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## Re-imagining the value of brachial ankle pulse wave velocity as a biomarker of cardiovascular disease risk – a call to action on behalf of VascAgeNet

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### DISCLOSURES

There are no conflicts of interest to declare.

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## Abstract

This review critiques the literature supporting clinical assessment and management of cardiovascular disease (CVD) and CVD risk stratification with brachial-ankle pulse wave velocity (baPWV). First, we outline what baPWV actually measures - arterial stiffness (AS) of both large central elastic arteries and medium-sized muscular peripheral arteries of the lower-limb. Second, we argue that baPWV is not a surrogate for carotid-femoral pulse wave velocity. While both measures are dependent on the properties of the aorta, baPWV is also strongly dependent on the muscular arteries of the lower extremities. Increased lower extremity AS amplifies and hastens wave reflections at the level of the aorta, widens pulse pressure, increases afterload, and reduces coronary perfusion. Third, we used an established evaluation framework to identify the value of baPWV as an independent vascular biomarker. There is sufficient evidence to support: i. proof of concept; ii. prospective validation; iii. incremental value; and iv. clinical utility. However, there is limited or no evidence to support v. clinical outcomes; vi. cost-effectiveness; viii. methodological consensus; or ix. reference values. Fourth, we address future research requirements. The majority of the evaluation criteria (i. proof of concept, ii. prospective validation, iii. incremental value, iv. clinical utility, and ix. reference values) can be supported using existing cohort datasets, whereas the v. clinical outcomes and vi. cost-effectiveness criteria require prospective investigation. The viii. methodological consensus criteria will require an expert consensus statement. Finally, we finish this review by providing an example of a future clinical practice model.

## Keywords

Pulse wave velocity; arterial stiffness; biomarker; vascular ageing; cardiovascular disease risk

## INTRODUCTION

Cardiovascular disease (CVD) risk management may be improved by incorporating arterial stiffness (AS), a measure of biological *vascular aging*, within standard clinical practice.

Brachial-ankle pulse wave velocity (baPWV, see Figure 1), a composite measure of central and peripheral AS,<sup>1</sup> has been widely adopted in parts of East Asia, with the Japanese Society of Hypertension Guidelines recommending use of baPWV for hypertension management.<sup>2</sup> Despite incorporation within the 2023 European Society of Hypertension (ESH) guidelines<sup>3</sup>, in which it is recommended as a screening tool for hypertension mediated organ damage, baPWV has received sparse attention in Western countries. This review focuses on the use of baPWV as a vascular biomarker to aid in the clinical management of CVD risk. Definitions for key terms and concepts used throughout the review are provided in Table 1. After reading this review, readers should be able to better understand:

1. the physiological principles of baPWV;
2. baPWV is a unique *vascular biomarker* and not a surrogate for carotid-femoral pulse wave velocity (cfPWV) or other measures of AS;
3. the evidence supporting the use of baPWV as a vascular biomarker;
4. future research requirements.

## VASCULAR AGEING AND ARTERIAL STIFFENING

The deterioration in vascular structure and function over time are the hallmarks of *vascular ageing*. Vascular ageing is attributable to *atherosclerosis*, the narrowing of the artery by the deposition of atheromatous plaque, and *arteriosclerosis*, the stiffening and thickening of the arterial wall.<sup>4, 5</sup> Although vascular ageing is a natural phenomenon associated with chronological age, there is wide inter-individual variability as a function of lifestyle, environmental and/or genetic factors.<sup>6</sup>

*Arterial stiffness* describes the resistance of the arterial wall to deformation. The arterial wall comprises endothelial cells, vascular smooth muscle cells (VSMC), and connective scaffolding proteins - principally collagen and elastin (see Figure 1). Elastin predominates in central arteries, ensuring a high elastic potential and the capacity to cushion the flow and pressure oscillations caused by intermittent cardiac left-ventricular ejection.<sup>7</sup> Collagen fibres and VSMCs predominate in muscular peripheral arteries, which means a lower elastic potential but a greater propensity for alterations in tone. The transition from a compliant aorta to relatively stiffer muscular arteries generates an impedance mismatch or stiffness gradient.<sup>7, 8</sup> The stiffness gradient attenuates the cyclical forward pressure wave into a smooth consistent blood flow, prevents transmission of pulsatile energy to the micro-circulation, and moderates wave reflection and, therefore, cardiac workload.<sup>7, 8</sup>

*Arterial 'stiffening'* is an arteriosclerotic process resulting from the gradual fragmentation, calcification, and loss of elastin fibres, the accumulation of stiffer collagen fibres, calcification and senescence of VSMCs, inflammation, and endothelial dysfunction contributing to a loss of elasticity or increase in the myogenic tone of the vessel wall.<sup>7, 9</sup> Central arteries are susceptible to stiffening, whereas the stiffening of peripheral arteries is less pronounced (see Figure 1).<sup>10</sup> Arterial stiffening, particularly of the aorta, increases systolic and pulse blood pressure and the pulsatile load on the left ventricle, as well as the transmission of pulsatile energy to the micro-circulation, leading to damage of

target organs.<sup>7</sup> The differing impact of age, lifestyle factors and risk factors on central and peripheral arteries leads to progressive attenuation of the physiological impedance mismatching, with attenuation or reversal of the stiffness gradient.<sup>10, 11</sup> This amplifies and hastens wave reflection, increasing cardiac workload and the impairment of coronary perfusion.<sup>8</sup>

## OVERVIEW OF BAPWV

### MEASUREMENT OF BAPWV

*Pulse wave velocity* is the speed at which the forward pressure wave propagates along the arterial tree, and is calculated as arterial path length divided by pulse transit time (PTT). A higher PWV indicates a greater (detrimental) arterial stiffness. The PTT for baPWV is commonly measured using blood pressure cuffs equipped with oscillometric and volume-plethysmographic sensors. The cuffs are secured around the upper-arm(s) (brachial artery) and ankle(s) (tibial and peroneal arteries) and used to simultaneously record the underlying pulse pressure waveforms (Figure 2). The PTT is then calculated as the time interval between the brachial and ankle waveforms using the foot-to-foot method, where the ‘foot’ is detected using the ‘intersecting tangent’ method. Arterial path length is typically estimated automatically via height-based equations, but can be estimated using body surface measurements and calculated as the path length from suprasternal notch to the ankle minus the suprasternal notch to the brachium.<sup>12</sup>

