Expert consensus document on arterial stiffness: methodological issues and clinical applications

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In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular diseases. Indeed, the assessment of arterial stiffness is increasingly used in the clinical assessment of patients. Although several papers have previously addressed the methodological issues concerning the various indices of arterial stiffness currently available, and their clinical applications, clinicians and researchers still report difficulties in selecting the most appropriate methodology for their specific use. This paper summarizes the proceedings of several meetings of the European Network for Non-invasive Investigation of Large Arteries and is aimed at providing an updated and practical overview of the most relevant methodological aspects and clinical applications in this area.

Introduction

In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular (CV) diseases. Indeed, the assessment of arterial stiffness is increasingly used in the clinical assessment of patients. Although several papers have previously addressed the methodological issues concerning the various indices of arterial stiffness currently available, and their clinical applications,¹-⁷ clinicians and researchers still report difficulties in selecting the most appropriate methodology for their specific use. This paper summarizes the proceedings of several meetings of the European Network for Non-invasive Investigation of Large Arteries. A Medline research was performed to identify the relevant literature concerning arterial stiffness, wave reflection, and pressure wave analysis. The reference list was then contrasted with the authors' database. This consensus document is aimed at providing an updated and practical overview of the most relevant methodological aspects and clinical applications in this area.

Basic principles of arterial stiffness

An understanding of the basic principles of haemodynamics is mandatory to appreciate fully the advantages and limitations of the various methodologies and indices used to assess arterial stiffness, and their potential clinical applications. Earlier physicists such as Young (1808), Poiseuille (1840), Moens (1878), and Korteweg (1878) established hydraulic and elastic theory. Physiologists/physicians, such as Marey (1860), Mahomed (1872), and Mackenzie (1902), developed various types of sphygmmographs and made important contributions to the analysis of the pressure wave. Later, it appeared that the mechanical behaviour of large arteries was extremely complex and provided serious difficulties, both on the theoretical and technical aspects. Indeed, arteries have marked anisotropy, exhibit non-linear visco-elastic properties, and have powerful adaptive mechanisms.⁸,9 Moreover, no single arterial segment has identical viscoelastic properties, and it is impossible to extrapolate segmental arterial properties to the whole arterial tree. Despite these obstacles, simple parameters derived either from the Windkessel model or based on arterial wave propagation have been developed. Safar¹⁰ and O’Rourke⁸,¹⁰ have extensively contributed to the clinical applications of these concepts, which proved useful not only in representing
basic mechanical behaviour of the arterial system but also in predicting outcome and refining therapy.

**From models to measurement of systolic blood pressure in clinical practice**

In the Windkessel model, the arterial system is compared to a fire-hose system: the inverted air-filled dome, which cushions flow pulsations generated by an intermittently operating pump, is likened to the large arteries, the wide-bore hose acting as a conduit, and the fire-hose nozzle is likened to the peripheral arterioles.\(^8\,11\) This model separates the 'conduit' and 'cushioning' functions of the arterial tree and provides a useful means to illustrate the changes seen in hypertension: an increase in total peripheral resistance and a decrease in arterial compliance. When only resistance is increased, mean blood pressure rises—with an equal increment in systolic and diastolic blood pressures. However, when there is an additional reduction in compliance, mean blood pressure increases to the same extent, but pressure oscillations are increased, resulting in a disproportionate increase in systolic blood pressure and little change in diastolic blood pressure.\(^8\,11\)

The Windkessel model, however, has two major limitations. First, the arterial tree does not have separate conduit and cushioning functions: both functions are features of the aorta and its major branches, which are distensible tubes. In addition, there is a progressive loss of the cushioning function, from the ascending aorta (the most elastic artery) to the more muscular and less elastic peripheral arteries, and an increasingly predominant conduit function of large arteries from the heart to the periphery. Secondly, the Windkessel model makes the assumption that pulse-wave velocity (PWV) is of infinite value. This could not be the case, because of the heterogeneity of pressure wave velocity along the arterial tree. The respective amounts of cushioning and conduit functions in adjacent arterial segments determine this heterogeneity. Particularly, peripheral arteries are stiffer than central arteries in healthy subjects, and this phenomenon leads to an increase in the amplitude of the pressure wave in the vessels, from the heart to the periphery, known as pressure amplification. In addition, the stiffness of medium-sized peripheral arteries is modulated by the vasomotor tone, either depending on the endothelial function or the sympathetic nervous system\(^12\,13\) or the renin–angiotensin system.\(^14\)

For these reasons, it is probably better to apply propagative models to the circulatory system. These assume that the velocity with which a pulse wave travels along a given artery has a finite value. Frank in 1920\(^5\) and Bramwell and Hill in 1922\(^6\) derived the Moens–Korteweg equation \(c_0 = \sqrt{Eh/2R\rho}\), where \(c_0\) represents wave speed, \(E\) the Young’s modulus in the circumferential direction, \(h\) the wall thickness, \(R\) the radius, and \(\rho\) the density of fluid) as \(c_0 = \sqrt{(V \cdot dP/\rho \cdot dV)}\), where \(dV\) is the change in arterial volume \((V)\) and \(dP\) is the change in pressure driving the change in volume. This equation is currently widely used in the clinical research and clearly illustrates the facts that the propagation of the pulse wave is inversely related to the distensibility of the arterial tube, expressed as \(dV/V \cdot dP\). Thus, rather than the Windkessel model, a more realistic model of the arterial tree would be a propagative model consisting of a simple distensible tube which terminates at the peripheral resistance, but whose distributed elastic properties permit the generation of a pressure wave which travels along the tube.\(^8\,9\,17\)

When modelling the arterial tree, O’Rourke and others\(^8\,9\) have also suggested that because the tube’s end has a high level of resistance, waves are reflected and retrograde waves are generated. This would account for the secondary fluctuations of the pressure waveform in diastole and differences in the amplitude of the pressure wave between central and peripheral arteries and fits well with pathophysiological observations. In particular, it explains why an increase in the arterial stiffness increases central PP, with an associated increased systolic BP.

In the human body, wave reflections originate in various locations, including peripheral bifurcations of conducting arteries\(^17\) and smaller muscular arteries. The geometry, number of arterioles, and the architecture of the microvascular network play an important role in wave reflection. Indeed, arterial and arteriolar constriction results in reflection points closer to the heart, leading to earlier aortic wave reflections.\(^18\,19\) In addition, with increased arterial stiffness, as observed, for example, in older subjects or hypertensive patients, the reflected wave travels more rapidly along the arterial tree. Thus, both small and large arteries contribute to early reflected waves which arrive in early systole, superimpose on the forward wave, and boost the systolic pressure further, whereas blood pressure falls sharply in diastole with reduced diastolic fluctuations.

