Arterial stiffness as a noninvasive tissue biomarker of cardiac target organ damage

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Abstract: The primary prevention of cardiovascular (CV) disease is hindered by the inadequacy of traditional risk factors to stratify CV risk. The presence of cardiac target organ damage (cTOD), as detected by measures of left ventricular (LV) hypertrophy and dysfunction, is associated with future CV outcomes, but is not currently assessed in asymptomatic individuals. Arterial stiffness contributes to cTOD and may represent a biomarker that can detect vascular dysfunction before the clinical manifestations of cTOD. Measurement of arterial stiffness may provide insight into premature risk for cTOD and afford opportunity for early intervention to prevent further damage. The purpose of this review is to examine the utility of arterial stiffness as a noninvasive biomarker of subclinical cTOD. To this end, we will examine the evidence supporting the association between arterial stiffness and measures of cTOD. We will then explore the developmental origins of arterial stiffness and cTOD and outline the progression of CV damage that occurs with age. We discuss the mechanistic role of pressure from wave reflections as a crucial link between arterial stiffness and cTOD. Finally, we examine these associations in context by exploring sex and racial differences in arterial stiffness as related to cTOD. Our comprehensive examination of the literature suggests that early identification of arterial stiffness would be a useful biomarker of future cTOD risk.

Keywords: arterial stiffness, left ventricular hypertrophy, wave reflections, blood pressure

Biomarkers of cardiac target organ damage (cTOD)

Prevention of cardiovascular (CV) disease (CVD) remains a major public health priority.1 Hypertension and its associated complications serve as a primary substrate for the pathogenesis of CVD. Increasingly, new recommendations in the management of hypertension and hypertensive CVD risk prediction call for the assessment of subclinical target organ damage.2,3 Subclinical (asymptomatic) target organ damage is an intermediate step between chronic risk factor exposure and future clinical events (eg, stroke, myocardial infarction, heart failure).2,5

The National Institutes of Health define a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”6

A biomarker can be a circulating biomarker, in which sampling occurs in the blood, urine, or tissue, or can be an imaging or tissue biomarker recorded from an ultrasound (eg, left ventricular [LV] hypertrophy [LVH] or carotid intima media thickness) or other “imaging” modality (eg, applanation tonometry, pulse wave analysis).7–9

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Desirable features of a biomarker for cTOD are as follows: the biomarker should be reproducible, stable, cost-effective, acceptable to the patients, capture known physiology, provide novel insight into pathophysiology, and be responsive to therapy; it should explain a significant proportion of the outcome independent of other risk factors and aid in incremental risk prediction; it should have established normal/reference limits and standardized methodology; and, finally, change in the biomarker should alter outcome and help guide disease management. This biomarker should be applicable to men and women as well as different ages and different races/ethnicities.

In order to truly understand the structural and/or functional changes of target organs, use of novel tissue biomarkers have been proposed. Measurement of arterial stiffness may be such a tissue biomarker. Arterial stiffness integrates the cumulative impact of genetic factors, epigenetic factors, lifestyle factors, CV risk factors, and environmental factors on the arterial wall over time. This is important, as individual risk factors can fluctuate over time and their measurement, recorded at the time of risk assessment, may therefore be unreliable and not reflect their true impact on the arterial wall. The purpose of this review will be to explore the potential utility of measuring arterial stiffness and its associated hemodynamic sequelae (ie, increased pressure from wave reflections and pulse pressure [PP] amplification) as novel biomarkers of subclinical cTOD. Earlier detection and/or prediction of cTOD with measures of arterial stiffness may afford opportunity for prevention before overt damage occurs.

