Hypertension is a significant public health issue as it is estimated that 1 billion people worldwide have elevated blood pressure. By the year 2025 it has been estimated that this will rise to 1.56 billion people, with 1 in 3 adults aged over 20 years of age hypertensive.

The World Health Organisation has reported that suboptimal blood pressure is the number one attributable risk for death throughout the world. Hypertension is a highly prevalent risk factor for cardiovascular disease such that individuals with hypertension have a 2-3 fold increased relative risk for any cardiovascular disease event compared to age matched normotensive individuals. Furthermore, having pre-hypertension raises the risk for high blood pressure in the future [1].

There are no physical symptoms of elevated blood pressure, so preventing or maintaining control of hypertension is important to prevent the associated risks. Therefore the ability to identify patients at risk of cardiovascular disease and subsequently monitor the effects of treatment could lead to improved outcomes for hypertensive patients.

**Background**

High blood pressure is defined as having a systolic pressure (SBP) above 140 mmHg or a diastolic pressure (DBP) of 90 mmHg or taking antihypertensive medication [1] and is classified as either primary or secondary hypertension.

i. Primary hypertension – about 90-95% of individuals with hypertension are categorised with primary hypertension, as there is no obvious cause of the elevated blood pressure. Although no direct cause has been identified, there are many factors that increase the risk of developing hypertension, such as a sedentary lifestyle, smoking, high stress, obesity and high alcohol consumption.

ii. Secondary hypertension – hypertension is caused by an identifiable underlying cause, such as endocrine diseases, kidney disease or pregnancy. Secondary hypertension is less common that primary hypertension, effecting approximately 5% of patients with hypertension.

The severity of hypertension is based on systolic and diastolic blood pressure ranges as follows:

<table>
<thead>
<tr>
<th></th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>90-119</td>
<td>60-79</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1</td>
<td>150-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥ 160</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Isolated systolic hypertension (ISH)</td>
<td>≥140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

In the USA alone, it is estimated that 76.4 million adults (≥ 20 years of age) have hypertension, this equates to 1 in 3 adults. Among these hypertensive adults, 78% are aware of their condition and 68% are on antihypertensive medication. Of those being treated, only 64% have their hypertension under control, suggesting that current methods of monitoring anti-hypertensive treatment can be improved [1].

Individuals with hypertension have a 2-3 fold increased relative risk for any cardiovascular disease event compared to age matched normotensive individuals. While hypertension
increases the risk of any manifestation of cardiovascular disease, the most significant increases are observed for stroke and heart failure. In addition, hypertension is associated with a shorter life expectancy of approximately 5 years [1].

It is estimated that a further 29% of the adult population in the USA have pre-hypertension and that these individuals are at an elevated risk of cardiovascular outcomes across all age spectrums. Pre-hypertension is associated with a 1.5 to 2-fold increased risk of major cardiovascular events and these individuals are 1.65 times more likely to have above normal cholesterol levels, a high BMI and/or diabetes compared to individuals with normal blood pressure levels [1].

**Central blood pressure measurement in hypertension.**

Blood pressure is the pressure that is exerted on the walls of the arteries due to the ejection of blood from the heart. Due to the pulsatile nature of blood flow, arterial blood pressure has a characteristic waveform and the contour of this waveform changes throughout the arterial tree. The pressure waveform is generated in the left ventricle and travels down the arterial tree, where it is reflected at multiple peripheral sites. As such, the arterial pressure waveform at any point in the arterial tree is a composite of the forward wave and backward travelling (reflected) wave. In healthy and compliant arteries the reflected wave merges with the incident wave during diastole and thereby augmenting coronary perfusion. In stiffer vessels, the pulse waves travel faster and the reflected wave returns while the cardiac cycle is still in systole, increasing systolic pressure and thus increasing left ventricular load. As a result, pulse pressure (PP) increases, as does augmentation pressure (AP), and augmentation index (AIx), which are measures of arterial stiffness. [2, 3].

While the prognostic value of brachial blood pressure is well established, there is ample evidence of the pathophysiological importance of central blood pressure. Central haemodynamic measurements are important markers and manifestations of early organ damage, an area that European hypertension guidelines now consider to be important when quantifying total cardiovascular risk [4].

Central blood pressure has been shown to be a powerful independent predictor of major cardiovascular events [5, 6, 7, 8]. Pulse pressure, and in particular central pulse pressure (CPP) have been shown to better predicting cardiovascular events than brachial blood pressure. A cross-section analysis of the Strong Heart Study (SHS) found that in the 3520 people assessed CPP was more strongly related to vascular hypertrophy and atherosclerosis than systolic pressure, in a group of high risk, but untreated patients.

Data from same study showed in a 5-year follow-up that CPP was a better predictor of cardiovascular events than brachial pulse pressure, both before and after adjustment for the presence of carotid atherosclerosis [8].

