a major determinant of arterial stiffness, and the brachial-ankle PWV has been shown to increase with age. In a systematic review, the significances of the effects of age, blood pressure, and other conventional risk factors for cardiovascular disease on the carotid-femoral PWV were examined, and the results revealed that the contribution of the risk factors other than age and blood pressure to increase of the carotid-femoral PWV was small or insignificant.

   High blood pressure is associated with increased functional arterial stiffness via increase of the arterial wall tension. Some prospective studies have demonstrated that persistent elevation of blood pressure is associated with accelerated structural stiffening of the large- to middle-sized arteries and that age may exert a synergistic effect on this acceleration of arterial stiffening.

2. **Glucose and Lipid Metabolism**
   The brachial-ankle PWV is increased not only in subjects with diabetes but also in those with glucose intolerance. In a prospective study conducted previously, raised plasma glucose was found to accelerate age-related increase of the brachial-ankle PWV. In subjects with abnormal glucose metabolism, in addition to hyperglycemia and hyperinsulinemia, elevated
sectional studies have reported that obesity is associated with increase of the brachial-ankle PWV\(^35, 36\), the influence of confounding factors, such as metabolic syndrome and/or sleep apnea, have not yet been fully excluded.

4. Other Risk Factors for Cardiovascular Disease

Other cardiovascular risk factors, such as renal dysfunction, as assessed by the serum creatinine or cystatin C levels and pulmonary dysfunction are also reported to be associated with an increase of the brachial-ankle PWV\(^37-40\). Increased brachial-ankle PWV values have also been reported in subjects with osteoporosis or sarcopenia\(^40-42\).

5. Mechanisms of Increased Arterial Stiffness

Endothelial dysfunction, elevated blood pressure, increased heart rate, and/or sympathetic activation increase the functional arterial stiffness\(^6, 7\). On the other hand, several mechanisms are thought to affect the structural arterial stiffness. The arterial media is composed of smooth muscle cells and extracellular matrix (collagen and elastin)\(^43-45\). These constituents of the media and the interactions among them are the major determinants of structural arterial stiffness\(^6, 7, 10\). Conventional risk factors for CV disease induce dysregulation of the balance between collagen and elastin, resulting in the overproduction of abnormal collagens and diminished production of normal elastin\(^43-45\). Aging and hypertension cause thinning, splitting, fray-
Value Distribution (Reference Limits and Discrimination Limits)

1. Age and Pathophysiological Abnormalities

Age is a major determinant of the brachial-ankle PWV. [male: \( \text{baPWV} = 0.20 \times \text{age}^2 - 12.13 \times \text{age} + 1341.34 \) \( (R^2 = 0.16, P < 0.01) \) and female: \( \text{baPWV} = 0.16 \times \text{age}^2 - 4.40 \times \text{age} + 977.52 \) \( (R^2 = 0.37, P < 0.01) \)]\(^{20}\), and gender difference has been reported in the values of the brachial-ankle PWV\(^{20}\). Even after adjustments for these factors, the brachial-ankle PWV was higher in subjects with manifest/subclinical organ damage than in those without organ damage [e.g., diabetic triopathy\(^{46}\), subclinical cerebral damage\(^{47}\), cognitive dysfunction\(^{48}\), renal dysfunction\(^{49, 50}\), cardiac diastolic dysfunction\(^{51}\), left ventricular hypertrophy\(^{52}\), and/or increased carotid intima-media thickness\(^{53}\)].

2. Coronary Artery Disease and Cerebrovascular Disease

The brachial-ankle PWV is related to the coronary calcium score in asymptomatic patients\(^{54}\). Moreover, the brachial-ankle PWV is increased in subjects with coronary heart disease and/or cerebral vascular disease\(^{55-58}\). However, the markers reflecting the arterial stiffness, including the brachial-ankle PWV, may not be applicable for the screening of coronary heart disease and/or cerebrovascular disease because increased arterial stiffness is not a specific phenomenon to coronary heart disease or cerebrovascular disease.

Mechanisms of the Initiation and Progression of Cardiovascular Disease

Carotid ultrasound examination is a morphological assessment tool for atherosclerotic vascular damage\(^{59}\). It may reveal the atherosclerotic burden, includ-
the amount of this stored blood in the aorta is an important determinant of the coronary blood flow.\textsuperscript{6, 60} With increased arterial stiffness, the amount of stored blood in the aorta during systole decreases (Fig. 2).