Arterial stiffness as a biomarker for cTOD

Arterial compliance reflects the ability of large central elastic arteries such as the aorta and carotid to expand and recoil during systole and diastole. This buffering capacity functions to dampen the amplitude of fluctuations in pressure and flow in the systemic circulation, thereby preventing transmission of excess pulsatile energy into target organs. Loss of arterial compliance or an increase in the stiffness of the vessel alters ventricular–vascular coupling such that arterial load is increased, contributing to the pathogenesis of cTOD and ultimately heart failure (described in more detail below). Increased arterial stiffness is associated with systemic subclinical target organ damage, including but not limited to renal dysfunction, brain white matter hyperintensities and infarcts, retinal damage, and peripheral skeletal muscle perfusion. Arterial stiffness can be influenced by any factor that alters vascular wall structure (elastin, collagen, smooth muscle) or function (endothelium). Age and blood pressure (BP) remain the most consistent correlates of arterial stiffness and, while traditional CVD risk factors are loosely associated with arterial stiffness, this is not always a consistent finding. Numerous factors that may alter vascular structure (atherosclerosis, calcification/medial calcific sclerosis, tortuosity, elastin breakdown, collagen deposition, fibrosis) and function (inflammation, oxidative stress, autonomic nervous system modulation, renin–angiotensin–aldosterone system activation, and endothelial function) appear to associate with arterial stiffness at any given moment in time, but key moderators of change in arterial stiffness over time include hemodynamic load (quantified as the product of heart rate and BP) and change in central obesity. Thus it must be stressed that, although the atherosclerotic process affects arterial stiffness (ie, presence of a plaque/atheroma may alter the mechanical function of the vessel wall), arterial stiffening is a process distinct from atherosclerosis. A weak relationship exists between postmortem aortic plaque burden and antemortem arterial stiffness.

The current gold standard measure of arterial stiffness is aortic pulse wave velocity (PWV). Aortic PWV can be measured by assessing the transit time between the PP wave at the carotid and femoral artery. PWV is simple, non-invasive, and reproducible; standardized measurement protocols exist, and reference values have been established in adults and children. Finally, with recent advances in technology, the measure is on its way toward being almost entirely automated.

Aortic stiffness using PWV predicts adverse CV events independent of traditional risk factors (eg, BP). Aortic stiffness also helps to discriminate between patients at low and high risk of adverse CV outcomes when added to conventional risk factors. Addition of aortic PWV to the Framingham Risk Score improves model fit for CVD event prediction, reclassifying 15.7% of intermediate risk patients properly into higher (14.3%) or lower (1.4%) risk. Finally, limited data in select patient populations suggest that failure to improve PWV, despite normalizing other risk factors, confers increased risk for CV mortality. Guidelines set out by the European Society of Hypertension have also recognized arterial stiffness in the stratification of CV risk as a marker for asymptomatic target organ damage, but the decision to adopt assessment into US guidelines remains controversial.

Arterial stiffness is not only a measure of target organ damage itself, but may prove useful in identifying individuals...
at risk for subclinical cTOD. LV mass can increase from either wall thickening in response to pressure overload, termed “concentric remodeling,” or from chamber dilation in response to volume overload, termed “eccentric remodeling.” The cause for ventricular enlargement comes from the increase in myocardial oxygen demand as a result of the increase in pressure load from the peripheral arteries, referred to as vascular afterload, in an attempt to regulate stress placed upon the ventricle (ie, compensation, preserved wall tension). If left unchecked, the left ventricle may dilate, leading to ischemia, scarring, fibrosis, and, ultimately, heart failure (decompensation). In addition to structural changes in the myocardial wall, cTOD is also associated with alterations in cardiac function, manifesting as diminished myocardial contraction velocity/prolonged myocardial contraction, inadequate relaxation, and reduced diastolic filling.

As alluded to above, elevated BP is considered to be the primary driving factor underlying the development of LVH. Interestingly, changes in arterial stiffness precede longitudinal increases in BP and development of hypertension. As will be discussed in detail below, changes in arterial stiffness and central hemodynamic burden are intimately entwined in each step of LVH development (Figure 1). Numerous studies now note associations between arterial stiffness and markers of subclinical cTOD in numerous clinical cohorts (Table 1). Regression of LVH via various pharmacological interventions is associated with reductions in arterial stiffness. Even when BP is controlled with antihypertensive agents, aortic stiffness remains a continued indicator of LV mass in hypertensive patients, suggesting continued utility as a marker of cTOD and true measure of vascular afterload in response to therapy.

Arterial stiffness is associated with LV systolic and diastolic dysfunction. Arterial stiffness also contributes to altered LV twist mechanics, reduced LV synchronicity, myocardial deformation, coronary flow reserve, and left atrium enlargement. Stiffening of the large central arteries (ie, aorta and carotid) has also been implicated in the progression of LVH to heart failure. Animal models have demonstrated that experimentally decreasing aortic compliance via prostheses or silicon gel application result in significant increases in LVH/LV mass, without affecting diastolic pressure, cardiac output, or peripheral resistance per se. Interestingly, change in arterial stiffness has also been implicated in the transition from chronic compensated to acute decompensated heart failure. Taken together, these findings suggest a strong association between arterial stiffness and cTOD.