### WHAT PHYSIOLOGICAL CONSTRUCT DOES BAPWV MEASURE?

There is a prevalent, but mistaken, view that baPWV solely reflects the stiffness of peripheral arteries<sup>13</sup>. baPWV does incorporate the medium-sized muscular peripheral arteries of the lower-limbs, but also the elastic descending aorta (Figure 1). The proximal portion of the aorta is excluded from baPWV, at least theoretically, which can be attributed to the use of the brachial artery as the proximal measurement site. Following ventricular ejection, pulse pressure waves simultaneously propagate along the heart-brachial and heart-descending aorta arterial segments. It is assumed that the distance propagated and PTT for these pulse pressure waves are equitable. This theoretically results in the descending aorta serving as the start point for baPWV.<sup>1, 14</sup> This assumption is made for cfPWV, as the heart-carotid arterial segment is inconsistent with the path of blood flow for the region of interest. While the start point of baPWV is the descending aorta, it is still influenced by the preceding segments and the heart-brachial arterial segment. The importance of upper-limb PWV is often overlooked as it is expected to change little with age,<sup>15</sup> but an increase or decrease in heart-brachial PWV may bias the baPWV outcome by increasing or decreasing the brachial-ankle PTT.

### DISADVANTAGES OF BAPWV

**Measurement of baPWV may be inappropriate in some patient populations.—** The presence of cardiovascular pathology can impact the accuracy of baPWV measures. Stenosis in the lower-limbs, aortic stenosis, aneurysm, or regurgitation may lead to a pseudo-underestimation of baPWV.<sup>16, 17</sup> Stenosis in the subclavian arteries may lead to

a pseudo-overestimation of baPWV. Measurement of baPWV may be inappropriate if the patient presents with one of the aforementioned conditions.

**Height-based formulas to estimate arterial path length are inaccurate.**—Arterial path length is typically estimated using height-based formulas, which may be advantageous for clinical practice but lack accuracy. Compared to magnetic resonance imaging (MRI), height-based formulas overestimated path length by ~11%.<sup>18</sup> This contributes to absolute values of baPWV being substantially higher than all other regional PWV measures. MRI and height-based path lengths are highly correlated, indicating this problem may be rectified with an appropriate adjustment factor, but population-specific validation is required.<sup>18</sup>

## ADVANTAGES OF BAPWV

### Measurement of baPWV is simple and automated.

A prominent advantage of baPWV is its ease of assessment, with PPT being determined non-invasively and automatically using oscillometry. Limited training is needed for the baPWV operator, since the technique does not differ from any cuff-based blood pressure measurement. This simplicity, combined with an inherent low-patient burden, means baPWV may be easily applied in clinical practice.

### Measures of baPWV can be determined with accuracy and precision.

baPWV has shown good agreement ( $r=0.87$ ) with central PWV obtained by invasive recording.<sup>19</sup> baPWV can be determined with good reliability (intra-observer, between-visit day to day) and good reproducibility with low operator bias (inter-observer, same day).<sup>20</sup> Comparative studies have reported higher between-day intraclass-correlation coefficients for baPWV (0.84) compared to cfPWV (0.70).<sup>20</sup>

### The ankle brachial index (ABI), systolic interarm blood pressure difference (IAD) and pulse wave analysis (PWA) can be determined concurrently with baPWV.

The ABI is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery, with a threshold of  $\leq 0.9$  typically indicating significant stenosis and lower-extremity peripheral artery disease (PAD) or  $>1.4$  indicating vascular calcification.<sup>21</sup> An IAD of  $\geq 10$  mmHg indicates significant upper extremity stenosis and PAD.<sup>22</sup> ABI and IAD can identify the presence of stenosis and inform the suitability of baPWV measurement. PWA entails using a generalized transfer function to estimate the aortic pressure waveform, from which central hemodynamic variables such as central blood pressure and arterial wave reflection indices are derived.<sup>23, 24</sup> These complimentary outcomes will be further discussed in the Potential Clinical Practice Model section.

## BAPWV IS A STANDALONE MARKER OF CVD RISK

baPWV is commonly perceived as a surrogate of the referent PWV measure, cfPWV. baPWV and cfPWV do reflect overlapping regional arterial properties and functions and share similar associations with CVD risk factors (Figure 1).<sup>25, 26</sup> However, baPWV also incorporates the medium-sized muscular arteries of the lower extremities,<sup>26</sup> the stiffness

of which can increase with age<sup>16, 27</sup> and predicts stroke and CVD, including heart failure and myocardial infarction.<sup>28</sup> Increased stiffness of the muscular lower-limb arteries may principally contribute to CVD by amplifying and hastening wave reflections at the level of the aorta. This increases systolic blood pressure and widens pulse pressure, augmenting cardiac workload and increasing afterload whilst reducing coronary perfusion. The inclusion of this larger vascular territory means baPWV can provide additional, or at least different, cardiovascular information. Compared to cfPWV, baPWV is more strongly associated with cardiovascular structure and function, including left ventricular mass and diastolic function.<sup>29, 30</sup> Although whether this translates to a differentiation of hard outcome prognosis over the longer-term between PWV measures is unclear.

## EVIDENCE SUPPORTING USE OF BAPWV AS A VASCULAR BIOMARKER

Within this section we critique whether there is evidence to support the use of baPWV as an *intermediate outcome*. An intermediate outcome is a surrogate measure for a *clinical endpoint*, e.g., CVD morbidity or mortality. A vascular biomarker can be considered an intermediate outcome if it is associated with the intended clinical endpoint and is on the *causal pathway* between exposure (e.g., behaviour or treatment) and effect (i.e., predicts clinical benefit/harm).<sup>31</sup> A vascular biomarker can be considered suitable for clinical use if it satisfies the aforementioned, confers meaningful prediction of clinical benefit/harm superior beyond existing biomarkers (e.g., lipids), and is practical for use in the intended setting (i.e., can be implemented). Below we consider the nine criteria for the evaluation of novel biomarkers of CVD risk presented by the American Heart Association (AHA)<sup>32</sup> and endorsed by the European Society of Cardiology (ESC) and the Association for Research into Arterial Structure and Physiology (ARTERY) Society.<sup>33</sup> For each of the nine criteria we provide a definition, an overview of the key evidence, and indicate important gaps in the literature.

