

## HEMODYNAMICS OF HYPERTENSION

# Central Aortic Blood Pressure and Pulse Wave Velocity as Additional Markers in Patients with Hypertension

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## ABSTRACT

Arterial stiffness is a pathological manifestation of cumulative vascular damage resulting from various known and unknown vascular risk factors. Central aortic pressure and pulse wave velocity are the two most commonly used and the most informative non-invasive measures of arterial stiffness. Numerous studies have documented incremental value of these measures in a variety of clinical conditions, most notably, hypertension. In hypertensive subjects, assessment of arterial stiffness not only provides incremental information about vascular risk, it also helps in guiding therapeutic decision making and serves as a tool for monitoring response to antihypertensive therapy.

**Keywords:** Arterial stiffness, Arteriosclerosis, Subclinical atherosclerosis, Vascular damage.

**How to cite this article:** Kasliwal RR, Mahansaria K, Bansal M. Central Aortic Blood Pressure and Pulse Wave Velocity as Additional Markers in Patients with Hypertension. *Hypertens J* 2015;1(2):73-82.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Cardiovascular diseases (CVDs) are among the major killers in the modern world and the last few decades have seen an unprecedented increase in the incidence and prevalence of CVDs, particularly in low-income and low-middle income economies such as India.<sup>1,2</sup> To combat the global burden of mortality and morbidity due to CVDs, several risk assessment tools have been developed to guide treatment and preventive measures at a population level.<sup>3-12</sup> These risk assessment tools take various known risk factors into consideration, including hypertension (HTN), diabetes mellitus (DM), smoking,

obesity, family history, age and gender; among others. One major limitation of these risk assessment tools is that while they can successfully predict the probability of an individual developing CVD, they cannot accurately identify the individuals who are actually going to develop CVDs. This is mainly because the relationship between the vascular risk factors and development of atherosclerosis is imperfect, and also because of the fact that the risk assessment tools take into consideration only the known risk factors, leaving room for the yet unknown risk factors to cause vascular damage. This has prompted research into developing modalities for directly identifying vascular damage at a subclinical stage to better guide CVD prevention and treatment strategies.<sup>13</sup> These include flow-mediated dilation, finger plethysmography, digital thermal monitoring, pulse wave analysis (PWA), pulse wave velocity (PWV) assessment, pulse contour analysis, carotid wall distensibility coefficient, carotid intima-media thickness (CIMT),<sup>14-19</sup> ankle brachial index (ABI),<sup>20,21</sup> coronary calcium score (CCS),<sup>11,22-29</sup> etc.

Hypertension is one of the major risk factors that contribute to the development of CVDs.<sup>30,31</sup> Significant reduction in cardiovascular (CV) mortality due to an effective battle against high blood pressure (BP) may be considered one of the greatest medical success stories of the past century.<sup>32</sup> For these reasons, measurement of brachial BP has become embedded in routine clinical assessment throughout the world and a reduction in the same taken as a surrogate marker for the reduction of the burden of CVDs.<sup>33</sup>

However, over the past 20 to 30 years, there has been a significant improvement in our knowledge of vascular hemodynamics and this has dramatically changed the approach to hypertensive patients. There has been an increasing recognition of the value of arterial stiffness as a marker of vascular damage, particularly in patients with HTN. Hypertension is the most important contributor of arterial stiffness and the reverse is also true with arterial stiffness being the most important mechanism responsible for CV damage resulting from HTN. This review summarizes the present evidence supporting the use of arterial stiffness measures, such as PWV and central aortic pressure as predictive markers for

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subclinical vascular damage in hypertensive subjects and their role in guiding BP management.

**Arterial Stiffness**

A delicate balance between the structural and cellular components that make up the vascular tree is responsible for proper functioning. Conditions like ageing, HTN, DM, chronic kidney disease (CKD), atherosclerosis and other pathological conditions can disrupt this balance through various mechanisms and lead to reduced arterial distensibility, a condition defined as arterial stiffening.