**Proximal and distal arterial stiffness**

The elastic properties of conduit arteries vary along the arterial tree; with more elastic proximal arteries and stiffer distal arteries. This heterogeneity is caused by the molecular, cellular, and histological structure of the arterial wall, which differs between the various parts of the arterial tree.\(^21\,24\) For example, in humans, the PWV increases from 4–5 m/s in the ascending aorta to 5–6 m/s in the abdominal aorta then 8–9 m/s in the iliac and femoral arteries.\(^8\,23\) In the middle-aged normotensive subjects, the cross-sectional distensibility, assessed with echotracking systems, decreases from 40 kPa\(^{-1}\) × 10\(^{-3}\) in the thoracic aorta\(^25\) to 10–20 kPa\(^{-1}\) × 10\(^{-3}\) in the carotid artery\(^26\) and 5 kPa\(^{-1}\) × 10\(^{-3}\) in the radial artery.\(^27\)

This heterogeneity in the arterial stiffness has important physiological and pathophysiological consequences. Indeed, a pressure wave which is propagated along a viscoelastic tube devoid of reflection sites is progressively attenuated, with an exponential decay along the tube. In contrast, a pressure wave which propagates along a viscoelastic tube with numerous branches is progressively amplified, from central to distal conduit arteries due to wave reflections. Particularly, in peripheral arteries, wave reflections can amplify the pressure wave because reflection sites are closer to peripheral sites than to central arteries, and PWV is higher in a peripheral stiffer artery. The net result is that the amplitude of the pressure wave is higher in peripheral arteries than in central arteries, the so-called 'amplification phenomenon'.

Thus, because of pulse pressure amplification between central and peripheral arteries, it is inaccurate to use...
brachial pulse pressure as a surrogate for aortic or carotid pulse pressure, particularly in young subjects. Local stiffness, which is calculated as the ratio of pulse pressure to the relative change in diameter, may be overestimated by introducing brachial pulse pressure instead of central pulse pressure into the calculations.

**Box 1: Position statement: Brachial and central PP.**

Because of pulse pressure amplification between central and peripheral arteries, it is inaccurate to use brachial pulse pressure as a surrogate for aortic or carotid pulse pressure, particularly in young subjects.

The ‘stiffness gradient’ along the arterial tree can also generate wave reflections and exaggerate the pressure amplification directly. In younger subjects, the central arteries are usually more elastic than peripheral arteries. However, this gradient can be reversed with ageing or hypertension. Indeed, the stiffness of the common carotid artery is six-fold higher in a 20-year-old normotensive subject than at the age of 70. Moreover, in elderly patients with hypertension or diabetes, the carotid artery may become stiffer than either the common femoral or radial arteries, which stiffen little with age or hypertension. In summary, the most accepted model of the arterial tree is a propagative model. This consists of a visco-elastic tube whose distributed elastic properties permit generation of a forward pressure wave which travels along the tube and whose numerous branch points and high level of resistance of tube’s end generate retrograde waves. The higher the arterial stiffness, the higher the speed of travel of forward and retrograde waves.

### Methodological issues

#### Non-invasive determination of arterial stiffness

In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and non-invasively, at various sites along the arterial tree. A major advantage of the regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters strongly linked to wall stiffness. Reviews have been published on methodological aspects. Tables 1–3 give the main features of various methods, the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Device and methods used for determining regional, local, and systemic arterial stiffness and wave reflections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regional Stiffness</strong></td>
<td><strong>Device</strong></td>
</tr>
<tr>
<td>Complior</td>
<td>Mechatransducer</td>
</tr>
<tr>
<td>Sphyg mocor</td>
<td>Tonometer</td>
</tr>
<tr>
<td>WallTrack</td>
<td>Echotracking</td>
</tr>
<tr>
<td>Artlab</td>
<td>Echotracking</td>
</tr>
<tr>
<td>Ultrasound systems</td>
<td>Doppler probes</td>
</tr>
<tr>
<td><strong>Local stiffness</strong></td>
<td></td>
</tr>
<tr>
<td>WallTrack</td>
<td>Echotracking</td>
</tr>
<tr>
<td>NIUS</td>
<td>Echotracking</td>
</tr>
<tr>
<td>Artlab</td>
<td>Echotracking</td>
</tr>
<tr>
<td>Various vascular ultrasound syst.</td>
<td>Echotracking</td>
</tr>
<tr>
<td>MRI device</td>
<td>Cine-MRI</td>
</tr>
<tr>
<td><strong>Systemic stiffness</strong> (waveform shape analysis)</td>
<td></td>
</tr>
<tr>
<td>Area method</td>
<td>Diastolic decay</td>
</tr>
<tr>
<td>HDI PW CR-2000</td>
<td>Modif. Windkessel</td>
</tr>
<tr>
<td>SV/PP</td>
<td></td>
</tr>
<tr>
<td><strong>Wave reflections</strong></td>
<td></td>
</tr>
<tr>
<td>Sphyg mocor</td>
<td>AIX</td>
</tr>
<tr>
<td>Pulse Trace</td>
<td>Finger photoplethysmography</td>
</tr>
</tbody>
</table>

All superficial arteries, including particularly those mentioned.

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**Table 2** Recommendations for standardization of subject conditions (adapted from Ref. 31)

<table>
<thead>
<tr>
<th>Confounding factor</th>
<th>In practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room temperature</td>
<td>Controlled environment kept at 22 ± 1°C</td>
</tr>
<tr>
<td>Rest</td>
<td>At least 10 min in recumbent position</td>
</tr>
<tr>
<td>Time of the day</td>
<td>Similar time of the day for repeated measurements</td>
</tr>
<tr>
<td>Smoking, eating</td>
<td>Subjects have to refrain, for at least 3 h before measurements, particularly from drinking beverages containing caffeine</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Refrain from drinking alcohol 10 h before measurements</td>
</tr>
<tr>
<td>Speaking, sleeping</td>
<td>Subjects may neither speak nor sleep during measurements</td>
</tr>
<tr>
<td>Position</td>
<td>Supine position is preferred. Position (supine, sitting) should be mentioned</td>
</tr>
<tr>
<td>White coat effect</td>
<td>Influence on blood pressure and pressure-dependent stiffness</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Be aware of possible disturbance</td>
</tr>
</tbody>
</table>
recommendations for standardization of subject conditions, and indices of regional stiffness.