### i. PROOF OF CONCEPT

**Definition.**—Capacity to distinguish between subjects with and without CVD morbidity. Commonly tested with a cross-sectional study and quantified by determining whether the difference between groups is significant. Ideally, these findings are replicated in independent study populations.

**Evidence.**—Compared to non-diseased controls, baPWV is greater in patients with CAD<sup>19</sup>, heart failure with preserved ejection fraction<sup>34</sup>, target organ damage (cardiac, arterial, chronic kidney disease)<sup>35</sup>, CVD risk factors<sup>36, 37</sup>, and abnormal cardiovascular structure and function<sup>29, 30, 34</sup>.

**Gaps.**—The existing research has predominantly been conducted in East Asia, particularly Japan. Confirmatory research is required but there is no evidence to suggest the utility of baPWV may differ between countries and ethnicities.

## ii. PROSPECTIVE VALIDATION

**Definition.**—Ability to predict the development of future CVD morbidity or mortality. Typically tested with a prospective cohort, nested case-cohort, or case-control study and quantified as an odds ratio (OR), risk ratio (RR) or hazard ratio (HR) adjusted for risk factors including age and blood pressure.

**Evidence.**—Several meta-analyses have been published summarizing the capacity of baPWV to predict CV events and mortality<sup>38-40</sup>. In 2017, Ohkuma *et al.*<sup>38</sup> estimated the pooled HR using individual data from 14,673 Japanese adults (across eight studies) without a history of CVD. Following a mean follow-up of 6.4 years, participants in the fifth quintile (> 18.8 m/s) versus first quintile (<12.9 m/s) had a 3.5-fold (95% confidence interval (CI): 2.1 to 5.7) greater risk of developing CVD. These findings by Ohkuma *et al.*<sup>38</sup> mostly corroborate the 2012 report by Vlachopoulos *et al.*<sup>39</sup> who calculated the pooled RR from 18 cohort studies (total n = 8,169). Following a mean follow-up of 3.6 years, participants with high versus low baPWV (using high/low cut-points specified by each study) were at greater risk for total CV events (RR: 3.0, 95%CI: 1.6 to 5.3) and CV mortality (RR: 5.4, 95%CI: 2.2 to 13.3). And, contrary to the findings by Ohkuma *et al.*<sup>38</sup>, were at greater risk for all-cause mortality (RR: 2.5, 95%CI: 1.6 to 3.9). In 2021, Sang *et al.*<sup>40</sup> focused on patients with atherosclerotic CVD: compared to low baPWV, participants with high baPWV (using high/low cut-points specified by each study) were at greater risk for CV events (HR: 2.6, 95%CI: 1.6 to 4.0) and cardiovascular mortality (HR: 2.7, 95%CI: 1.9 to 3.8).

**Gaps.**—baPWV is consistently associated with CV events in participants with and without a history of CVD<sup>38-40</sup>. Prospective validation studies are required to confirm the applicability of these findings beyond East Asia.

## iii. INCREMENTAL VALUE

**Definition.**—Capacity of a novel biomarker to add predictive information beyond established biomarkers or models, such as the American College of Cardiology (ACC)/ American Heart Association (AHA) atherosclerotic cardiovascular disease risk score. Typically tested with a prospective cohort study, in which the participants are followed over time and the number of outcome events (i.e., CVD morbidity or mortality) is recorded. The incremental value of the new biomarker can be quantified by comparing the change in OR, RR, HR, or the global chi-squared ( $X^2$ ). Though it should be noted that these statistics are not standardized and can be misleading for prognosis analysis. An alternative statistic is the *c*-index, which is used to determine how well a risk marker discriminates between individuals at different risk levels. For binary outcome variables the *c*-index is equivalent to the area under the receiver operating characteristic curve (AUC).

**Evidence.**—In the largest study to date,<sup>41</sup> 6,359 Korean adults (40–79 yrs) without a documented history of CVD were followed for a median period of 4 years. The AUC for CV events was superior for baPWV (AUC: 0.70, 95%CI: 0.68 to 71) compared to the 2013 ACC/ AHA a risk score (AUC: 0.62, 0.61 to 0.63). baPWV also conferred incremental value to the 2013 ACC/AHA risk score, improving the  $X^2$  from 21 to 50.<sup>41</sup> For patients with a history of CVD or suspected CAD, baPWV also conferred additional prognostic value

to computed tomography angiography<sup>42</sup>, single-photon emission computed tomography,<sup>43</sup> flow-mediated dilation (endothelial function),<sup>44, 45</sup> hs-CRP,<sup>46</sup> and ABI.<sup>47</sup>

**Gaps.**—Only two prospective studies have investigated the general population. Additional prospective studies are warranted, particularly in general populations beyond East Asia.

#### iv. CLINICAL UTILITY

**Definition.**—Usefulness to clinical practice, in particular the ability of the new biomarkers to move patients from one risk category to another and thereby modify treatment. As a more powerful alternative to the *c*-statistic, the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) tests are often used to test whether the new biomarker improves the ability to discriminate between groups.

**Evidence.**—Among a general population of 4,251 Chinese adults, with and without a history of CVD, baPWV was added to a model which included mean arterial pressure as the initial exposure variable and fatal/nonfatal CV and cerebrovascular endpoints as the outcomes.<sup>48</sup> The addition of baPWV improved discrimination (IDI: 1.6%, 95%CI: 0.2 to 2.9) and net reclassification (NRI: 52%, 95%CI: 29 to 75). This supports the findings from previous individual-participant data meta-analysis by Ohkuma *et al.*<sup>38</sup> While no known studies have investigated whether baPWV measurements can improve disease management, a limited number of studies have investigated the baPWV response to treatment. A meta-analysis of 17 randomized controlled clinical trials reported non-significant changes in baPWV or cfPWV following treatment with angiotensin-converting enzyme inhibitors.<sup>49</sup> However, baPWV improved (i.e., decreased) by 1.3 m/s (95%: -2.1 to -0.5) when Japanese adults (n = 80) with type 2 diabetes were treated for 2 years with a sodium-glucose cotransporter 2 inhibitor (tofogliflozin), when compared to a usual care group (n = 74).<sup>50</sup> A meta-analysis (n = 6 baPWV studies)<sup>51</sup> reported that diet plus exercise therapy had a moderate effect on baPWV (standardized mean difference = -0.5, 95%CI: -0.8 to -0.2), a systematic review (n=7 studies)<sup>52</sup> reported that combined resistance and aerobic training in post-menopausal women (n=16 to 101, mean age = 54 to 79 years) reduced baPWV by 0.6–2.1 m/s, and a 20-week quasi-experimental study<sup>53</sup> reported that combined exercise plus statin treatment decreased baPWV from 17.5 m/s (SD: 3.6) to 16.3 m/s (SD: 2.7) despite a non-significant change in blood pressure.

