Current Cardiology Reports (2023) 25:1337–1349
https://doi.org/10.1007/s11886-023-01951-1

GLOBAL CARDIOVASCULAR HEALTH (L SPERLING AND D GAITA, SECTION EDITORS)

Arterial Stiffness and its Impact on Cardiovascular Health

Rachel Anne Xuereb[1] · Caroline J. Magri[1,2] · Robert G. Xuereb[1]

Accepted: 25 August 2023 / Published online: 7 September 2023

Abstract

Purpose of Review Cardiovascular diseases are the leading cause of mortality globally. Identifying patients at risk is important to initiate preventive strategies. Over the last few decades, the role of the endothelium and its impact on arterial stiffness have been recognised as playing a pivotal role in cardiovascular disease. This review will focus on the effect of arterial stiffness in different patient cohorts with regard to cardiovascular morbidity and mortality, as well as its use in clinical practice.

Recent Findings Arterial stiffness is associated with a range of cardiovascular risk factors and is an independent predictor of cardiovascular mortality. The gold standard for evaluating arterial stiffness is pulse wave velocity. Recently, cardio-ankle vascular index has been implemented as an easy and highly reproducible measure of arterial stiffness. Moreover, certain pharmacologic agents may modify arterial stiffness and alter progression of cardiovascular disease.

Summary The endothelium plays an important role in cardiovascular disease. Implementing assessment of arterial stiffness in clinical practice will improve stratification of patients at risk of cardiovascular disease and help modify disease progression.

Keywords Arterial stiffness · Cardiovascular disease · Cardio-ankle vascular index · Pulse wave velocity · Hypertension · Cardiovascular risk assessment

Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality globally [1]. Risk factor identification is useful to stratify patients at risk for the development of CVD and initiate therapy. However, this has proven insufficient to limit CVD, and hence more precise stratification of CV risk is needed. In fact, the lack of a unifying hypothesis that explains all aspects of the initiation and progression of atherosclerosis has limited definitive therapy. This, in turn, has led to raised interest in the role of the endothelium and its impact on arterial stiffness.

Endothelial dysfunction has been recognised as the first phase in the development of atherosclerosis. There is progressive modification of the structure and function of the vascular system due to a variety of CV risk factors, especially hypertension, in the initial phases of atherosclerosis. Hypertension is a major modifiable CV risk factor, and a remodelling process of the vasculature is especially prominent with progressive elevation of systolic and diastolic pressure, which predate clinically identifiable atherosclerosis [1, 2]. This includes hypertrophy and hyperplasia of smooth muscle cells within the vascular tree. Moreover, the continuous deposition of a variety of proteins, including collagen, together with progressive loss of the elastic matrix result in arterial stiffening. The latter is exacerbated by progressive deposition of calcium within the vascular smooth muscle cells; this occurs with aging but is further amplified in hypertensive patients with end-organ damage [3]. Furthermore, the reduction in the ability of the arterial tree to dilate is a significant factor in the initiation and progression of hypertension, thus creating a vicious cycle with structural modification of the resistance and capacitance vessels that may subsequently become fixed, resulting in a progressive reduction of vascular compliance.

Arterial stiffness may be assessed by a variety of methods, e.g. pulse wave velocity, that provide reproducible measurements. These have been demonstrated to be predictive of subsequent coronary events and may improve CV

✉ Rachel Anne Xuereb
rachel-anne.xuereb@gov.mt

Caroline J. Magri
caroline-jane.magri@gov.mt

Robert G. Xuereb
robert-g.xuereb@gov.mt

[1] Department of Cardiology, Mater Dei Hospital, Msida, Malta

[2] University of Malta, Msida, Malta

risk stratification and therapy in high-risk individuals [4, 5]. Additionally, modification of arterial stiffness could provide a therapeutic target for intervention to potentially reduce CV events. This review will focus on the underlying pathophysiology, will give a brief outline of available methods to quantitate arterial stiffness and consequently discuss factors that alter the progression of vascular changes. These provide prognostic insight regarding the role of arterial stiffness as an emerging risk factor for the development of CVD and enhance its implementation in routine clinical practice.