Regional measurements of arterial stiffness

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the thoracic and abdominal aorta makes the largest contribution to the arterial buffering function, and aortic PWV is an independent predictor of outcome in a variety of populations. However, all arterial sites have potential interest. Indeed, the forearm circulation is where blood pressure is commonly measured, and the lower limb arteries are specifically altered by atherosclerosis. Measurement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

PWV measurements

The measurement of PWV is generally accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness. Carotid-femoral PWV is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle (LV) 'sees' and are thus responsible for most of the pathophysiological effects of arterial stiffness. Carotid-femoral PWV has been used in the epidemiological studies demonstrating the predictive value of aortic stiffness for CV events (Table 4). In contrast, PWV measured outside the aortic track, at the upper (brachial PWV) or lower limb (femoro-tibial PWV), has no predictive value in patients with end-stage renal disease (ESRD).

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke change in diameter</td>
<td>Change in diameter during systole = systolic diameter (Ds) – diastolic diameter (Dd) (mm)</td>
</tr>
<tr>
<td>Stroke change in lumen area</td>
<td>Change in lumen area during systole, $\Delta A = \pi (D_s^2 - D_d^2)/4$ (mm$^2$) with $D$ = internal diameter and $\Delta P$ = local pulse pressure</td>
</tr>
<tr>
<td>Wall cross-sectional area</td>
<td>Surface of a cross-section of the arterial wall, $WCSA = \pi (D_e^2 - D_i^2)/4$ (mm$^2$) with $D_e$, external diameter and $D_i$, internal diameter, measured in diastole</td>
</tr>
</tbody>
</table>

**Table 3** Indices of arterial stiffness applied to geometrical measurements of large arteries with ultrasounds (adapted from Ref. 4)

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PWV is usually measured using the foot-to-foot velocity method from various waveforms. These are usually obtained, transcutaneously at the right common carotid artery and the right femoral artery (i.e. 'carotid-femoral' PWV), and the time delay ($\Delta t$ or transit time) measured between the feet of the two waveforms (Figure 1). A variety of different waveforms can be used including pressure, distension, and Doppler. The distance ($D$) covered by the waves is usually assimilated to the surface distance between the two recording sites. PWV is calculated as PWV = $D$ (meters)/$\Delta t$ (seconds).

However, distance should be measured precisely because small inaccuracies may influence the absolute value of PWV. The shorter the distance between two recordings sites, the greater the absolute error in determining the transit time. Some investigators recommend either (i) using the total distance between the carotid and femoral sites of measurement or (ii) subtracting the distance from the carotid location to the sternal notch from the total distance or (iii) subtracting the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral site of measurement. All three procedures are approximations and absolute differences are unimportant in intervention studies with repeated measures. However, when comparing two populations or pooling data for normal values or for meta-analyses, differences in the methods used to assess the path length will be critically important.

Some limitations should be underlined. The femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes, and peripheral artery disease. In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity, particularly in men, and large bust size in women can make distance measurements inaccurate.

The most commonly used method for estimating transit time is the foot-to-foot method. The foot of the wave is defined at the end of diastole, when the steep rise of the wavefront begins. The transit time is the time of travel of the foot of the wave over a known distance.

**Box 2: Position statement: PWV. Carotid-femoral PWV is considered as the 'gold-standard' measurement of arterial stiffness.**

Methods based on pressure sensors

Pressure waveforms can be recorded simultaneously to provide automated measurement of PWV using a number of
devices. The Complior System™ (Colson, Les Lilas, France) employs dedicated mechanotransducers directly applied on the skin. The transit time is determined by means of a correlation algorithm between each simultaneously recorded wave. The operator is able to visualize the shape of the recorded arterial waves and to validate them. Three main arterial sites can be evaluated, mainly the aortic trunk (carotid-femoral) and the upper (carotid-brachial) and lower (femoral-dorsalis pedis) limbs. This system was used in most of the epidemiological studies demonstrating the predictive value of PWV for CV events (Table 4).

Pressure waves can also be recorded sequentially from different sites, and transit time calculated using registration with a simultaneously recorded ECG. In the SphygmoCor system (ArtCor, Sydney, Australia), a single high-fidelity applanation tonometer (Millar) to obtain a proximal (i.e. carotid artery) and distal pulse (i.e. radial or femoral) recorded sequentially a short time apart and calculates PWV from the transit time between the two arterial sites, determined in relation to the R-wave of the ECG. The time between the ECG and the proximal pulse is subtracted from the time between ECG and distal pulse to obtain the pulse transit time. The initial part of the pressure waveform is used as a reference point. It is also possible to check offline the variability of measurement over a range of pulses, according to each algorithm. Since the measurements are made a short time apart, the change in the isovolumic period of the LV or heart rate variability has little or no effect on measured pulse transit times.

Japanese researchers advocated the use of brachial-ankle pulse-wave velocity (baPWV) and showed the aortic PWV was the primary independent correlate of baPWV, followed by leg PWV. Previous remarks concerning the calculation of the path length apply here. In small cohorts of either elderly community-dwelling people or coronary heart disease patients, baPWV was an independent predictor for CV deaths and events.

Methods using mechanotransducers or high-fidelity applanation tonometers are well accepted for carotid-femoral PWV measurement.

**Methods based on Doppler probes and other methods**

The distension waves obtained from the high-definition echotracking devices (discussed subsequently) can be used to calculate PWV. As described earlier for the SphygmoCor...
device, PWV is calculated from waves successively obtained at a short time interval at two arterial sites (common carotid and femoral artery, for instance), using the R-wave of the ECG for calculating the time delay.

The transit time, required for the determination of PWV, can be measured between two flow pulses simultaneously recorded by continuous Doppler probes or again sequentially with ECG gating. Measurements are usually made at the root of the left subclavian artery (i.e. suprasternal notch on the skin) and near the bifurcation of the abdominal aorta (i.e. umbilicus level on the skin). Transit time is automatically calculated following automatic recognition of the foot of the pulse. This method was used for showing the predictive value of aortic PWV for CV events in diabetic patients and provides a more accurate assessment of ‘aortic’ PWV when compared with carotid-femoral, although whether this has any specific advantage remains to be seen.

Other devices are available to calculate a PWV-based stiffness index. These devices are not so precise as those mentioned earlier, as some propose aberrant transit tracts (i.e. ankle-arm) or estimate distance from height (i.e. height in sitting position). Some do not correct for electromechanical dissociation of cardiac action or try to correct for it using a model. The latter device demonstrated that aorto-brachial PWV predicted CV events in hypertensives.