### Arterial stiffness and pressure from wave reflections: mechanistic insight into cTOD

The association between arterial stiffness and cTOD is partially moderated by effects on pressure from wave reflections. In clinical practice, brachial BP is often used as a crude proxy of vascular afterload; however, brachial pressures are poor surrogates for central pressure (considered a much better indicator of true afterload and coronary perfusion pressure), owing to the elastic properties of the central arteries and subsequent stiffness-mediated effects on timing and magnitude of PP transit and transmission. According to wave transmission/reflection theory, the BP waveform is an amalgam of forward- and backward-traveling waves. LV ejection instigates the genesis of a forward-traveling pressure wave, the magnitude of which depends largely on the ventricular contraction and the elastic properties of the aorta. This pressure wave may be partially reflected from peripheral vessels as it travels down the vascular tree, with the speed and intensity/magnitude of this reflection affected by several hemodynamic factors, including arterial stiffness and physical distance to the peripheral reflection sites (ie, a smaller arteriole, vessel branch point, regional discontinuity in arterial compliance, etc). In this manner, increases in forward- and/or backward-traveling waves play a role in determining afterload and PP amplitude via augmentation of systolic pressure.

**Figure 1** Working theoretical framework linking arterial stiffness and wave reflections to increased LV work and hypertrophy.

**Abbreviations:** LV, left ventricular; LVH, LV hypertrophy.
As the pressure wave travels from the heart to the periphery, both systolic and PP increase markedly, while mean pressures decrease only slightly (−2 mmHg) due to viscous dampening.78 Thus, both systolic pressure and PP are greater in the arm and leg than in the ascending aorta.80 This PP amplification ensures that pulsatile load is lower in the periphery, both systolic and PP increase markedly, while mean pressures decrease only slightly (−2 mmHg) due to viscous dampening.78 Thus, both systolic pressure and PP are greater in the arm and leg than in the ascending aorta.80 This PP amplification ensures that pulsatile load is lower in the periphery.