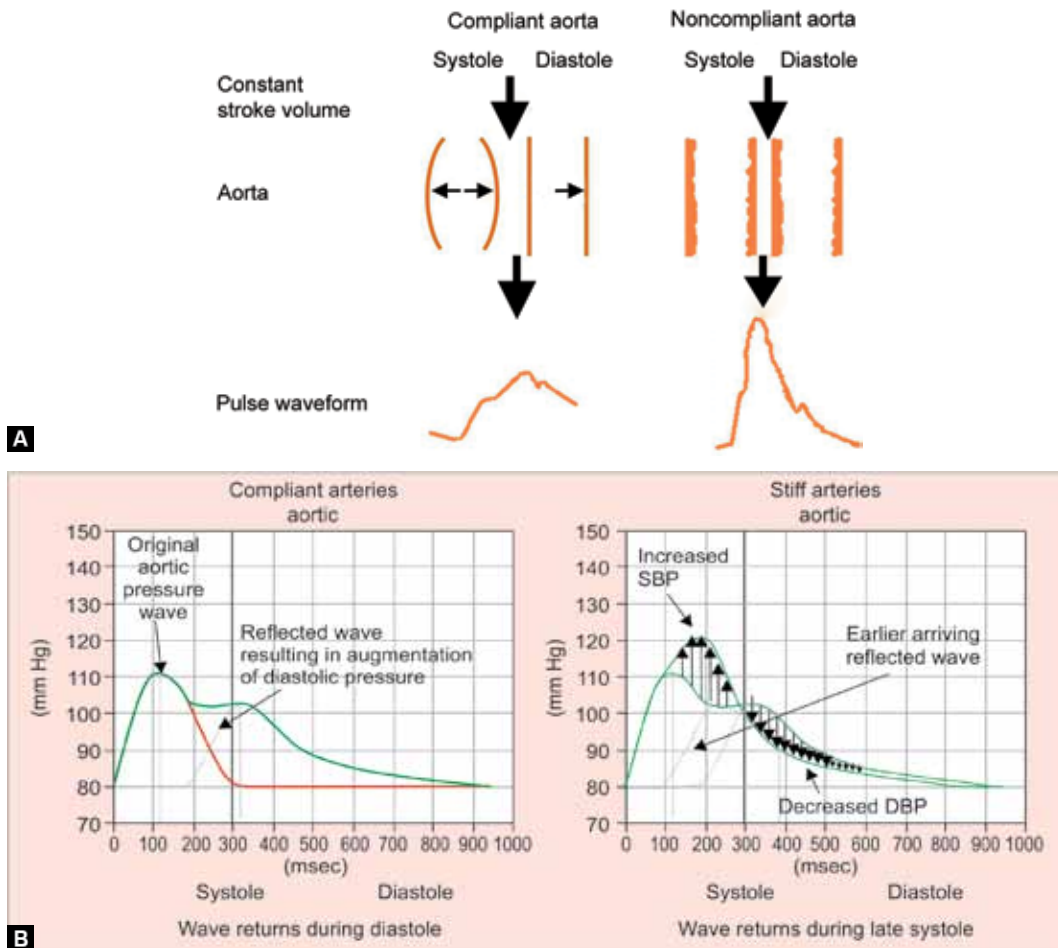
On a pathological level, arterial stiffness can be described as a sum of (a) passive stiffness<sup>34</sup> characterized by dysfunction of elastin and collagen fibers, and (b) active stiffness<sup>35</sup> characterized by dysfunction at a cellular level including endothelial dysfunction and vascular smooth muscle cell (VSMC) alterations.<sup>36</sup> While, inflammation causes elastin fiber loss, calcification and decreased nitric oxide production contributing to increased arterial age and stiffness;<sup>37</sup> formation of advanced glycation end products causes irreversible protein glycation of collagen fibers leading to formation of dysfunctional collagen,<sup>38,39</sup> that are structurally inadequate.<sup>40</sup>

At the cellular level, active stiffness is influenced by the VSMC tone, which itself is affected by vascular mediators such as Angiotensin II,<sup>41</sup> endothelin,<sup>42</sup> oxidant stress<sup>43</sup> and nitric oxide. Hormonal conditions like chronic hyperglycemia and hyperinsulinemia stimulate the renin-angiotensin-aldosterone system and lead to over expression of angiotensin type I receptor in vascular tissue,<sup>44</sup> promoting development of wall hypertrophy and fibrosis,<sup>45</sup> thus contributing to arterial stiffening.

As most of these pathophysiological mechanisms are commonly triggered in patients with HTN increased arterial stiffness is a commonly encountered vascular abnormality in hypertensive patients.

**Anatomy and Physiology of a Pulse Wave (Figs 1A and B)**

Arterial pressure waveform at any point in the vascular tree is a composite of two distinct components: the forward pressure wave and the reflected pressure wave.<sup>46</sup> The forward wave is the BP wave originating from the interaction between the left ventricular ejection activity and the mechanical properties of large arteries, while the reflected wave is the wave returning from the peripheries.