Under a healthy condition of the arterial tree, the speed of propagation of the pulse wave (incident (heart to periphery) and reflected (periphery to the heart)) is not so high; therefore, the reflected wave returns to the central aorta during diastole.\textsuperscript{6, 60} This phenomenon elevates the diastolic blood pressure and contributes to maintenance of the coronary blood flow (Fig. 1: left figure). In case of increased arterial stiffness, the elevation of the diastolic pressure by the reflected pulse wave is reduced because the reflected pulse wave returns during systole as a result of increase in the pulse wave propagation speed (Fig. 1: right figure). Therefore, the coronary blood flow is impaired.

**C: Pulsatile Nephropathy and Encephalopathy**

Attenuation of the cushioning effect of elastic arteries amplifies the pressure pulsatility and increases the transmission of pulsatile energy to the peripheral microcirculation (Fig. 3). Exposure of small vessels to high pressure and flow levels results in microvascular damage, particularly, in high-blood flow organs such as the brain and kidney,\textsuperscript{6, 7, 61, 62} the so-called, pulsatile nephropathy and encephalopathy.\textsuperscript{62} Recent prospective studies have demonstrated that increased brachial-ankle PWV is a risk factor for the progression of renal function and cognitive function decline.\textsuperscript{63-65}

**D: Arterial Remodeling and Atherogenic Actions**

The arterial wall is exposed to the following two mechanical stresses: circumferential stress (stretch) and shear stress. Increased arterial stiffness is associated with abnormalities of both stresses owing to fluctuations of the pressure and speed of blood flow in the arterial lumen.\textsuperscript{60} These stresses trigger signaling cascades in the arterial wall contributing to vascular growth, such as tyrosine kinase, phosphatidyl inositol-3-kinase, protein kinase C, epithelial sodium channel, and/or nicotinamide adenine dinucleotide phosphate oxidase signaling, and activation of these signaling cas-

### Table 3. Approach as a high-risk patient

- Re-confirmation of the status of control of the risk factors for cardiovascular disease.
- Screening for subclinical cardiovascular disease (interview, physical examination (abdominal aneurysm, edema, heart enlargement, abnormal heart sounds, heart murmur, vascular bruit).
- Routine examinations (blood biochemical examination, electrocardiogram, chest X-ray),
- Other necessary examinations
Is Brachial-Ankle PWV Useful for Risk Stratification for Cardiovascular Disease? (Value as a Predictor of the Prognosis Independent of Other Established Markers)

Several prospective studies have suggested that brachial-ankle PWV is an independent predictor of the prognosis. A meta-analysis was conducted through a systematic search of the literature published in PubMed from 2001 to 2015. Thirty articles examining the prognostic value of brachial-ankle PWV in prospective studies were identified\textsuperscript{63, 69-98} (Table 3). Of these, four studies examined the prognosis twice in the same cohorts\textsuperscript{75-90}, and only one aggregate data meta-analysis is available to examine the usefulness of brachial-ankle PWV as a predictor of future cardiovascular events\textsuperscript{99}. Age is an important determinant of arterial stiffness; therefore, PWV may be considered as a marker of aging, serving as an overall marker of death. We conducted another aggregate data meta-analysis of 14 articles (13,346 subjects) to examine whether brachial-ankle PWV can serve as a predictor of cardiovascular events or cardiovascular death. A random-effect model was used and between-studies heterogeneity was estimated based on the I\textsuperscript{2}. The analysis identified the brachial-ankle PWV as an independent marker to predict future cardiovascular events. The pooled odds ratio (95% CI) for CVD/CVD death was 2.74 (1.85–4.06) when the highest baPWV group was compared with the lowest baPWV group in the random effects model (I\textsuperscript{2}=73\%) (Fig. 4).

Regarding the cutoff value of brachial-ankle PWV, the guideline for non-invasive vascular function test (Japanese Circulation Society 2013) proposed the value of 1800 cm/sec based on the above-mentioned articles\textsuperscript{13}. The ankle brachial pressure index, identified as an independent predictor of future cardiovascular events\textsuperscript{100}, can be measured simultaneously with the equipment used to measure the brachial-ankle PWV\textsuperscript{8}. The ankle brachial pressure index measured by the oscillometric method has been shown to be strongly correlated with the ankle brachial pressure index measured by the Doppler method\textsuperscript{101}. Brachial-ankle pressure index values of \textasciitilde0.90 imply the presence of peripheral arterial disease and also a poor prognosis\textsuperscript{6, 100}. Thus, brachial-ankle PWV measurements are applicable to a wide spectrum of pathophysiological states related to cardiovascular disease. Based on this background, we propose the use of the stenostiffness index approach for the management/prevention of cardiovascular disease (Fig. 5). In this approach, first, the presence of peripheral arterial disease is ruled out when the ABI is <0.90. Then, in cases where ABI is \textasciitilde0.90 but <1.00, it is proposed that the accuracy of the pressure wave recording be confirmed. The per-
Clinical chart for the management of cardiovascular disease/its risk factors using baPWV/ABI