At 5.6 years follow up, quartiles of central PP predicted cardiovascular outcomes more strongly than quartiles of brachial PP. Having a central PP, ≥ 50 mmHg, doubled the risk of heart attack or stroke in both men and women, in the presence or absence of diabetes, and in people younger or older than 60 years of age [5], as shown in Figure 1.

---


2 The Strong Heart Study is an observational study of prevalent and incident cardiovascular disease and their risk factors in American Indians.
Central blood pressure has also been demonstrated to have prognostic importance in the elderly. Central blood pressure better predicted cardiovascular events and was strongly associated with cardiac and vascular remodelling in a group of normotensive and untreated hypertensive individuals 65 years of age and older compared to brachial pressure [7].

The above results concur with findings from the Anglo-Cardiff Collaborative Trial II, concluding that central blood pressure cannot be inferred from brachial blood pressure. In this trial, stratification of individuals by brachial pressure revealed considerable overlap in aortic pressure, such that 70% of subjects with normal brachial systolic pressure (based on brachial blood pressure classification) actually had central pressures equal to those with Stage 1 hypertension [9].

The importance of central blood pressure as significant predictor of cardiovascular events has been demonstrated in studies over a range of diseases, such as coronary artery disease [10, 11] end stage renal disease [12] and diabetes [13].

In addition, measures of arterial stiffness such as central Alx have also been shown to be independent predictors of CV events in hypertensive patients and an independent predictor of all cause mortality in end stage renal disease patients. Increased arterial stiffness is also associated with higher CV events in patients undergoing percutaneous coronary interventions [14,15,16]. Increased Alx and central systolic pressure are associated with left ventricular hypertrophy (LVH), a known risk factor for coronary events, in individuals with hypertensive [17]. Alx has also previously been shown to associated with LVH in renal patients [18] and to predict LV mass regression during antihypertensive therapy [19, 20].

The burden of familial arterial hypertension on arterial stiffness in young healthy individuals has also been observed [(Kyvelou, 2008 1322 /id), 22, 23]. Most recently, offspring with a positive parental history of hypertension have been shown to have higher central Alx compared with offspring with normotensive parents, independent of age and blood pressure levels. Furthermore, higher Alx values were observed when both parents were hypertensive compared to only one hypertensive parent [22] as shown in Figure 2.
Central Aortic stiffness (measured by PWV) in Hypertension.

Aortic stiffness has also been shown to be a powerful predictor of adverse cardiovascular events in hypertensive patients. Aortic Pulse Wave Velocity (PWV) is a direct measurement of aortic stiffness and is considered to be the gold standard of arterial stiffness measurements [24]. Aortic PWV is a measure of the speed the arterial pulse waves are travelling along the aortic and aorto-iliac pathway. The pressure waves are recorded from two sites along this pathway at the carotid and femoral arteries. A higher Pulse Wave Velocity due to stiffer arteries is associated with CV risk, the European society of Hypertension defines patients with a PWV of 12m/s or greater as hypertensive.

Aortic PWV has been shown to be an independent predictor of primary coronary events in patients with essential hypertension [25]. In this study, a group of 1045 essential hypertension patients with no overt disease were followed longitudinally over an average of 5 years. The relative risk (RR) of a coronary or cardiovascular event increased with increasing PWV, for each 3.5 m/s increase in PWV the RR was 1.41. This confirms earlier findings from a cross-sectional study where aortic PWV was found to be strongly associated with the presence and extent of atherosclerosis in treated and untreated essential hypertension patients [26]. In all patients, determination of CV risk improved in the Framingham risk equation when PWV was included. (compared to not being included in the equation).

A number of studies in the general population and other diseases have found that aortic PWV, is also an independent predictor of cardiovascular and all cause morbidity and mortality [27, 28, 29, 15].

Pharmacological treatment and Central Blood pressure in Hypertension.

Reduction of brachial blood pressure is the key aim in the treatment of hypertension. However, during the last decade, it has become apparent that antihypertensive drugs may reduce cardiovascular events beyond brachial blood pressure and these effects could be accounted for by the protective properties of the drugs in subclinical organ damage or intermediate end points, such arterial stiffness or central blood pressure.
In the largest prospective evaluation of cardiovascular drugs on central blood pressure and haemodynamics to date, the CAFE study\(^3\) clearly showed that differential effects can be seen in central blood pressure despite a similar effect on brachial blood pressure. Central systolic and pulse pressures were significantly lower in patients taking amlodipine/perindopril therapy compared with patients on atenolol/thiazide, while no difference in brachial blood pressure reduction was observed. Moreover, these results are considered to contribute to the superior cardiovascular outcomes observed in the main ASCOT trial and importantly, these differences would not have been detected if only brachial blood pressure was measured [14].