**Figs 1A and B:** Factors determining central aortic pressure: (A) Effect of aortic compliance on central aortic pressure, and (B) effect of peripheral arterial stiffness on central aortic pressure



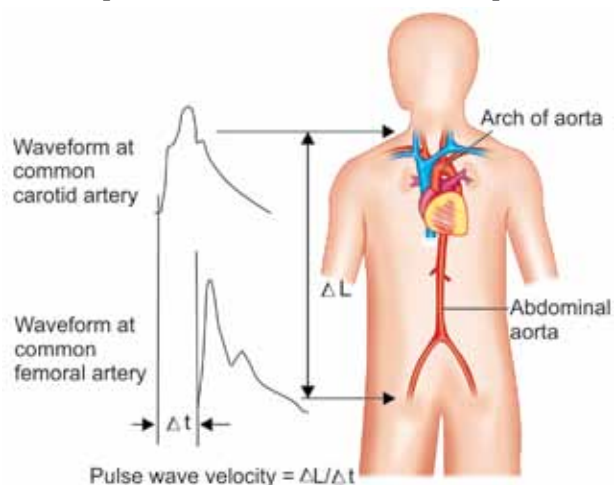
In healthy subjects the main reflection sites of the CV system are the arterial bifurcations and the terminal arterioles, which define the systemic vascular resistance. In normal vessels, the reflected wave tends to arrive back at the aortic root during diastole and thus helps in maintaining diastolic BP without significantly increasing systolic BP. However, in the stiff arteries, pressure pulse wave travels at faster speed and therefore the reflected wave arrives back at the central arteries earlier, during systole, adding to the forward wave and augmenting the systolic pressure,<sup>47</sup> while diastolic pressure falls. These changes in central aortic systolic BP and diastolic BP are further augmented by the progressive loss of the 'buffer function' of aorta on the cardiac output as the aorta stiffens.<sup>48</sup> The increase in aortic systolic BP increases cardiac afterload whereas the reduction in aortic diastolic BP levels hampers coronary blood flow.<sup>49</sup> Accordingly, central aortic pressure is the main factor determining the development of left ventricular hypertrophy seen with arterial hypertension.<sup>50,51</sup>

### Measurement of Arterial Stiffness

As mentioned earlier, technological advances have enabled clinicians to measure arterial stiffness non-invasively through various methods. The measurement of PWV and central aortic PWA are generally accepted as noninvasive, robust, and reproducible methods to determine arterial stiffness.<sup>52,53</sup> Carotid artery pressure is often used as a surrogate for aortic pressure because of the close proximity of these arterial sites.

### Pulse Wave Velocity

Pulse wave velocity (PWV) is the velocity at which the pressure pulse wave travels along the arterial system. Since the pulse wave travels at a faster speed in the



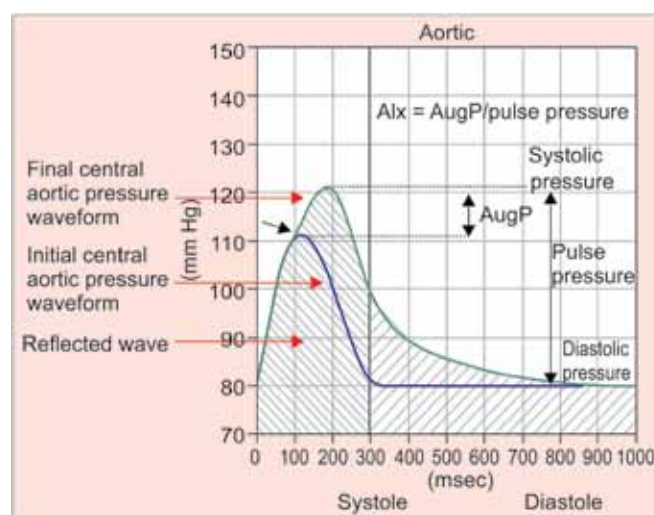
**Fig. 2:** 'Foot-to-foot' method for noninvasive measurement of carotid-femoral pulse wave velocity.  $\Delta t$ , the time delay between the arrival of pulse at common carotid artery and at the femoral artery;  $\Delta L$ , distance between the two measurement points

stiffer arteries, higher PWV indicates increased arterial stiffness.<sup>54</sup> Pulse wave velocity is commonly measured using the 'foot to foot method' in which pulse waveforms are recorded at two different points in the vascular system and the time delay between the feet of each pressure waveform is recorded (Fig. 2). The distance between these two points divided by the time difference provides the PWV within that segment.