Fig. 5. Schema of the steno-stiffness index approach for the management of subjects with atherosclerotic cardiovascular diseases and/or cardiovascular risk factors.

cent mean arterial pressure (>45%) and/or upstroke time (180 msec) have also been shown to be useful for the screening of PAD. Therefore, when ABI ≤ 0.90, 0.90 < ABI < 1.00 and/or the brachial-ankle PWV >1800 cm/sec, approach as a high-risk case is proposed. The details of the approach for high-risk case are described in Table 3. As a next logical step, a meta-analysis of individual participants’ data is proposed to clarify the usefulness of the brachial-ankle PWV in combination with the ankle brachial pressure index to predict future cardiovascular events.

Does Brachial-Ankle PWV Serve as a Surrogate Endpoint for Intervention? (Therapeutic Regression and its Relation to Improvement of the Prognosis)

1. Effects of Treatment

Several studies have reported that medical treatments for cardiovascular risk factors lead to improvement of the brachial-ankle PWV. Antihypertensive therapy and treatment with statins have been shown to improve the brachial-ankle PWV. Although blood pressure is a major determinant of the brachial-ankle PWV, the aforementioned treatments exerted significant beneficial effects independent of their effects on the blood pressure. However, in most of these studies, the changes of the brachial-ankle PWV were examined over observation periods of only 1–2 years. Arterial stiffness progresses with aging, and no study till date has examined whether these medications can counteract age-related progression of arterial stiffening. Among the antihypertensive drugs, several studies have reported that renin-angiotensin system blockers are more effective than other antihypertensive drugs for obtaining improvements of the arterial stiffness.

2. Relation to Prognosis

The carotid intima-media thickness and size of...
carotid plaques as assessed by carotid ultrasound are established markers to predict future cardiovascular events\(^9\). However, the 2013 ESH/ESC Guidelines for the management of arterial hypertension reported that the sensitivities of these parameters to detect treatment-induced changes, time to change, and prognostic value of the change are limited\(^11\). Therefore, the carotid intima-media thickness and size of carotid plaques are not suitable markers to assess the effect of treatment on the prognosis in patients with cardiovascular disease. As of the end of April 2015, only one prospective study examining the association of the prognosis with improvement of the brachial-ankle PWV by treatment had been reported\(^119\). Orlova et al reported that improvement of the brachial-ankle PWV obtained after 6 months of conventional therapy was a reliable marker of a more favorable prognosis in patients with coronary artery disease\(^115\). Further studies are needed to evaluate the applicability of brachial-ankle PWV as a marker to assess the effect of treatment on the prognosis.

**Conclusion: Clinical Applications (Screening, Diagnosis, Prognostication, and Treatment)**

In addition to predicting future cardiovascular events\(^53\), brachial-ankle PWV can also predict the development of hypertension or stage III chronic kidney disease\(^53, 64, 116, 117\). Therefore, measurement of the brachial-ankle PWV may also be useful to identify the pathophysiologic abnormalities related to arteriosclerotic cardiovascular disease in the early stages\(^6\). Lifestyle modifications are recommended for subjects below 60 years of age who show brachial-ankle PWV values of ≥1400 cm/sec\(^118\).

The 2013 ESC/ESH guideline for arterial hypertension describes the carotid-femoral PWV as a marker of organ damage, and a carotid-femoral PWV of ≥10 m/sec is one of the markers for the start of antihypertensive medication\(^114\). On the other hand, the JSH 2014 and JAS guideline 2012 do not mention the significance of PWV in the risk stratification for cardiovascular disease\(^119, 120\). However, the brachial-ankle PWV satisfies most of the criteria listed for the establishment of a marker as a useful marker in the management of cardiovascular disease and/or its risk factors shown in Table 1 (except the relation with the improvement of prognosis). Therefore, brachial-ankle PWV is close to becoming established as a valuable marker in the management of arteriosclerotic cardiovascular disease and/or its risk factors.

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**Conflict of Interest Statement**

Hirofumi Tomiyama and Akira Yamashina received fees for lectures from Omron Health Care company.

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