**Gaps.**—Additional prospective studies, in independent populations and beyond East Asia, are required to quantify whether baPWV improves risk stratification.

#### v. CLINICAL OUTCOMES

**Definition.**—Whether use of the biomarker improves clinical outcomes. Optimally tested with a randomized controlled clinical trial and quantified by comparing outcomes for participants who are clinically managed using a new biomarker versus participants who are managed using standard care.

**Evidence.**—No known direct evidence exists to support the clinical outcomes criteria. However, the 2019 Japanese Society of Hypertension Guidelines for the Management



of Hypertension recommend measurement of baPWV for managing hypertension<sup>2</sup>. The recommendation was based on the available research supporting the predictive ability (i.e., prospective validation) and incremental value of baPWV.<sup>38</sup> baPWV was also included in the 2023 ESH guidelines.<sup>3</sup>

**Gaps.**—Clinical trials are required to determine whether treatment strategies based on baPWV measurement improve clinical outcomes.

#### vi. COST-EFFECTIVENESS

**Definition.**—Whether use of the biomarker improves clinical outcomes sufficiently to justify the additional costs. Typically determined by comparing the incremental cost to the incremental benefit. The incremental benefit is typically quantified as the change in life expectancy, the quality adjusted life-years (QALY), and the incremental cost-effectiveness ratio (ICER). The incremental costs include the downstream costs that can be attributed to the new biomarker, including follow-up testing and therapies prescribed.

**Evidence.**—No known studies have investigated the cost-effectiveness of baPWV. Cost-effectiveness is likely high, considering *clinical utility* and low operation costs, namely: (i) a single oscillometric device could be used to simultaneously measure blood pressure, ABI, IAD and baPWV; (ii) consumable requirements are minimal, including reusable cuffs; and (iii) minimal operator training requirements – akin to ABI. While baPWV cost-effectiveness data is unavailable, data is available for ABI. A recent Markov model<sup>54</sup> focused on 10-year CV event risk among women in the general Italian population. The additional cost associated with ABI screening, when added to the Framingham Risk Score, was €10/patient, the incremental QALY was 0.0039/patient, and the ICER was €27.99/QALY.

**Gaps.**—baPWV-specific cost-effectiveness are required.

#### vii. EASE OF USE

**Definition.**—Whether measurement procedures are simple enough to permit widespread adoption.

**Evidence.**—The most prominent advantage of baPWV is its simplicity of use, with automated measurement following cuff placement.

**Gaps.**—Implementation studies are warranted to determine best practice guidelines for implementing baPWV within clinical practice.

#### viii. METHODOLOGICAL CONSENSUS

**Definition.**—Uniformity of biomarker measurements in different clinics. Required to compare obtained measurement values against reference values.

**Evidence.**—Though some scientific societies have provided guidelines on the clinical use of different techniques assessing AS,<sup>55</sup> no specific guidelines exist to standardize baPWV methodology.

**Gaps.**—A consensus statement is required to help ensure measurement procedures are uniform across clinics, including consideration to: the required operator training; quality control; subject preparation; testing environment; data collection; cuff placement; outcome reporting; and path length determination.

## ix. REFERENCE VALUES

**Definition.**—The availability of published reference or cut-off values.

**Evidence.**—Reference values, relative to age and blood pressure, have been published for the Japanese population.<sup>36</sup> Several East Asian studies have suggested cut-points for CV risk assessment, albeit the cut-point range is wide, 14 to 18 m/s, and a limited number of adults older than 70 years of age have been included.<sup>36, 56, 57</sup>

**Gaps.**—Additional studies, including in non-Asian populations, are required to determine the expected change in baPWV with age, with respect to biological sex and blood pressure.

## FUTURE DIRECTION

Below, we summarize the important gaps in the literature, provide suggestions for addressing the gaps, then finish with an example of a potential clinical practice model.

### GAPS IN THE LITERATURE

As summarized above and in Table 2, there is sufficient evidence to support criteria *i* to *iv*. The priority scores were driven up (worse) by the need for data beyond East Asia and moderated by the fact that between-country differences in the association between baPWV and CV outcomes are likely attributable to modifiable risk factors rather than race/ethnicity.

There is limited or no evidence to support the *v*, *vi*, *viii* and *ix*. Studies are required to discern the usefulness of baPWV in guiding treatment decisions, and to determine whether the baPWV-guided treatment improves life expectancy and quality of life. Additionally, to guide clinical management with baPWV, data are required to generate reference values that are applicable to diverse populations. However, the reference values will only be of true value if there is measurement conformity across clinics. As such, a consensus statement is required to standardize the way baPWV is measured. The priority for addressing the *cost-effectiveness* criteria has been scored 2 (low), considering the expected *clinical utility* and low operating costs. The priority for addressing clinical outcomes, methodological consensus, and reference values have been scored 4 (high) to 5 (very high), considering that these are major impediments for persuading clinicians to change their clinical practice.

Criteria *vii* has been scored a 3 (medium). The score was driven up due to the low operator training requirements and moderated by the lack of best practice guidelines for clinical practice adoption. Adopting a new clinical management tool is disruptive to existing clinical practices and many barriers may exist, including but not limited to where/how the new tool fits within existing workflow models, potential changes to infrastructure, and alterations to clinical decision making. To address this gap, the current focus on *evidence-based research* needs to extend to *implementation science*. Most evidence-based research is not

incorporated into routine clinical practice. Implementation science is a discipline which seeks to understand the barriers and facilitators to clinical practice adoption, and design and test different strategies to scale evidence-based practices.