Of the various segments of the arterial system, carotid-femoral PWV is considered to be the gold standard as it, being closest to the aorta, best reflects aortic stiffness and has the maximum epidemiological evidence-base to support its use.<sup>55-58</sup> Brachial-ankle PWV is another extensively studied PWV measurement and is an excellent alternative when carotid-femoral PWV is not available.<sup>52,59,60</sup> A number of devices based on pressure sensors (e.g. Periscope<sup>®</sup>, Complior<sup>®</sup>, PulsePen<sup>®</sup> or SphygmoCor<sup>®</sup>), echotracking (WallTrack<sup>®</sup> or Artlab<sup>®</sup>) or Doppler ultrasound are available for measurement of PWV in clinics.

### Central Aortic Pulse Waveform Analysis

Pulse wave analysis involves identification and analysis of different components of the central pressure waveform.<sup>61</sup> As mentioned earlier, arterial stiffness augments both the forward pulse wave and the reflected wave. The extent of augmentation of systolic pressure in the central aorta provides a composite estimate of wave reflection and systemic arterial stiffness and is commonly expressed as augmentation index (AIx) (Fig. 3). Augmentation index is the difference between the 2nd and 1st systolic peaks divided by the central aortic pulse pressure (PP)



**Fig. 3:** Central aortic pressure waveform depicting different components. Augmentation pressure (AugP) is the difference between the initial aortic systolic pressure (early systolic inflection, bold arrow) and the final aortic systolic pressure. Augmentation index (AIx) is calculated as the ratio of augmentation pressure to central aortic pulse pressure (in percent)

and expressed as percentage.<sup>62</sup> Central AIx is derived noninvasively from the radial pressure wave using a mathematical fourier transfer function.<sup>63</sup> It has been described as a measure of the timing and magnitude of pressure wave reflections from the peripheral circulation and their superimposition on the incident pressure wave. In effect, central AIx is the percentage of central PP attributable to pressure wave reflections.

## Clinical Significance of Measuring Central Aortic Pressure and Arterial Stiffness

### *Prediction of Cardiovascular Risk*

A meta-analysis<sup>64</sup> of 11 longitudinal studies found that the age and risk factor adjusted pooled relative risk (RR) of total CV events was 1.088 for a 10 mm Hg increase of central systolic pressure, 1.137 for a 10 mm Hg increase of central PP, and 1.318 for a 10% absolute increase of central AIx. Furthermore, it was found that a 10% increase of central AIx was associated with a RR of 1.384 for all-cause mortality. Another meta-analysis of 17,635 participants<sup>65</sup> found that the pooled age and sex-adjusted hazard ratios (HRs) per 1-SD change in loge aPWV were 1.35 for coronary heart disease, 1.54 for stroke, and 1.45 for CVD. After adjusting for conventional risk factors, aPWV remained a predictor of coronary heart disease (HR: 1.23), stroke (HR: 1.28) and CVD events (HR: 1.30).

A number of studies have shown that measures of arterial stiffness predict risk of CV mortality, total mortality, fatal and nonfatal coronary events and fatal strokes in different patient subsets including hypertensives,<sup>66-68</sup> diabetics,<sup>69</sup> elderly subjects,<sup>70,71</sup> patients with end-stage renal disease<sup>72</sup> as well as in the general population.<sup>73,74</sup> Central AIx and PP have shown an independent predictive value for all-cause mortality in ESRD patients<sup>75,76</sup> and CV events in hypertensives<sup>67,77</sup> and patients with coronary disease and those undergoing PCI.<sup>78</sup> Among the Indian population subsets too, various studies have demonstrated relationship of arterial stiffness to various conventional and nonconventional CV risk factors, such as diabetes,<sup>79,80</sup> hypertension,<sup>80-82</sup> tobacco use,<sup>83</sup> obesity<sup>84-86</sup> and metabolic syndrome.<sup>87</sup> More importantly, increased arterial stiffness has also been noted in children<sup>88</sup> and young adults<sup>84</sup> and associated with incident coronary artery disease (CAD)<sup>89,90</sup> and peripheral arterial occlusive disease.<sup>91</sup>