A similar study (REASON\(^4\)) in 470 high risk patients with essential hypertension followed for 12 months found that perindopril/indapamide combination therapy significantly reduced central systolic blood pressure more than treatment with atenolol. As in CAFE, there was a similar reduction in diastolic blood pressure between the 2 arms demonstrating that the central pressure effect needed to be measured [30].

The findings seen in the CAFE and REASON studies are consistent with a number of smaller studies short term studies in hypertensive patients [31, 32, 33, 34, 35, 36, 37, 38, 30]. One early study examined 4 major cardiovascular drug classes (calcium channel blocker, diuretic, ACE inhibitor, and beta blocker) and found that brachial blood pressure measurements did not accurately predict the effects on central blood pressure [38]. Changes in central SBP were underestimated for patients on ACE inhibitors and calcium channel blockers (CCB), while changes in central PP were underestimated in patients on ACE inhibitors and overestimated on beta blockers, as shown in Figure 3.

---

3 CAFE study - Conduit Artery Function Evaluation study was a major sub-study within the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) conducted across 5 centres in the UK and Ireland. Over 2000 patients with either untreated hypertension (SBP ≥ 160mm Hg or DBP ≥ 100 mmHg) or treated hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) participated in the study and were followed for up to 4 years, during which time multiple blood pressure measurements were obtained.

4 REASON project – pREterax in regression of Arterial Stiffness in a controlled double-bliNd study was a multicentre trial conducted across 13 countries.
The J-CORE\textsuperscript{5} study examined the effects of an angiotensin II receptor blocker (ARB), Olmesartan, combined with either a CCB or a diuretic on blood pressure and arterial stiffness. Despite the same reduction in brachial blood pressure in the two treatment groups, the ARB combined with a CCB significantly lowered central systolic pressure and two measures of arterial stiffness, aortic PWV and heart rate adjusted Augmentation Index [36].

A recent study has also shown that an individual class of hypertensive drug should not be considered as a homogenous group and differences in hemodynamics can be observed. In this study, a new relatively new beta blocker, Nebivolol, which is considered to have ancillary vasodilatory properties, provided a significantly greater reduction in central PP, AIx and PP amplification compared with atenolol, a standard beta blocker, in patients with essential hypertension [33].

**Pharmacological treatment and Central Aortic stiffness.**

Aortic PWV is also considered an important therapeutic target. An improvement in aortic PWV in patients with end stage renal disease in response to ACE inhibitor therapy was associated with a reduction in mortality and an improvement in survival rate [39].

A sustained decrease in aortic PWV has been observed in treated hypertensive patients followed in routine clinic practice. Over a period of 5 years, a group of treated essential hypertension patients showed a large and sustained decrease in aortic PWV, as well as central systolic blood pressure and pulse pressure, contrasting with a smaller change in brachial systolic blood pressure and no change in brachial pulse pressure [40].

A number of the classes of antihypertensive drugs have been shown to reduce aortic PWV in hypertensive patients, including beta blockers, calcium channel blockers, angiotensin II receptor antagonists and ACE inhibitors [41, 42, 43, 44]. In a group of patients with systolic hypertension, two different beta blockers, atenolol and nebivolol significantly reduced aortic PWV compared to a placebo treatment [41]. In a different study, the atenolol and a combination therapy of perindopril / indapamide both significantly reduced aortic PWV to a similar degree in essential hypertensive patients followed for 12 months [45].

Results from the J-CORE study showed that along with a significant reduction in central systolic blood pressure from a combined ARB / CCB combination, aortic PWV in the combination therapy group was significantly lower than when combined with a diuretic, even after adjustment for mean pressure. The combination of lowered central systolic pressure and aortic PWV, both independent predictors of cardiovascular morbidity in hypertensive patients, allowed for suggestions that ARB / CCB therapy may lead to a favourable effect on cardiovascular outcomes beyond that achieved by ARB / diuretic treatment [36].

**Perspective**

Central blood pressure and measures of arterial stiffness have been shown to independent and significantly better predictors of cardiovascular outcomes than brachial pressure in patients with hypertension. While the prognostic value of brachial blood pressure is well established, there is ample evidence of the pathophysiological importance of central blood pressure as a marker for outcomes and a target for antihypertensive therapy. Results from a large number of studies have highlighted that blood pressure lowering drugs can have differential effects on central blood pressure and arterial properties despite a similar effect on

---

\textsuperscript{5} J-CORE study – Japan-Combined treatment with Olmesartan and a calcium channel blocker versus Olmesartan and diuretics Randomised Efficacy study was a 24 week prospective randomized trial in 207 hypertensive patients.
brachial blood pressure. Furthermore, although central blood pressure cannot be inferred from brachial blood pressure measurements, central haemodynamics can now be reliably assessed non-invasively in the clinic.
References