## ADDRESSING THE GAPS IN THE LITERATURE

This section has been broken down into two parts. Part one (short-term) considers research that can be conducted to address the evaluation criteria. Part two (long term) goes beyond the evaluation criteria, considering future refinement of the methodology itself.

**SHORT-TERM**—A number of the evaluation criteria, particularly *i to iv and ix*, can be further supported using existing cohort datasets. Example datasets include the Atherosclerosis Risk in Communities (ARIC), Multi-Ethnic Study of Atherosclerosis (MESA), Jackson Heart Study (JHS), Hispanic Community Health Study / Study of Latinos (HCHS/SOL), Framingham Heart Study (FHS), German National Cohort (NAKO), The Study of Health in Pomerania (SHIP), the COMPLETE Health Study, and The Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) 3 study.

The *viii. methodological consensus* criteria can largely be addressed by bringing together an expert team and adapting guidelines, which have been developed for cfPWV. However, there are some unique considerations for baPWV which may require additional research, including a path length formula suited to Western populations. The NAKO study,<sup>58</sup> which calculated baPWV using direct body surface measurements in more than 200,000 adults, may assist with validating a path length formula.

The *v. clinical outcomes* and *vi. cost-effectiveness criteria* will require prospective investigation, whereby primary care clinicians are randomized to adopt baPWV or to persist with usual patient care for a defined period. This will facilitate determination of the impact of baPWV on clinical management, including therapeutic prescription, and CV outcomes.

**LONG-TERM**—The above (short-term) discussion considers baPWV as *standalone* biomarker, which may not be the best approach for clinical management. Consider that the same device can be used to measure blood pressure, ABI, IAD and baPWV, each of which provides different CV information. Further research is required to determine whether the combined use of these biomarkers improves risk stratification and clinical management. There is also scope for utilizing artificial intelligence/machine learning to distinguish CV phenotypes and more objective treatment recommendations.

## POTENTIAL CLINICAL PRACTICE MODEL

The intent of this section is not to make specific recommendations pertaining to the implementation of baPWV within clinical practice, but rather to stimulate much needed discourse. The simplicity and automation of measurement, low cost of measurement device, and inherent low-patient burden, means baPWV may be readily integrated into clinical practice and succeed where other PWV biomarkers have yet to gain traction. Nonetheless, in addition to satisfying the nine evaluation criteria discussed above, thought needs to be afforded to how baPWV will be implemented. In this section we present a theoretical model

to indicate how baPWV *may* be used in clinical practice as part of a screening routine by a primary care physician to gain an holistic snapshot of a patient's cardiovascular health. *This* model encompasses ABI, IAD and PWA, and although the evidence supporting their use is not unequivocal<sup>59-62</sup>, these measures can be assessed concurrently with baPWV and may enhance reclassification beyond risk scores.<sup>22, 63, 64</sup> PWA derived outcomes including central blood pressure and arterial wave reflection may be particularly useful for enhancing diagnostic accuracy of heart failure<sup>65</sup> and improving clinical care.<sup>66</sup>

Figure 3 outlines a potential clinical practice model in the form of a decision tree. Traditional risk factors are initially used to stratify all-cause CVD risk, followed by the measurement of ABI and IAD. A positive (i.e. unhealthy) ABI (< 0.9 or > 1.4) or IAD (> 10 mmHg systolic BP) test would indicate advanced peripheral atherosclerosis and very high risk for myocardial infarction and stroke. A patient may be prescribed advanced imaging and then intensive treatment in the form of lifestyle behaviors, medication, and/or surgery. If the ABI and IAD are 'negative' (healthy), additional information provided by baPWV and PWA will be considered. If the baPWV score is positive (see Reference Values section) the patient may be allocated to intensive preventive treatments for all-cause CV event risk, acute coronary syndrome, and/or target organ damage risk. A positive PWA score may indicate the need to prescribe medications to decrease cardiac afterload, such as anti-hypertensive medications<sup>66</sup>. If both the baPWV and PWA scores are negative, the patient may be sent home with a wearable patch which continuously sends sensitive PWA and baPWV data to the cloud.<sup>67</sup> The in-clinic and ambulatory data will be harmonized in clinical management software and used to generate a CV phenotype and treatment plan. The first generation of the software may use a decision tree-based machine learning algorithm,<sup>68</sup> advancing to more complex algorithms or artificial intelligence with subsequent generations.

## CONCLUSIONS

The overarching goal of this article was to harmonize and critique the literature supporting *clinical management* of CVD risk with baPWV. In the introduction we listed four aims, each of which are restated and addressed below, related to a better understanding of:

### 1. Physiological principles of baPWV.

baPWV characterizes the AS of large central elastic arteries and medium-sized muscular peripheral arteries of the lower-limb (see Figure 1).

### 2. baPWV is a unique *vascular biomarker*.

While baPWV and cfPWV strongly agree, due to both incorporating the aorta,<sup>25, 26</sup> baPWV is dependent on the medium-sized peripheral muscular arteries of the lower extremities (see Figure 2). Increased lower extremity AS may principally contribute to CV by amplifying and hastening wave reflections at the level of the aorta, widening pulse pressure, increasing afterload, and reducing coronary perfusion. baPWV and cfPWV are distinct biomarkers and attempts to quantify baPWV as a surrogate for cfPWV undermine the true values of both measures.

### 3. Evidence supporting the use of baPWV as a vascular biomarker.

To address this aim we used the nine criteria presented by the AHA<sup>32</sup> and endorsed by the ESC and ARTERY.<sup>33</sup> The evidence is summarized in Table 2. There is sufficient evidence to support the criteria: *i. proof of concept*; *ii. prospective validation*; *iii. incremental value*; and *iv. clinical utility*. There is limited or no evidence to support the criteria: *v. clinical outcomes*; *vi. cost-effectiveness*; *viii. methodological consensus*; or *ix. reference values*.

### 4. Future research requirements.

The majority of framework criteria (*i. proof of concept, ii. prospective validation, iii. incremental value, iv. clinical utility, and ix. reference values*) can be supported using existing cohort datasets. Prospective investigation is required for criteria *v. clinical outcomes* and *vi. cost-effectiveness*. The *viii. methodological consensus* will require an expert consultation.