Based on the available evidence, it has been suggested that increased arterial PWV can serve as a useful tool for screening for presence of coronary atherosclerosis.<sup>89,90</sup> However, for this purpose, it is helpful to combine it with CIMT. Presence of both normal brachial-ankle PWV

and normal CIMT has been found to have high negative predictive value for excluding coronary atherosclerosis. Conversely, when both PWV and CIMT are increased, there is high probability of co-existing CAD.<sup>89,90</sup>

The assessment of arterial stiffness can also be used for monitoring the impact of various therapeutic measures on vascular structure and function. Several nonpharmacological treatments, such as exercise training,<sup>92</sup> dietary changes including weight loss,<sup>93</sup> low salt diet,<sup>94</sup> moderate alcohol consumption,<sup>95</sup> fish oil,<sup>96</sup> etc. have been shown to reduce arterial stiffness. The effect of various antihypertensive drugs on arterial stiffness is discussed below.

### *Central Aortic Pressure for Guiding Antihypertensive Treatment*

A study by McEniery et al<sup>97</sup> in >10,000 subjects demonstrated a substantial overlap of central and brachial BP between categories of hypertension. Over 70% of individuals categorized as having 'high-normal' brachial systolic pressure based on Joint European Cardiology and Hypertension Society guidelines<sup>56</sup> had similar aortic pressures corresponding to those with stage 1 hypertension. Moreover, 30% of males and 10% of females with normal brachial BP had aortic pressures in common with individuals with stage 1 hypertension.

Central pressure is more closely correlated with widely accepted surrogate measures of CV risk, such as CIMT<sup>98,99</sup> and left ventricular mass,<sup>100-102</sup> than brachial pressure in several cross-sectional studies, as well as a few prospective studies. In the pREterax in regression of Arterial Stiffness in a contrOLled double-bliNd (REASON) study,<sup>103</sup> regression of left ventricular mass was more strongly related to changes in central compared with brachial pressure and, after adjustment, only central pressure remained predictive. Similarly, with anti-hypertensive therapy, the reduction in CIMT has been shown to relate better with the fall in central pressure than the fall in brachial BP.<sup>104,105</sup>

These findings have important clinical implications because, by focusing only on brachial BP at present, we may be over-treating some subjects with relatively low central pressures, and under-treating others who have elevated central pressure, just because their have brachial systolic pressures are within currently recommended therapeutic ranges. Moreover, different antihypertensive drugs may affect central aortic pressure differentially,<sup>103,106-108</sup> and therefore, lead to dissimilar CV benefits.

The Anglo-Scandinavian cardiac outcomes trial (ASCOT)<sup>109</sup> showed a greater reduction in CV events among patients treated with a calcium channel blocker





amlodipine compared with patients treated with the  $\beta$ -blocker atenolol, without any difference being noted in the reduction of brachial systolic BP values between the groups treated. The potential mechanism underlying these differences was explained by the landmark conduit artery functional endpoint (CAFE) study,<sup>106</sup> which was a sub-study of the larger ASCOT trial. It showed that the two antihypertensive regimens had differential effects on peripheral BP and central aortic pressure. A greater decrease in central systolic BP and in central PP occurred in subjects randomized to amlodipine +/- perindopril as compared to those treated with bendroflumetiazide +/- atenolol, in spite of similar reductions in brachial systolic BP. Based on these findings, the authors concluded that the greater reduction in CV events in the group treated with amlodipine/perindopril was likely to be due to a greater effect of these drugs in lowering central systolic BP. A similar finding was seen in the REASON study<sup>103,107</sup> also, which showed a significant reduction in LV mass and a greater decrease in central pressure after 1 year of treatment with low dose perindopril + in dapamide combination as compared to atenolol. Other studies including the heart outcomes prevention evaluation (HOPE) study<sup>110,111</sup> and the LIFE study<sup>112,113</sup> have also shown that the clinical benefit of treatment with ACEIs (ramipril) or ARBs (losartan) extend beyond just reduction in brachial BP only and may be attributed to reduced target organ damage resulting from a reduction in arterial stiffness and central aortic pressure. The results of these studies lend support to the hypothesis that an inadequate reduction in central pressure may be associated with an adverse outcome. To date, anti-hypertensive drugs have been shown to exert variable effects on PWV and arterial stiffness (Table 1). Further research work is needed to categorize anti-hypertensive drugs on the basis of their actions on PWV and arterial stiffness.