Local determination of arterial stiffness

Local arterial stiffness of superficial arteries can be determined using ultrasound devices. Carotid stiffness may be of particular interest, since in that artery atherosclerosis is frequent. All types of classical, bi-dimensional vascular ultrasound systems can be used to determine diameter at diastole and stroke changes in diameter, but most of them are limited in the precision of measurements because they generally use a video-image analysis. At present, some researchers also measure local arterial stiffness of deep arteries like the aorta using cine magnetic resonance imaging (MRI). However, most of pathophysiological and pharmacological studies have used echotracking techniques (Table 1).

A major advantage is that local arterial stiffness is directly determined, from the change in pressure driving the change in volume, i.e. without using any model of the circulation (Figure 2). However, because it requires a high degree of technical expertise and takes longer than measuring PWV, local measurement of arterial stiffness is only really indicated for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, rather than for epidemiological studies. Nevertheless, ultrasound is currently the only means to determine, non-invasively, the elastic properties of the arterial wall material (Young’s elastic modulus, discussed subsequently), and the relationship between intima-media thickness (IMT) and elastic properties, or the influence of inward or outward remodelling on arterial distensibility.

Echotracking devices were developed to measure diameter in end diastole and stroke change in diameter with a very high precision. The two first devices were the Wall Track System and the NIUS02. These apparatus use the radiofrequency signal to obtain a precision 6–10 times higher than with video-image systems, which are limited by the spatial resolution of pixel analysis. Indeed, the precision in determining stroke change in diameter is as low as 1 μm for echotracking systems and ~150 μm (i.e. the size of the pixel) with video-image analysers. For absolute distance measurement, the standard deviation extends from 9 to 25 μm for echotracking systems and from 54 to 60 μm with video-image analysers.

Echotracking systems have other major advantages over video-image systems: from the same ultrasound data, the IMT can be extracted, which allows the Young’s elastic modulus to be determined (discussed subsequently); it is possible to determine the pressure–diameter curve of the artery, thus to

![Figure 2](image-url)
determine arterial stiffness for any given BP from the time delay between two adjacent distension waveforms, it is possible to calculate the local PWV pathophysiological and therapeutic changes in arterial stiffness can be related to geometrical changes (lumen area and IMT).

Most of these parameters required the measurement of blood pressure. This should be local pressure, which is usually obtained by applanation tonometry of the vessel in question, and calibration of the waveform to brachial mean and diastolic pressures obtained by integration of the brachial or radial waveform or automatic calculation using transfer function processing (Sphygmocor, AtCor, Sydney Australia). All the superficial arteries are suitable for the geometrical investigation, particularly the common carotid, common femoral, and brachial arteries.

Table 3 gives the definition of various indices used to describe the elastic properties of blood vessels, non-invasively obtained with ultrasound measurements. For the calculation of wall properties, it is assumed that the cross-section of an artery is circular. The elastic properties of the artery as a hollow structure are assessed through arterial distensibility, determined from the systolic-diastolic variations in arterial cross-sectional area and local pulse pressure. The elastic properties of the arterial wall material are estimated by Young’s incremental elastic modulus, which takes into account the thickness of the arterial wall. The IMT is taken as a surrogate for arterial wall thickness. Young’s elastic modulus, or incremental elastic modulus, which gives information on the wall material, should not be confused with Peterson’s elastic modulus, which is inversely related to cross-sectional distensibility, and elastic properties of large arteries as hollow structures. Calculation of Young’s modulus from IMT assumes that the wall is homogeneous, and load-bearing, so that values may be underestimated.

Although carotid-femoral PWV and carotid stiffness provide similar information on the impact of ageing on large artery stiffness in normal subjects, this is not the case for high blood pressure and/or diabetes. In these cases, the aorta stiffened more than the carotid artery with age and other CV risk factors. Thus, aortic stiffness and carotid stiffness cannot be used as interchangeable predictors in high-risk patients.

### Systemic arterial stiffness

A methodology based on an electrical circuit, based on a modified Windkessel model, has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave CR-2000 Research Cardiovascular Profiling System; Hypertension Diagnostics Inc., Eagan, MN, USA). This technique is based on the arterial pulse recording at the level of the radial artery and identifies the reflections in diastole as a decaying sinusoidal wave.

Systemic arterial compliance can also be determined using the “area method” which requires measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. Systemic arterial compliance is then calculated from the formula: $\text{SAC} = \frac{\text{Ad}}{[\text{Ps} - \text{Pd}]}$, where Ad is the area under the blood pressure diastolic decay curve from end systole to end diastole, Ps the end-systolic blood pressure, and Pd the end-diastolic blood pressure (calibrated against brachial arterial pressure). Finally, a crude approximation of systemic compliance has been used in the past: the ratio between stroke volume and pulse pressure. However, this method multiplies the difficulty in accurately determining stroke volume and pulse pressure at the ascending aorta non-invasively.

In summary, the methods used for the non-invasive determination of systemic arterial stiffness are based on analogies with electrical models combining capacitance and resistance in series. As such, they rely on numerous theoretical approximations following direct measurement of one peripheral, and often distal, parameter. Their theoretical, technical, and practical limitations that impact on their widespread application in the clinical setting have been discussed and compared with the methods used for the non-invasive determination of regional stiffness. Until now, they did not provide evidence, in a longitudinal study, that systemic arterial stiffness or systemic arterial compliance has independent predictive value for CV events.

### Non-invasive determination of wave reflections

#### Central pulse-wave analysis

As described earlier, the arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. In elastic vessels, because PWV is low, reflected wave tends to arrive back at the aortic root during diastole. In the case of stiff arteries, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure. This phenomenon can be quantified through the augmentation index (AIx) defined as the difference between the second and first systolic peaks (P2 – P1) expressed as a percentage of the pulse pressure (Figure 3). Apart from a high PWV, also changes in reflection sites can influence the AIx. In clinical investigation, not only DBP and height, which are related to reflection sites, but also age and aortic PWV are the main determinants of the AIx.
Arterial pressure waveform should be analysed at the central level, i.e. the ascending aorta, since it represents the true load imposed to the LV and central large artery walls. Aortic pressure waveform can be estimated either from the radial artery waveform, using a transfer function, or from the common carotid artery waveform. On both arteries, the pressure waveform can be recorded non-invasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (Sphygmocor, AtCor, Sydney Australia) to calculate the aortic pressure waveform from the radial waveform. Indeed, in contrast to the carotid artery, the radial artery is well supported by bony tissue, making optimal planimetry easier to achieve.