<table>
<thead>
<tr>
<th>Study</th>
<th>cTOD measure</th>
<th>Measure of stiffness</th>
<th>Population studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saba et al117</td>
<td>Echo of LV</td>
<td>rAix (+), Ep (NS), β (NS)</td>
<td>67 NT subjects (age 47±15 years, 72% M)</td>
</tr>
<tr>
<td>Marchais et al18</td>
<td>Echo of LV</td>
<td>cIPWV (NS), rAix (+)</td>
<td>44 ESRD subjects (estimated age 43±14 years, 82% M, 55% treated HTN)</td>
</tr>
<tr>
<td>Roman et al117</td>
<td>Echo of LV</td>
<td>β (+)</td>
<td>276 subjects (estimated age 53±15 years, 65% M, 71% untreated HTN)</td>
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<tr>
<td>Nitaka et al11</td>
<td>Echo of LV</td>
<td>baPwv (+)</td>
<td>49 ESRD subjects (age 60±2 years, 55% M)</td>
</tr>
<tr>
<td>Lekakis et al10</td>
<td>Echo of LV</td>
<td>rAix (+), A (++)</td>
<td>48 untreated HTN subjects (age 56±12 years, 69% M)</td>
</tr>
<tr>
<td>Hashimoto et al19</td>
<td>Echo of LV</td>
<td>cIPWV (NS), rAix (+)</td>
<td>77 untreated HTN subjects (age 56±10 years, 70% M)</td>
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<tr>
<td>Watabe et al14</td>
<td>Echo of LV</td>
<td>baPwv (+)</td>
<td>798 subjects (age 63±11 years, 33% M, 21% treated HTN)</td>
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<tr>
<td>Schillaci et al149</td>
<td>Echo of LV</td>
<td>cPwv (NS &lt;40 years &lt;+), aAix (NS &lt;40 years &lt;+), baPwv (+)</td>
<td>237 HTN subjects (estimated mean age 47 [range 18–88] years, 58% M)</td>
</tr>
<tr>
<td>Hashimoto et al173,117</td>
<td>Echo of LV</td>
<td>cPwv (+), rAix (+), AP (+), aAix (+)</td>
<td>46 untreated HTN subjects (age 57±8 years, 70% M)</td>
</tr>
<tr>
<td>Chow et al170</td>
<td>Echo of LV</td>
<td>rAix (+)</td>
<td>47 total subjects, 68% with systemic lupus erythematosus (age 17±5 years, 13% M)</td>
</tr>
<tr>
<td>Ou et al171</td>
<td>MRI</td>
<td>cPwv (+), β (+) C (+)</td>
<td>60 total subjects, 67% with aortic coarctation repair (age 12±8 years, 60% M)</td>
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<tr>
<td>Hashimoto et al181</td>
<td>Echo of LV</td>
<td>cIPWV (NS), aAix (+)</td>
<td>98 untreated HTN subjects (age 55±9 years, 67% M)</td>
</tr>
<tr>
<td>Hashimoto et al181</td>
<td>Echo of LV</td>
<td>cIPWV (NS), aAix (+)</td>
<td>61 HTN subjects underwent anti-HTN treatment (age 57±8 years, 64% M)</td>
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<tr>
<td>Weber et al184</td>
<td>Echo of LV</td>
<td>iPwv (+), rAix (NS), AP (NS)</td>
<td>336 subjects undergoing coronary angiography (age 63±11 years, 49% M, 69% HTN)</td>
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<tr>
<td>Toprak et al184</td>
<td>Echo of LV</td>
<td>aIPwv (+), Ep (+)</td>
<td>786 subjects (age 36±5 years, 42% M, 7% treated HTN)</td>
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<td>Urbina et al184</td>
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<td>cIPWV (+), rAix (+), GSI (+)</td>
<td>670 subjects (age 18±3 years, 35% M)</td>
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<tr>
<td>Andrikou et al172</td>
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<td>cIPWV (+)</td>
<td>428 untreated HTN subjects (age 52±10 years, 60% M)</td>
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<tr>
<td>Rabkin and Chan184</td>
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<td>hIPwv (+), cIPwV (NS)</td>
<td>20 subjects underwent anti-HTN treatment (age 68±9 years, 60% M)</td>
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<tr>
<td>Su et al172</td>
<td>Echo of LV</td>
<td>baPwv (+)</td>
<td>1,146 subjects (estimated age 61±12 years, 57% M, 69% HTN)</td>
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<tr>
<td>Russo et al145</td>
<td>Echo of LV</td>
<td>GSI (–), F (NS, M)</td>
<td>981 subjects (estimated age 72±9 years, 38% M, 80% HTN)</td>
</tr>
<tr>
<td>Chung et al174</td>
<td>ECG</td>
<td>baPwv (+)</td>
<td>984 HTN subjects (estimated age 61±12 years, 60% M)</td>
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<tr>
<td>Kirs et al175</td>
<td>Echo of LV</td>
<td>cIPWV, rAix (+)</td>
<td>75 subjects (estimated age 51±7 years, 72% M, 47% HTN)</td>
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<tr>
<td>Hsu et al176</td>
<td>Echo of LV;</td>
<td>baPwv (+)</td>
<td>270 subjects (estimated age 57±12 years, 56% M, 61% HTN)</td>
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<tr>
<td>ECG</td>
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<tr>
<td>Wongphen and Boonyasirinant177</td>
<td>MRI</td>
<td>cPwv (NS)</td>
<td>113 HTN subjects (age 69±10 years, 49% M)</td>
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Notes: (+) indicates a strongly positive association with cTOD; (+) indicates a moderately positive association with cTOD; (−) indicates a negative association with cTOD; (NS) indicates that association with cTOD was not significant.