### Reproducibility of Measures of Arterial Stiffness

A screening test should be reliable, reproducible, easy to perform and cost effective to warrant its use in regular clinical practice. One of the first studies analyzing the reproducibility of PWA was published by Wilkinson

et al.<sup>114</sup> They found that PWA was a simple and reproducible technique with which to measure PWV and AIx with very little interobserver variability. Recently published data from the atherosclerosis risk in communities study (ARIC)<sup>115</sup> found that the repeatability of PWV was under acceptable parameters for all PWV measures in a multicenter, population-based study of older adults and supported its use in epidemiologic studies. However, they also recommended that quantifying PWV measurement variation is critical for applications to risk assessment and stratification and eventual translation to clinical practice. Another study<sup>116</sup> comparing the cost effectiveness of noninvasive assessment of central BP against brachial BP for diagnosis of HTN found central BP monitoring to be more cost effective for both men and women across all age groups.

### Future Directions

A growing body of evidence suggests that central systolic BP and central PP are accurate markers of the actual pressure load imposed on the left ventricle and are better measurements than peripheral systolic BP and peripheral PP.<sup>117</sup> In addition, numerous studies suggest that parameters of central hemodynamics predict the occurrence of CV events independently of brachial BP values.<sup>52</sup>

For a biomarker to be integrated into clinical practice, it should meet the following criteria:<sup>118</sup> (a) it must differ between subjects with and without outcomes; (b) it must predict future outcomes in prospective studies; (c) it must add predictive information on top of established risk markers; (d) it must be cost efficient; (e) it must reclassify patients' predicted risk to a sufficient extent; and (f) its use must improve outcomes when evaluated in a randomized study. So far, measurement of arterial stiffness and central BP have fulfilled criteria (a) to (d) sufficiently and more research is being published every day supporting value of PWV, PWA and AIx as markers of CV risk.<sup>119,120</sup> However, more evidence is needed to determine if these markers also satisfy the criteria (e) and (f).

Of particular note is a prospective, randomized, open-label, blinded end point (PROBE) study by Sharman et al<sup>121</sup> which addressed the use of central aortic BP as a guide for treatment. Patients were randomized to treatment decisions that were guided by best-practice usual care for BP (using office BP, home BP, and 24-hours ambulatory BP) or the addition of a central aortic BP intervention (measured using radial applanation tonometry). A key element of the study was the guidelines and recommendations given to the treating practitioners for titration of therapy. The 5 recommendation scenarios describe the combination of central aortic BP with the

**Table 1:** Effects of anti-hypertensive drugs on pulse wave velocity and arterial stiffness

• Diuretics ↔
• CCBs ↓
• ACEIs ↓
• ARBs ↓
• Vasodilating $\beta$ -blockers ↓
• Angiotensin receptor/neprilysin ↓ inhibitor (parameter study)

other BP measures (office, home, 24-hour ambulatory BP) so as to increase, maintain, or decrease the therapy. They concluded that guidance of hypertension management with central BP resulted in a significantly different therapeutic pathway than conventional cuff BP, with less use of medication to achieve BP control and no adverse effects on left ventricular mass, aortic stiffness, or quality of life. However, the implications of these observations with respect to the long-term CVD risk remain to be proven.

The 2010 guidelines of the ACC/AHA for assessment of CVD risk in asymptomatic adults<sup>122</sup> did not recommend routine measurement of PWV for CVD risk assessment in asymptomatic adults, mainly on the basis of the lack of evidence supporting the ability of PWV to reclassify risk in asymptomatic adults or general population. Later on, after the publication of few large studies mentioned earlier, the recent 2013 ESH/ESC guidelines for the management of arterial hypertension<sup>56</sup> have recommended measurement of PWV for evaluation of subclinical organ damage in hypertensive patients (recommendation class IIa, Level of Evidence: B), and suggested a cutoff of 10 m/s to discriminate between normal aortic elasticity and aortic stiffening.<sup>123</sup> However, they also state that although the measurement of central aortic BP is of interest in terms of analyses for elucidating mechanisms related to pathophysiology, pharmacology, and therapeutics, further investigations are needed before central aortic BP can be recommended for routine clinical use. Indeed, trials are required to assess the impact of arterial stiffness guided management on hard CVD end points, where subjects are followed up for a longer period. At the same time, it is also important to establish normal ranges of various arterial stiffness parameters for different ethnic groups, a key prerequisite for wider use of these markers in clinical practice. However, as the new research emerges to address these pending issues, the next decade could very well be the decade of "arterial de-stiffening."<sup>68</sup>

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