Individual and generalized inverse transfer functions are applied to reconstruct the aortic waveform from radial tonometry. The estimation of central aortic pressures is accepted as more accurate than the estimation of Alx (discussed subsequently). In addition, brachial artery pressures are used as surrogates of radial artery pressures for the calibration of central pressures, and this may introduce some errors.

Despite these limitations, radial tonometry is popular, since it is simple to perform and well tolerated. Carotid tonometry requires a higher degree of technical expertise, but a transfer function is not necessary, since the arterial sites are very close and waveforms are similar.

There are two major issues in quantification of reflected waves on central pressure waveforms. First, it is necessary to assess the timing and the proportion of the reflected wave, i.e. the time necessary for the pressure wave to reach the reflection site (which is a theoretical site rather than an actual site, as the reflected wave is a composite of many reflected ‘wavelets’) and return. The reflection point is the point in time which coincides with the peak of the flow wave in the artery. The proportion of reflected pressure wave is assessed through the Alx. As it is calculated as the ratio between the augmentation pressure (pressure above the inflection point) and pulse pressure, it is dimensionless and usually expressed in percentage, but it does not depend on the absolute pressure. Although the use of a radial-to-aortic transfer function for the measurement of central systolic blood pressure has been well established, the accuracy of this approach for the determination of aortic Alx has been disputed. Indeed, the measurement of Alx is dependent on higher frequency signals than blood pressure measurement and the transfer function appears to be less accurate and to show greater between-subject variability at high frequencies.

The second issue, more challenging, is the estimation of absolute values of central pressures, including pulse pressure, augmentation pressure, or systolic blood pressure. Although the Alx is a relative measurement and can be calculated without calibration, central pulse pressure, augmentation pressure, and systolic blood pressure are absolute values and require calibration. Direct measurements obtained at the site of the common carotid artery using applanation tonometry can be calibrated according to the methods suggested by Kelly and Fitchett and Van Bortel et al., with adaptation (Figure 4). Calibration of the artery tonometer pressure wave is based on the observation that mean BP is constant throughout the large artery tree and that diastolic BP does not change substantially. In practice, BP is measured at the reference artery, in general, the brachial artery, with a validated BP device and PP is calculated as SBP minus DBP. Applanation tonometry is performed at carotid artery. From these data, the absolute value of PP at the target artery can be calculated. An alternative is to compute mean BP on the carotid pressure wave from the area of the wave in the corresponding heart period. Carotid mean BP is then set equal to brachial mean BP. Carotid PP is then computed from the diastolic BP and the position of mean BP on the carotid pressure wave. Carotid SBP is obtained by adding PP to DBP (Figure 4).

A transfer function may be useful when applanation tonometry cannot be applied at the site of the carotid artery, for instance, in obese subjects or in patients with major atherosclerotic plaques or calcified arteries, in whom this method may not be free from any risk. However, the use of a transfer function should be limited to the upper limb, where elastic properties remain relatively constant with age and disease, as previously discussed. It would allow assessing carotid artery and ascending aorta systolic BP and PP from radial artery PP.

Central Alx and central pulse pressure have shown independent predictive values for all-cause mortality in ESRD patients and CV events in patients undergoing percutaneous coronary intervention (PCI) and in the hypertensive patients of the CAFÉ study.

**Box 4: Position statement: Central pulse-wave analysis.**

Pulse-wave analysis should be optimally obtained at the central level, i.e. at the site of the carotid artery or the ascending aorta, and either directly recorded or computed from the radial artery waveform using a transfer function. Pulse wave should be analyzed through three major parameters: central pulse pressure, central systolic pressure, and the Alx.

**Pulse-wave analysis at peripheral sites**

Other techniques were derived from peripheral waveform shape analysis. The determination of the amplitude ratios of the second derivative of the pulse waveform, obtained by finger photoplethysmography (Fukuda Electric...
Co, Tokyo), was used to study the effects of ageing and vasoactive agents. From the second derivative of the plethysmogram, the amplitudes of the second ($b$) and first ($a$) inflections are calculated in order to determine their ratio $j b / a j$. This ratio has been shown to be related to arterial distensibility and severity of atherosclerosis. An advantage of the method is that the finger pulse can be obtained easily, thus making this device useful for epidemiological applications. A comparable device (Pulse Trace\textsuperscript{50}, Micro Medical, Rochester, UK) has been developed, on the basis of finger photoplethysmography, and validated in different settings and diseases.\textsuperscript{50,92}

Central and peripheral systolic and pulse pressures
Peripheral SBP and PP, most often measured at the site of the brachial artery, should not be confused with central SBP and PP, measured at the carotid site. Indeed, as described earlier, in peripheral arteries, reflection sites are closer than in central arteries, and reflected waves travel faster on peripheral arteries than on central arteries, which are less stiff in young subjects. Thus, according to the ‘amplification phenomenon’, the amplitude of the pressure wave is higher in peripheral arteries than in central arteries, and brachial SBP and PP overestimate central SBP and PP in young subjects.\textsuperscript{93}

Central pulse pressure, the Alx, and arterial stiffness
Because central SBP and PP, the Alx and PWV increase with age, hypertension, diabetes mellitus, and hypercholesterolaemia and are associated with target organ damage (LV hypertrophy (LVH), microalbuminuria, carotid IMT, and endothelial dysfunction) and clinical outcomes: they are often used interchangeably as indexes of arterial stiffness. This is an oversimplification and should not be the case for various reasons.

First, their determinants are different. Central SBP, central PP, and the Alx are dependent on the speed of wave travel, the amplitude of reflected wave, the reflection point, and the duration and pattern of ventricular ejection, especially with respect to change in heart rate and ventricular contractility,\textsuperscript{84} whereas aortic PWV, which is the speed of wave travel, represents intrinsically arterial stiffness, according to the Bramwell–Hill formula (Figure 1). Second, pathophysiological conditions and drugs may change central pulse pressure and the Alx without changing aortic PWV, suggesting a predominant effect on reflection wave, heart rate or ventricular ejection, and no change in aortic stiffness.\textsuperscript{76,94} Third, the Alx is much more sensitive to the effects of heart rate than aortic PWV.\textsuperscript{85,95–97} Fourth, in the normal population of the Anglo Cardiff Collaborative Study,\textsuperscript{98} the influence of age is higher on the Alx than on aortic PWV before the age of 50 and higher on aortic PWV than on the Alx after 50.