Abbreviations: βAix, aortic augmentation index; aIPWV, aortofemoral PWV; rAix, radial augmentation index; AP, augmented pressure; baPwv, brachial–ankle PWV; β, beta stiffness; cIPwv, carotid–femoral PWV; cPwv, central PWV; cTOD, cardiac target organ damage; DM, type 2 diabetes mellitus; ECG, electrocardiography; Ep, pressure–strain elasticity modulus; ESRD, end-stage renal disease; F, female; GSI, global stiffness index; hIPWV, heart–femoral PWV; HTN, hypertensive; iPwV, invasive PWV; LV, left ventricle; M, male; MRI, magnetic resonance imaging; NS, not significant; NT, normotensive; PWV, pulse wave velocity; rPwV, radial PWV; Echo, echocardiography.
because the myocardium appears to be particularly vulnerable to late systolic load. Changes in late systolic pressure are particularly crucial, as animal-based research has shown greater hypertrophy and fibrosis compared to early systolic loading, independent of pressure. In vivo research has demonstrated that cardiac myosin heavy chain synthesis increases approximately 35% within hours after a pressure overload, suggesting that reflection-based increases in afterload may precipitate cardiac remodeling in various clinical populations. Moreover, chronic pressure wave reflection-based increases in afterload adversely affect coronary perfusion and ventricular function.

Wave reflections influence myocardial work during late systole, resulting in greater myocardial stress, a primary determinant of systolic function and myocardial oxygen demand. Wave reflections arriving in late systole rather than diastole can impair diastolic function through decreased perfusion time, and are inversely associated with the isovolumetric relaxation period. Furthermore, LV early diastolic velocity, a measure of ventricular relaxation, is strongly associated with late systolic load, which is substantially determined by wave reflections and central arterial stiffness. Wave reflections have been associated with altered ventricular–vascular coupling and may have sufficient magnitude to directly alter ventricular wall motion. Reflected wave pressure adds to incident wave pressure but subtracts from forward flow, thereby negatively impacting ventricular ejection. Thus, the combination of increased cardiac stress, work, and oxygen demand, together with decreased cardiac perfusion, ejection, and relaxation, has been speculated by some as sufficient to precipitate exertional angina.

Two primary measures of wave reflection are augmentation index (Alx) and backward/reflected wave pressure (Pb) obtained from wave separation analysis. Alx is a measure of global wave reflections and is typically defined as the ratio of the reflected wave contribution to PP (known as augmentation pressure) relative to PP (Figure 2). Alx is dependent on both the timing of the reflected wave and magnitude, and cannot differentiate between the two. By simultaneously measuring pressure and flow in a vessel (or deriving a pseudo-flow waveform from the contour of the BP waveform), Pb can be measured. This method has been suggested as a more robust measure of pressure attributable to wave reflections (ie, wave reflection magnitude). Recently, Pb and Alx have been shown to be independently predictive of CV events, with Pb further predictive of all CV events and strongly predictive of congestive heart failure development following a median follow-up of 7.61 years. Additional findings suggest that Pb predicts CV mortality independent of conventional risk factors in men and women and high-risk patients, and is associated with hypertensive end organ damage. Moreover, changes in pressure from wave reflections are strong determinants of change in LV mass index following antihypertensive treatment, independent of changes in conventionally measured brachial BP. Taken together, these findings suggest that pressure from wave reflections with subsequent increases in late systolic load contributes to altered ventricular–vascular coupling, increased LV work, reduced coronary perfusion, and, ultimately, LVH (Figure 1).

**Developmental origins of arterial stiffness and cTOD**

It is well established that arterial stiffness and pressure from wave reflections increase with advancing age. In fact, it has been posited that one is only as old as his/her arteries. Factors in early adulthood and even childhood may, however, impact vascular and hemodynamic properties in later adulthood, importantly contributing to cTOD long before “old age” sets in. Our arteries may be the first organ to age, beginning from the moment we are born, and possibly even before we are born. Genomic analysis from the Framingham Heart Study suggests that the heritability of pressure wave reflections and PWV range from approximately 40%–66%. Heritability of PWV and Alx were 19% and 41%, respectively, and were significant, in a study of European families. Data from the Strong Heart Family Study revealed statistically significant heritability of arterial stiffness and Alx to range from approximately 18%–23%. Heritability of arterial stiffness has been estimated to be as high as 54% in young African Americans.

During prenatal life, if conditions in the intrauterine environment are suboptimal (due to poor maternal diet or other stressors), growth is restricted. The fetus responds by choosing a developmental pathway that will ensure survival given the particular intrauterine environment, and this is known as “fetal programming.” It likely induces morphological and physiological changes that predispose the individual to increased arterial stiffness. This is extremely important, as elevated arterial stiffness in adolescence is highly associated with LV mass, independent of BP and traditional CVD risk factors. Low birth weight is associated with LV mass in adolescence and with higher arterial stiffness in mid-adulthood. The fetal programming response within blood vessels may lead to increased...
intima-media thickness, smaller arterial diameters, and overall stiffer arteries (possibly due to reduced production of elastin). The life-long consequence of these adaptations is an increased risk for cTOD.