We finish this review by providing an example future clinical practice model (see Figure 3). This model assumes that the optimal value of baPWV will be extracted when it is not considered as a standalone biomarker, but rather is incorporated with traditional risk factors and complimentary outcomes.

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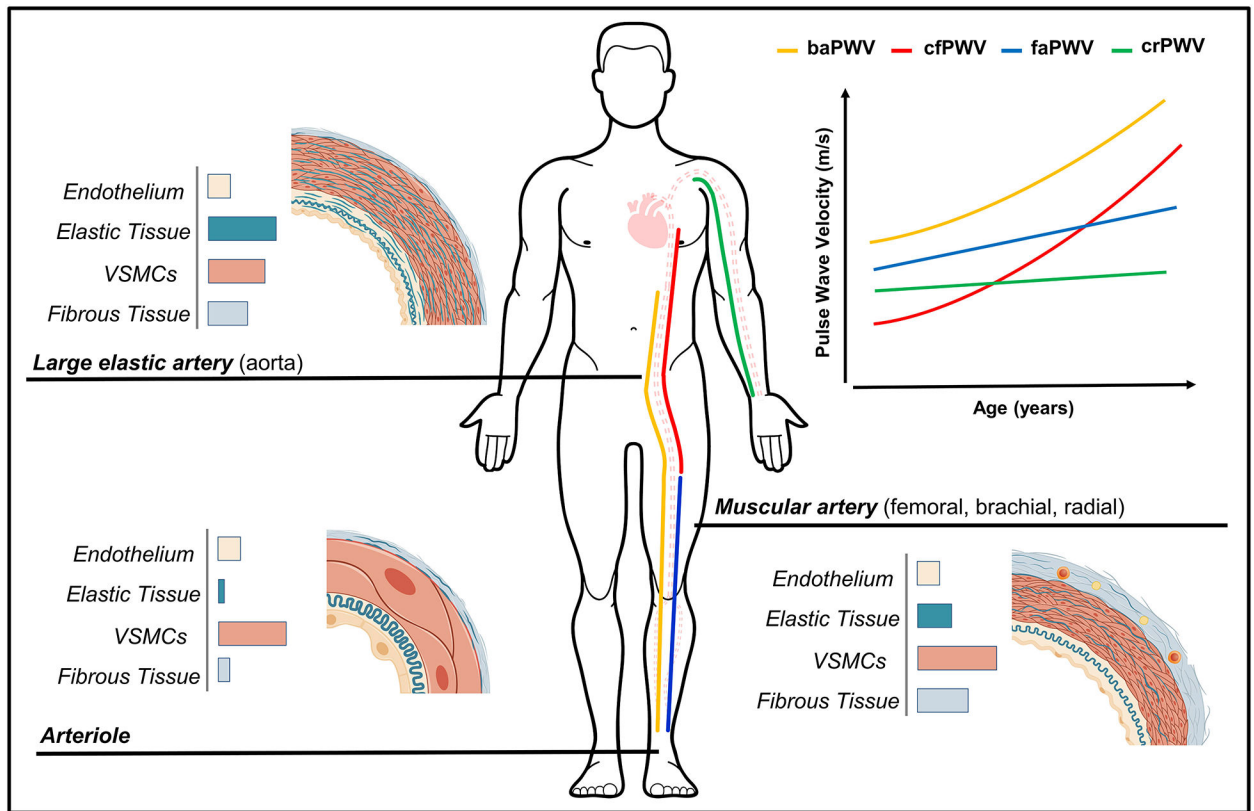
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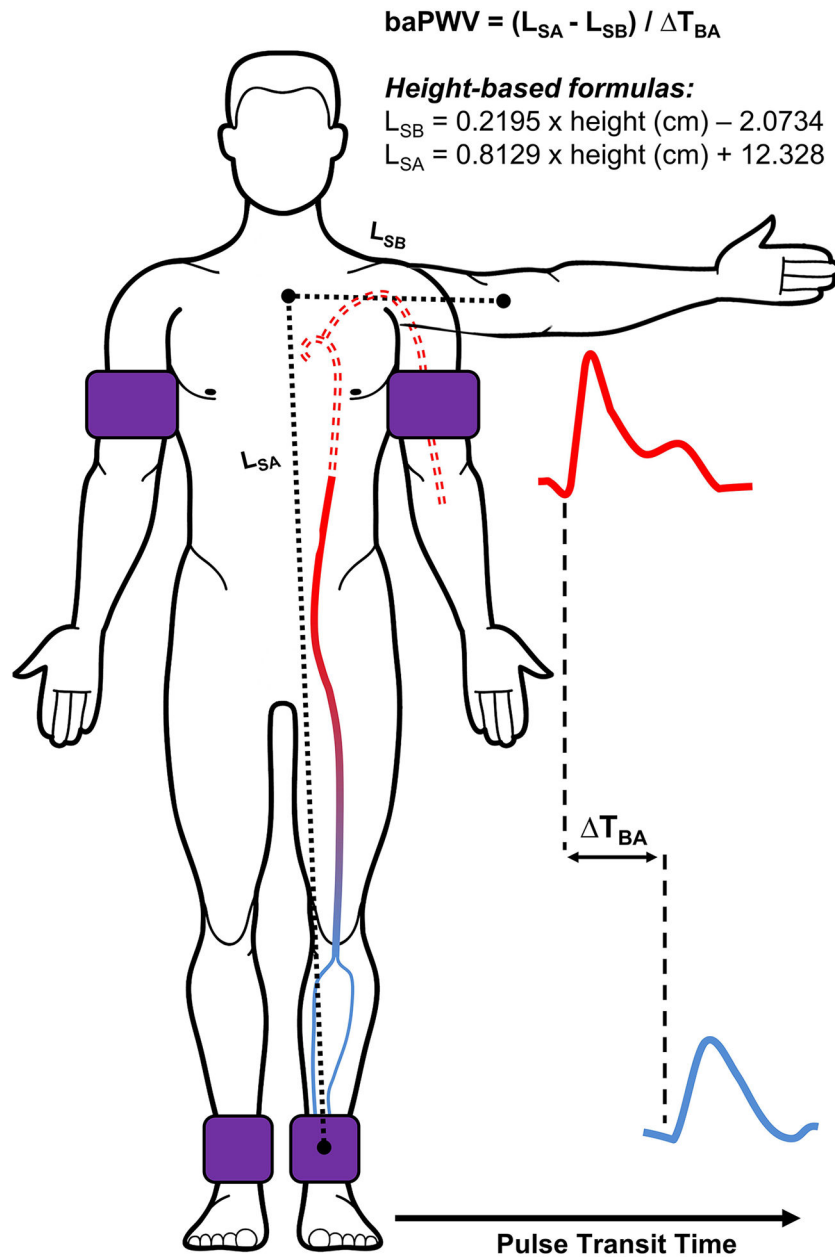