**Box 5: Position statement: Central and peripheral pulse pressures.** Brachial SBP and PP should not be confused with central SBP and PP, most often measured at the carotid site. Brachial SBP and PP overestimate central SBP and PP, especially in young subjects.\textsuperscript{93}

**Box 6: Position statement: Use of central pressure, the Alx, and PWV.** Central pressure, the Alx, and PWV cannot be used interchangeably as indexes of arterial stiffness. In contrast to PWV, which is a direct measure of arterial stiffness, central pressure and the Alx are only indirect, surrogate measures of arterial stiffness. However, they provide additional information concerning wave reflections. Central pulse-wave analysis should be optimally coupled with the measurement of aortic PWV to determine the contribution of aortic stiffness to wave reflections.

In summary, various arterial parameters can be measured and calculated in order to evaluate non-invasively the arterial stiffness and wave reflections. Various methods for arterial stiffness measurement are suggested to clinicians and...
researchers in Table 5. They have been established and ranked primarily according to various criteria: validation, limitations, predictive value, and degree of technical expertise, as discussed earlier.

Box 7: Position statement: Methods for measuring arterial stiffness in clinical practice and research.
1. Carotid-femoral PWV is the ‘gold standard’ for arterial stiffness, has the largest amount of epidemiological evidence for its predictive value for CV events, and requires little technical expertise.
2. Central pulse-wave analysis provides additional information concerning wave reflections. Central pressure and the AIx have demonstrated their predictive value in patients with ESRD, in hypertensives, and in CAD patients, and require little technical expertise.
3. Local arterial stiffness benefits from a certain amount of epidemiological evidence for its predictive value for CV events, requires a higher level of technical expertise, and is indicated for mechanistic analyses in pathophysiology, pharmacology, and therapeutics.

Clinical applications
Arterial stiffness and wave reflection are now well accepted as the most important determinants of increasing systolic and pulse pressure in ageing societies, thus afford a major contribution to stroke and myocardial infarction. First, we will summarize the main pathophysiological mechanisms through which an increase in arterial stiffness and wave reflections cause CV complications. Secondly, we will review three major clinical applications of arterial stiffness and wave reflections: pathophysiological studies, routine use, and intervention studies.

Pathophysiology of CV complications
A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central pulse pressure, thus systolic BP. SBP increases the load on the LV, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with LVH, a known risk factor for coronary events, in normotensive and hypertensive patients. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischaemia. The measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of the coronary arteries. Indeed, aortic stiffening accompanying age and CV risk factors is caused by various phenomena, including breaks in elastin fibers, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications, and diffusion of macromolecules within the arterial wall. All these phenomena are known to occur in parallel at the site of the coronary circulation.

An increased arterial stiffness can increase the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodelling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and
plaques \(^{56,104,105}\) the likelihood of plaque rupture, \(^{106}\) and the prevalence and severity of cerebral white matter lesions. \(^{107}\) The measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. Another explanation is given by the differential input impedance in the brain compared with other systemic vascular beds. \(^{108}\) Torrential flow and low resistance to flow in these organs expose small arterial vessels to the high-pressure fluctuations that exist in the carotid and vertebral arteries, and that increase three- to four-fold with age. \(^{108}\) Finally, coronary heart disease and heart failure, which are favoured by high PP and arterial stiffness, are also risk factors for stroke.

**Clinical application: pathophysiological studies**

Arterial stiffness and wave reflections are widely used in observational studies to analyse the determinants of haemodynamic changes observed in various clinical conditions and to understand the pathogenesis of their CV complications. In addition, the genetic and molecular abnormalities of arterial diseases have provided new insight into the molecular and cellular determinants of arterial stiffness. Together, these approaches have generated new hypotheses concerning the pharmacological and therapeutic means of preventing CV complications.

The molecular and cellular determinants of arterial stiffness have been reviewed in several publications.\(^{2,3,102,109}\) The stiffness of the vascular wall is dependent on the relative contribution of its two predominant scaffolding proteins: collagen and elastin. An overproduction of abnormal collagen and diminished quantities of normal elastin contribute to vascular stiffness. Recent immunohistochemical and ultrastructural studies afford strong arguments to consider that arterial stiffness is not only influenced by the amount and density of stiff wall material but mainly by its spatial organization.\(^{54}\)

A large number of publications and several reviews\(^{2,3,109}\) reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections (Table 6). Apart from the dominant effect of ageing,\(^{6,98}\) they include (i) physiological conditions, such as low birth weight,\(^{110}\) menstrual cycle,\(^{111}\) menopausal status,\(^{112}\) lack of physical activity;\(^{113}\) (ii) the genetic background such as a parental history of hypertension,\(^{114}\) diabetes\(^{115}\) or myocardial infarction,\(^{115}\) and genetic polymorphisms;\(^{116,117}\) (iii) CV risk factors such as obesity,\(^{118}\) smoking,\(^{119}\) hypertension,\(^{9,120}\) hypercholesterolaemia,\(^{117,121,122}\) impaired glucose tolerance,\(^{123,124}\) metabolic syndrome,\(^{118,124}\) types 1 and 2 diabetes,\(^{124,125}\) hyperhomocysteinemia,\(^{126}\) and high C-reactive protein level;\(^{127,128}\) (iv) CV diseases such as coronary heart disease,\(^{33}\) congestive heart failure,\(^{14}\) and fatal stroke;\(^{36}\) and (v) primarily non-CV diseases, such as ESRD,\(^{32,87}\) moderate chronic kidney disease,\(^{129}\) rheumatoid arthritis,\(^{130,131}\) systemic vasculitis,\(^{132}\) and systemic lupus erythematosus.\(^{132}\)

The contribution of these different factors to arterial stiffness and wave reflections has been studied in multivariate analyses: the major parameters to be taken into account, when evaluating the degree of arterial stiffness, are age and blood pressure and, to a lower extent, gender and classical CV risk factors.

**Clinical application: arterial stiffness for routine use**

A major reason for measuring arterial stiffness and wave reflections ‘routinely’ in clinical practice comes from the recent demonstration that arterial stiffness has an independent predictive value for CV events. Whether arterial stiffness is a marker of CV risk, an ‘intermediate’ endpoint, or a ‘surrogate’ endpoint for CV events will be reviewed as follows.

**Predictive value of arterial stiffness and wave reflections for CV events**

Indirect evidence for the influence of arterial stiffness on CV events comes from cross-sectional studies showing that arterial stiffness, on one hand, and CV risk factors for atherosclerotic lesions, on the other hand, are correlated (Table 6). A major limitation of these studies is their cross-sectional nature. Indeed, although these studies show a clear association between aortic stiffness and other markers of CV risk or atherosclerosis, it is not possible to conclude that arterial stiffness is predictive of CV events because patients were not followed up. In other words, these studies showed that arterial stiffness was a ‘marker’ of CV risk, but did not demonstrate its predictive value as intermediate endpoint.