**Sex differences in arterial stiffness, wave reflections, and cTOD**

Women are more likely than men to present with concentric remodeling, while chamber dilation is more common in men. A potential reason for this has been predicted to be due to sex differences in arterial hemodynamics. Namely, it is well established that women have higher arterial stiffness when compared to age-matched men. Women have larger reflected wave magnitude than men due to their shorter height and reduced distance between the heart and the peripheral reflecting sites. Additionally, smaller PP amplifications in women have been reported across studies. A recent study examined prepubescent children and showed that girls had a significantly higher aortic pulse wave augmentation when compared to boys of the same age and height. This is important, as this study also implies that body height does not account for all sex differences in wave reflections.

Given that women have greater pressure from wave reflections compared to men, sex differences in central hemodynamic burden may contribute to greater LV diastolic dysfunction and afterload in women. Interestingly, associations between arterial stiffness and LV mass may be greater in women compared to men. Similarly, the correlation between AIx and LV diastolic function has also been reported to be greater in women than in men. Regression of LVH with antihypertensive
therapy is attenuated in women compared to men, and it has been suggested that this is due to sex differences in arterial stiffness and pressure from wave reflections. Therefore, women may be particularly susceptible to the deleterious effects of increased arterial load from increased arterial stiffness and pressure from wave reflections.

Racial differences in arterial stiffness, wave reflections, and cTOD
cTOD is not only common but epidemic in African Americans, irrespective of the presence or absence of hypertension. African Americans are more susceptible than Caucasians to BP-mediated cTOD. Several studies note increased arterial stiffness, augmented pressure from wave reflections, and lower PP amplification in African Americans.Interestingly, these detrimental modulations are directly associated with wasted LV pressure effort, increased myocardial work, reduced coronary perfusion, and cTOD, even in individuals with brachial BP within accepted normal reference ranges. Racial differences in arterial stiffness manifest at an early age and subsequent changes in central pressures are associated with LV mass in young African American adolescents.

Concluding remarks
Throughout this review, we have discussed the research supporting the utility of aortic PWV and pressure from wave reflections as biomarkers of subclinical cTOD in both sexes, across a wide age range, in different races/ethnicities, and across numerous pathologies. Measuring aortic PWV may also be a useful means of improving CV risk stratification due to its ability to detect early cTOD, which is an important indicator of future CV events. The American Heart Association (AHA) recently reviewed the requirements that must be met to warrant inclusion of novel biomarkers into CV risk assessment. These requirements include: 1) proof of concept; 2) prospective validation; 3) incremental value (adding predictive information to traditional risk markers); 4) clinical utility; 5) clinical outcomes; and 6) cost-effectiveness.

Summary
1–2. Proof of concept and prospective validation: aortic PWV is a biomarker of subclinical cTOD and is predictive of future CV outcomes in prospective studies.
3. Incremental value: aortic PWV provides CV risk prediction value above and beyond established risk factors, which has been demonstrated to improve incremental CV risk stratification.
4. Clinical utility: improvement of CV risk stratification using aortic PWV allows for reclassification of individuals into higher or lower CV risk categories.
5–6. Clinical outcomes and cost-effectiveness: more research is needed on cost-effectiveness and whether reductions in arterial stiffness lead to a regression in cTOD and decreased risk of morbidity/mortality.

Although aortic PWV currently falls short of meeting all requirements as a novel biomarker in CV risk assessment set out by the AHA, current literature evidence supports its use in identifying subclinical cTOD. Use of this biomarker has the potential to improve CV risk stratification through detection of early cTOD and to provide opportunities for the development of interventions that may prevent and possibly reverse cTOD. Future prospective randomized clinical studies will determine whether improvement in aortic PWV, or another measure of arterial stiffness, will improve clinical outcome and support utility of PWV as an effective biomarker for early detection of cTOD risk.

Disclosure
The authors report no conflicts of interest in this work.

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