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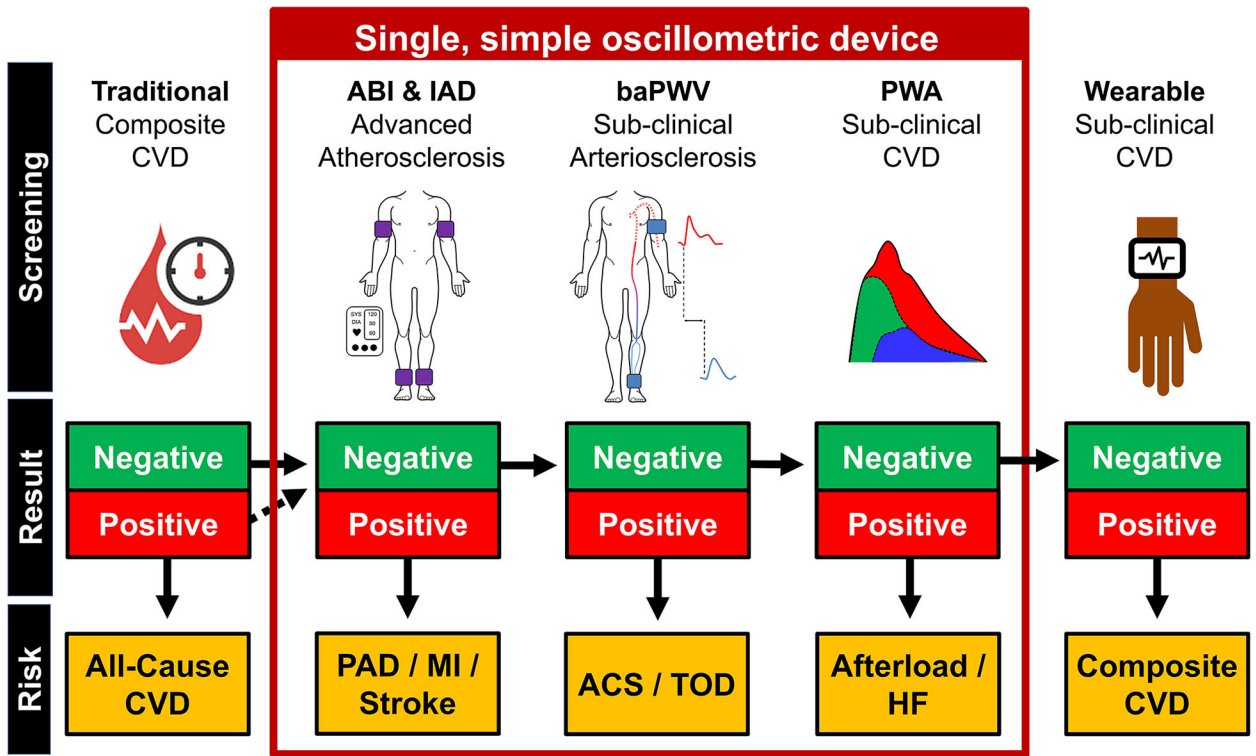


**FIGURE 1.**

Comparison of wall composition and changes in pulse wave velocity with age between central and peripheral arterial regions. cfPWV, carotid-femoral pulse wave velocity (central); faPWV, femoral-ankle pulse wave velocity (lower-limb); crPWV, carotid-radial pulse wave velocity; baPWV, brachial ankle pulse wave velocity (composite measure). baPWV summates the arterial properties between the descending aorta at the level of the brachial artery and the ankle, comprising of arteries or arterial regions (e.g. the aorta) with different structural and mechanical characteristics.

**FIGURE 2.**

Schematic for the measurement of brachial-ankle pulse wave velocity (baPWV). baPWV is estimated as the length between the sternal notch and the ankle ( $L_{SA}$ ) minus the sternal notch to brachium ( $L_{SB}$ ), as determined by body surface measurements or height-based formulas, divided by the time delay between brachial and ankle waveforms ( $\Delta T_{BA}$ ). *Note:* Solid line denotes effective path length.



**FIGURE 3.** Example of a potential future clinical practice model in the form of a decision tree. In this example, traditional risk factors will be measured and used to stratify all-cause cardiovascular disease (CVD) risk. Subsequently, ankle brachial index (ABI) and systolic interarm blood pressure difference (IAD) are measured. Positive ABI and/or IAD (*i.e.*, unhealthy, ABI score < 0.9 or > 1.4 and/or IAD ≥ 10 mmHg) scores indicates peripheral arterial disease (PAD) and increased myocardial infarction and stroke risk. If the ABI and IAD scores are negative (*i.e.* healthy, ABI: between 0.9 and 1.4; IAD < 10 mmHg), the additional information provided by brachial-ankle pulse wave velocity (baPWV) and pulse wave analysis (PWA) will be considered. A positive baPWV indicates increased risk for all-cause cardiovascular events, acute coronary syndrome (ACS) and/or target organ damage (TOD) risk. A positive PWA score may indicate increased afterload and increased heart failure (HF) risk. If both the baPWV and PWA scores are negative, the participant is sent home with a wearable device to collect ambulatory PWA and baPWV data, from which a composite CVD risk score is derived.

**TABLE 1.**

Key terminology definitions.