**Predictive value as intermediate endpoint**

Tables 4 and 7 summarize the longitudinal epidemiological studies which have demonstrated the independent predictive value of arterial stiffness, carotid pulse pressure, and the AIx, for CV events. The largest amount of evidence has been given for arterial stiffness, measured through carotid-femoral PWV. Aortic stiffness has independent predictive value for all-cause and CV mortalities, fatal and non-fatal.

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**Table 6 Clinical conditions associated with increased arterial stiffness and/or wave reflections**

<table>
<thead>
<tr>
<th>Ageing</th>
<th>CV risk factors</th>
<th>CV diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other physiological conditions</td>
<td>Obesity</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>Smoking</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Hypertension</td>
<td>Fatal stroke</td>
</tr>
<tr>
<td>Lack of physical activity</td>
<td>Hypercholesterolaemia</td>
<td>Primarily non-CV diseases</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Impaired glucose tolerance</td>
<td>ESRD</td>
</tr>
<tr>
<td>Parental history of hypertension</td>
<td>Metabolic syndrome</td>
<td>Moderate chronic kidney disease</td>
</tr>
<tr>
<td>Parental history of diabetes</td>
<td>Type 1 diabetes</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Parental history of myocardial infarction</td>
<td>Type 2 diabetes</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
<td>Hyperhomocysteinemia</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>High CRP level</td>
<td></td>
</tr>
</tbody>
</table>
coronary events, and fatal strokes in patients with uncomplicated essential hypertension, type 2 diabetes, ESRD, elderly subjects, and the general population. It is now well accepted that aortic stiffness is an intermediate endpoint for CV events.

The independent predictive value of aortic stiffness has been demonstrated after adjustment to classical CV risk factors, including brachial pulse pressure. This indicates that aortic stiffness has a better predictive value than each of classical risk factors. In addition, aortic stiffness retains its predictive value for CHD events after adjustment to the Framingham risk score, suggesting that aortic stiffness has an added value to a combination of CV risk factors. One reason may be that aortic stiffness integrates the damage of CV risk factors on the aortic wall over a long period of time, whereas BP, glycaemia, and lipids can fluctuate over time and their values, recorded at the time of risk assessment, may not reflect the true values damaging the arterial wall. Another explanation may be that arterial stiffness shows the patients in which arterial risk factors were translated into real risk.

Data are less consistent concerning arterial stiffness measured at other arterial sites. Carotid stiffness was predictive of CV events in a small number of patients with ESRD or following renal transplantation, but had no independent predictive value in a larger number of patients with manifest arterial disease. Upper and lower limb territories, due to their particular pathophysiology, may not reflect aortic, cerebral, and coronary artery damage. Indeed, in contrast to carotid-femoral PWV, neither brachial PWV nor femoro-tibial PWV was able to predict CV outcome in ESRD patients. Finally, central AIx and pulse pressure, either directly measured by carotid tonometry or estimated using a transfer function from radial artery tonometry, are both independent predictors of all-cause mortality in ESRD patients and CV events in patients undergoing PCI and in the hypertensive patients of the CAFE study, an ancillary study of the ASCOT trial (Table 7). However, data concerning the predictive values of both these parameters in other patient groups and in the general population are scarce. In older female hypertensive patients, data from the ANBP2 study showed no benefit in use of carotid application tonometry (AIx or total arterial compliance) over brachial cuff pressure in prognosis. Analytic methods in this study have been questioned.

### Table 7: Longitudinal studies reporting the independent predictive value of central pulse pressure and the AIx

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type of patient</th>
<th>Follow-up (years)</th>
<th>Mean age at entry (years)</th>
<th>Events</th>
<th>Type of patient (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central pulse pressure</td>
<td>All cause mortality</td>
<td>4.3</td>
<td>54</td>
<td>ESRD (180)</td>
<td></td>
</tr>
<tr>
<td>Carotid AIx</td>
<td>CV events</td>
<td>3.4</td>
<td>63</td>
<td>HT, ASCOT study (2073)</td>
<td></td>
</tr>
<tr>
<td>Carotid AIx</td>
<td>Severe CV events</td>
<td>3.4</td>
<td>66</td>
<td>Undergoing PCI (262)</td>
<td></td>
</tr>
<tr>
<td>Central pulse pressure</td>
<td>All cause mortality</td>
<td>4.3</td>
<td>63</td>
<td>HT, ASCOT study (2073)</td>
<td></td>
</tr>
<tr>
<td>Carotid AIx</td>
<td>CV events</td>
<td>3.4</td>
<td>63</td>
<td>HT, ASCOT study (2073)</td>
<td></td>
</tr>
</tbody>
</table>

### Box 8: Position statement: Predictive value of arterial stiffness and wave reflection for CV events

A large amount of evidence indicates that carotid-femoral PWV is an intermediate endpoint for CV events, either fatal or non-fatal. Aortic PWV has a better predictive value than classical CV risk factors entering various types of risk score. Central AIx and pulse pressure have shown an independent predictive value for all-cause mortality in ESRD patients and CV events in hypertensives and patients with coronary disease.

**Predictive value for the reduction in CV events**

Although measures of stiffness provide useful prognostic information concerning the occurrence of CV events, the
value of arterial stiffness for the reduction in CV events under treatment is yet to be unequivocally demonstrated. One major requirement is to determine whether a reduction in PWV is associated with a concomitant reduction in CV events, independently of the normalization of classical CV risk factors.

Arterial stiffness attenuation may reflect the true reduction of arterial wall damage, whereas BP, glycaemia, and lipids can be normalized in a few weeks by using antihypertensive, anti-diabetic, and lipid-lowering drugs, leading to a strong reduction in CV risk scores, but without yet any improvement of atherosclerotic lesions and arterial stiffness, which requires a long-lasting correction of biochemical abnormalities. A temporal dissociation is thus expected between the improvement of CV risk factors and a still high arterial stiffness.

A direct answer to the issue of the predictive value of aortic stiffness attenuation for the reduction of CV events has not yet been afforded in the general population, but Guerin et al.\(^\text{136}\) provided the first clear evidence in ESRD patients, showing that the insensitivity of PWV to reduced BP is an independent predictor of mortality. The impact of aortic stiffness attenuation on CV mortality, coronary events, and stroke remains to be established in other populations, particularly those at lower but still high CV risk, i.e. with hypertension, dyslipidaemia, diabetes, and moderate chronic kidney disease.

Whether the reduction in central PP is associated with a concomitant reduction in CV events, independently of the normalization of classical CV risk factors, remains to be demonstrated. There are indirect arguments. In the REASON study,\(^\text{139,140}\) only the perindopril/indapamide combination significantly attenuated carotid wave reflections, resulting in a selective decrease in central SBP and PP, leading to a related reduction in LVH\(^\text{140}\) in contrast to the lack of reduction in carotid PP and LVH observed with atenolol. The CAFE study,\(^\text{90}\) an ancillary study of the ASCOT study,\(^\text{136}\) showed that central Aix and pulse pressure were both independent predictors of CV events in hypertensive patients and that the reduction in central SBP and PP was higher in the amlodipine + perindopril group than in the atenolol + thiazide group, despite similar reduction in SBP and PP at the brachial level.

Box 9: Position statement: Predictive value of arterial stiffness and wave reflection for the reduction in CV events. Further studies are required to confirm the predictive value of arterial stiffness and wave reflection for the reduction in CV events in the long-term intervention studies.

Normal values in different European countries
To allow a better understanding of the predictive value of indices of arterial stiffness for an individual patient, normal values applicable to individual populations are required. This requires both a cross-sectional and longitudinal approach in order to remove the potential influence of birth cohort effects and provide greater evidence of predictive values and causality. Differences between population normative data should be explored, as they may help explain why CV risk varies between countries and what may be driving arterial stiffening.\(^\text{98}\)

Clinical application: arterial stiffness in the intervention studies
A large number of publications and several reviews\(^\text{1,3,31}\) reported the changes in arterial stiffness and wave reflections after various interventions, either non-pharmacological or pharmacological. They are summarized, although not exhaustively, in Table 8. Non-pharmacological treatments which are able to reduce arterial stiffness include exercise training,\(^\text{113}\) dietary changes [including weight loss,\(^\text{141}\) low salt diet,\(^\text{142}\) moderate alcohol consumption,\(^\text{143}\) garlic powder,\(^\text{144}\) alpha-linoleic acid,\(^\text{145}\) and fish oil\(^\text{146}\)], and hormone replacement therapy (HRT).\(^\text{147}\)

Pharmacological treatments which are able to reduce arterial stiffness include (i) antihypertensive treatment, such as diuretics,\(^\text{59,148}\) beta-blockers,\(^\text{99,149,150}\) ACE-inhibitors,\(^\text{99}\) AT1 blockers,\(^\text{151}\) and calcium-channel antagonists;\(^\text{152}\) (ii) treatments of congestive heart failure, such as ACE-inhibitors,\(^\text{14}\) nitrates,\(^\text{13,154}\) and aldosterone antagonists;\(^\text{155}\) (iii) hypolipidaemic agents such as statins;\(^\text{156}\) (iv) antidiabetic agents, such as thiazolidinediones;\(^\text{157}\) (v) sildenafil;\(^\text{158}\) and (vi) AGE-breakers, such as alagebrium (ALT-711).\(^\text{159}\)

Several issues remain to be addressed. First, the predictive value of the attenuation of arterial stiffness and wave reflections for the reduction of CV events should be assessed in the long-term, large-scale therapeutic trials. As already noted, we urgently need to conduct clinical trials to determine whether a reduction in arterial stiffness is a desirable therapeutic goal in terms of hard clinical endpoints such as morbidity and mortality. To our knowledge, this has been done only once, in patients with ESRD,\(^\text{138}\) and not in a population of patients with hypertension or at low CV risk. We also need to demonstrate whether a therapeutic strategy aiming at normalizing arterial stiffness and wave reflection proves to be more effective in preventing CV events than usual care.

It is important that future clinical trials also adopt a pharmacogenetic approach to define better the potential benefit of attenuating arterial stiffening. In particular, it would be

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Non-pharmacological and pharmacological treatment associated with a reduction in arterial stiffness</th>
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</thead>
<tbody>
<tr>
<td><strong>Non-pharmacological</strong></td>
<td><strong>Pharmacological</strong></td>
</tr>
<tr>
<td>Exercise training</td>
<td>Anti-hypertensive treatment</td>
</tr>
<tr>
<td>Dietary changes</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Low-salt diet</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>ACE-inhibitors</td>
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<tr>
<td>Garlic powder</td>
<td>AT1 blockers</td>
</tr>
<tr>
<td>Alpha-linoleic acid</td>
<td>Calcium channel antagonists</td>
</tr>
<tr>
<td>Fish oil</td>
<td>Treatment of congestive heart failure</td>
</tr>
<tr>
<td>HRT</td>
<td>ACE-inhibitors</td>
</tr>
<tr>
<td></td>
<td>Nitrates</td>
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<td>Hypolipidaemic agents</td>
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<tr>
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<td>Antidiabetic agents</td>
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<tr>
<td></td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td></td>
<td>AGE-breakers</td>
</tr>
<tr>
<td></td>
<td>Alagebrium (ALT-711)</td>
</tr>
</tbody>
</table>
Searching for target organ damage: measurement of arterial stiffness and wave reflection

The above paragraphs highlight the importance of arterial stiffness and wave reflection, not only for assessing CV risk but also for predicting CV outcomes. Arterial stiffening also provides direct evidence of target organ damage, which is of major importance in determining the overall CV risk of the hypertensive patient. Indeed, measurement of arterial stiffness and wave reflection may avoid patients being mistakenly classified as at low or moderate risk, when they actually have an abnormally high arterial stiffness or central PP placing them within a higher risk group. For instance, the predictive value of aortic PWV for primary CHD events in hypertensive patients was more marked for patients considered as at low risk, i.e. belonging to the first and second tertiles of the Framingham risk score, than for patients at high risk (i.e. belonging to the third tertile of the score), indicating that this low-to-intermediate risk population benefited the most of risk assessment with PWV. The current European and US guidelines for the diagnosis and treatment of hypertension define LVH and albuminuria as evidence of target organ damage, but not yet arterial stiffness and wave reflections. These recommendations were issued long before the LIFE and RENAAL trials showed unequivocally that the regression of LVH and albuminuria, respectively, were predictive of the reduction in CV events. Since 2003, corresponding to the release of the last guidelines, a large body of evidence has been accumulated, demonstrating the clinical value of arterial stiffness and wave reflections.

Box 10: Position statement: Arterial stiffness as target organ damage. Arterial stiffness and central pressure measurements should be considered as recommended tests for the evaluation of CV risk, particularly in patients in whom target organ damage is not discovered by routine investigations.

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Arterial stiffness: methods and applications


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