Term	Abbreviation>	Definition
<b>Ankle-brachial index</b>	ABI	Ratio of the systolic blood pressure measured at the ankle (tibial artery) to systolic blood pressure measured at the brachial artery.
<b>Area under the curve</b>	AUC	The area of the region enclosed by the curve line and the coordinate axis.
<b>Arterial stiffness</b>	AS	Fundamental mechanical behavior or rigidity of the material properties of the artery wall, determined by both structural and functional components.
<b>Arterial Stiffening</b>	--	The loss of arterial compliance or increased rigidity to deformation and/or changes in vessel wall properties.
<b>Arteriosclerosis</b>	--	The remodeling of the vasculature associated with stiffening, thickening, and dilatation of the arteries.
<b>Atherosclerosis</b>	--	An occlusive disease of the vasculature that occurs as a result of the deposition of lipid-laden plaques.
<b>Biomarker</b>	--	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
<b>C statistic</b>	--	The probability of concordance between predicted and observed survival. A measure of goodness of fit for binary outcomes in a logistic regression model.
<b>Cardiovascular disease</b>	CVD	A general term that describes heart, circulatory, and cerebrovascular disease.
<b>Causal pathway</b>	--	Steps in the linkage between a cause and outcome.
<b>Clinical endpoint</b>	--	An event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial.
<b>Clinical management</b>	--	A course of action for managing an individual's treatment.
<b>Evidence-based science</b>	--	Science informed by systematic research and underpinned by established theory.
<b>Global chi-squared</b>	X <sup>2</sup>	A statistical test used to compare observed results with expected results.
<b>Hazard ratio</b>	HR	An estimate of the ratio of the hazard rate in the treated versus the control group.
<b>Implementation science</b>	--	A discipline which seeks to understand the barriers and facilitators to clinical practice adoption.
<b>Integrated discrimination index</b>	IDI	A tool for evaluating the capacity of a marker to predict a binary outcome of interest.
<b>Systolic interarm blood pressure difference</b>	IAD	The absolute value of the difference in systolic blood pressure between left and right arms.
<b>Intermediate outcome</b>	--	A measurable indicator on the causal pathway to the final outcome.
<b>Net reclassification index</b>	NRI	A measure to assess the added value of predictor variables or used to assess the relative ability of 2 risk models to distinguish between low- and high-risk individuals.
<b>Odds ratio</b>	OR	A measure of association between a treatment/exposure and an outcome.
<b>Path length</b>	--	Length of arterial segment(s) the arterial pulse wave has propagated along. Estimated using body surface measurements or height-based formulas.

Term	Abbreviation>	Definition
<b>Pulse wave analysis</b>	PWA	Morphological analysis of blood pressure waveforms. Typically comprises of the recording of peripheral pressure waveforms with subsequent generation of a corresponding central waveform, permitting estimation of central hemodynamic variables including pressure and wave reflection.
<b>Pulse wave velocity</b>	PWV	The speed at which the arterial pulse wave propagates along an arterial segment.
<b>Quality of life</b>	QoL	The standard of health, comfort, and happiness experienced by an individual or group.
<b>Relative risk</b>	RR	The ratio of the risks for an event for the exposure group to the risks for the non-exposure group.
<b>Standard care</b>	--	Treatment approach that is accepted as appropriate and is widely or typically used by healthcare professionals.
<b>Vascular ageing</b>	--	Vascular ageing describes the deterioration in vascular structure and function over time that ultimately leads to damage in the heart, brain kidney, and other organs. Comprises of atherosclerotic and arterosclerotic processes.

TABLE 2.

Summary of evidence, gaps in knowledge, and research priorities.

	Criteria	Definition	Evidence		Gaps in Knowledge		Priority
			Evidence Summary	Score	Gaps	Score	
i	<b>Proof of concept</b>	Ability to distinguish between subjects	Distinguishes CAD, HF, TOD, CV pathology	4	4	Data: beyond East Asia	1
ii	<b>Prospective validation</b>	Future CVD morbidity/mortality predictive ability	High vs. low baPWV: CVD morbidity (HR: 2.6-3.4, RR: 3.0), CVD mortality (HR: 1.2-2.6, RR: 5.4), all-cause mortality (HR: 1.8-2.5)	4	4	Data: beyond East Asia	2
iii	<b>Incremental value</b>	Predictive information beyond standard risk markers	CV event prediction ↑ when added to ACC/AHA risk score (X <sup>2</sup> : 21 to 50), ABI (AUC: 0.72 to 0.83), CTIA (X <sup>2</sup> : 132 to 154), SPECT (X <sup>2</sup> : 24 to 27), FMD (AUC: 0.71 to 0.75), & hs-CRP (X <sup>2</sup> : 126 to 167)	4	4	Data: beyond East Asia & in general populations	3
iv	<b>Clinical utility</b>	Ability to move patients from one risk category to another	CV events: IDI = 1.6%, NRI = 52%.	3	3	Limited data from prospective studies in independent populations	3
v	<b>Clinical outcomes</b>	Impact of clinical management with biomarker on clinical outcomes	No data available	1	1	Clinical management: support for aiding treatment	4
vi	<b>Cost-effectiveness</b>	Incremental costs vs incremental benefits (life expectancy and QoL)	No data available, though likely high considering clinical utility & low examination costs	2	2	Clinical management: impact on life expectancy & QoL	2
vii	<b>Ease of use</b>	Simplicity of measurement procedures	Measurements automated following cuff placement	3	3	Implementation studies: best practices for implementing within clinical workflow	5
viii	<b>Methodological consensus</b>	Uniformity of measurements in different clinical settings.	No known guidelines exist	1	1	Consensus statement: measurement conformity across clinics, facilitating comparison to reference values	5
ix	<b>Reference values</b>	Availability of published reference or cut-off values	Reference values for Chinese populations	2	2	Data: beyond East Asia	4
			<b>Median evidence score</b>		4		

**Evidence Score / Gaps Priority Likert scale:** 1 = very low; 2 = low; 3 = medium, 4 = high, 5 = very high. **Abbreviations:** ACC/AHA, American College of Cardiology/American Heart Association; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; FMD, flow-mediated dilation; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; IDI, integrated discrimination improvement; NRI, net reclassification index; OR, odds ratio; RR, relative risk; QoL, quality of life; SPECT, single-photon emission computed tomography; TOD, target organ damage; X<sup>2</sup>, global chi squared.