Pathophysiology

The arterial walls are composed of three layers; the tunica intima, tunica media and tunica adventitia (Fig. 1). During aging and arterial stiffening, the relatively soft inner elastic membrane degrades, and the tunica intima thickens due to the increased deposition of extracellular membrane (ECM) proteins in the basement membrane [6]. On the other hand, the vascular smooth muscles of the tunica media switch from a contractile phenotype to a proliferative phenotype during arterial stiffening and increase the production of ECM, mainly collagen I and III. This increase in collagen fibre deposition increases the overall thickness and stiffness of the media during ageing [6]. In the tunica adventitia, fibrillar collagens and proteoglycans are abundant in the healthy arteries, but during atherogenesis, they contribute to the pathological retention of lipids in the vessel wall. Furthermore, in atherosclerotic plaques, the intima and/or media undergo calcification, which further contributes to arterial stiffening [6].

The distensibility of a healthy artery at physiological pressures is due to the intrinsic distensibility of the vessel's elastin and collagen fibre. With increasing pressure, the artery distends. However, the pressure and diameter changes are not linear [7]. Arterial stiffness, defined as the change in pressure/change in diameter, gradually increases with increasing pressure. On the other hand, distensibility decreases with increasing pressure. Collagen fibres are progressively recruited with increasing pressure levels, explaining the pronounced nonlinearity in the mechanical response of an artery when subjected to increasing pressure, with progressive stiffening of the artery [8]. The estimated half-life of elastin is 40 to 50 years [9••]. As a result, large arteries are naturally predisposed to stiffening with increasing age. As these arteries gradually lose their low-stretch elastin component, load is transferred to collagen, which has greater stiffness. These changes result in inability of large arteries to expand and to increase blood flow in diastole [10].

Endothelial dysfunction plays a pivotal role in the initiation of arterial stiffness, as depicted in Fig. 2 [6]. Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction including

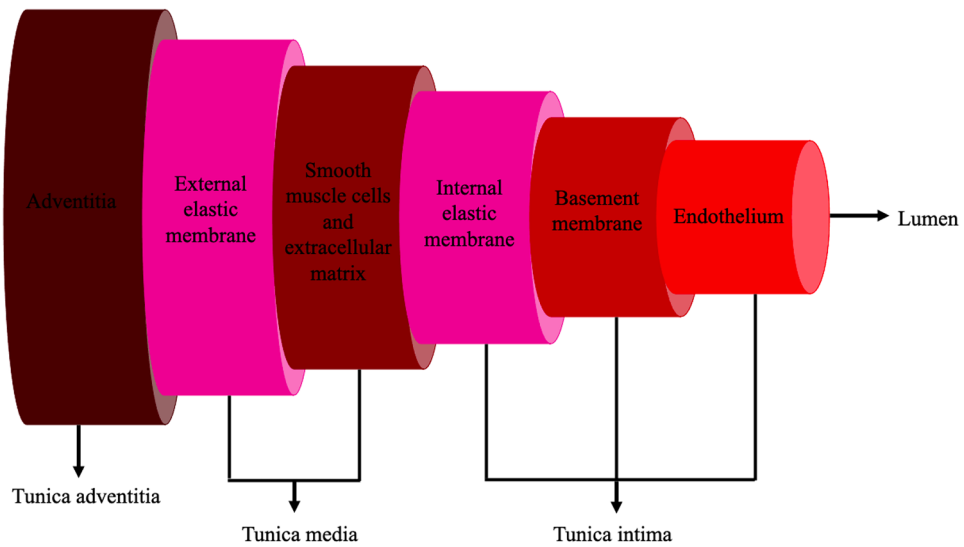

Fig. 1 Layers of the arterial wall: tunica intima, tunica media and tunica adventitia layer. These layers are separated by the internal and external elastic membranes respectively. The tunica intima consists of the endothelium and a thin subendothelial layer of extracellular matrix (ECM), called the basement membrane. The basement membrane is composed of ECM proteins, such as laminins and collagen IV. The tunica media is comprised of multiple layers of vascular smooth muscle cells and ECM. The ECM consists of elastin sheets and collagen fibres. Elastin contributes to the elastic properties of the blood vessel, whereas collagen fibres determine the expansibility of the blood vessel. The vascular smooth muscle cells control blood vessel contraction and alter vessel diameter, blood flow and arterial tone. The tunica adventitia contains a variety of cell types, including immune cells and fibroblasts. The ECM of the adventitia consists of fibrillar collagens and proteoglycans that contribute to the compressibility of the vessel wall

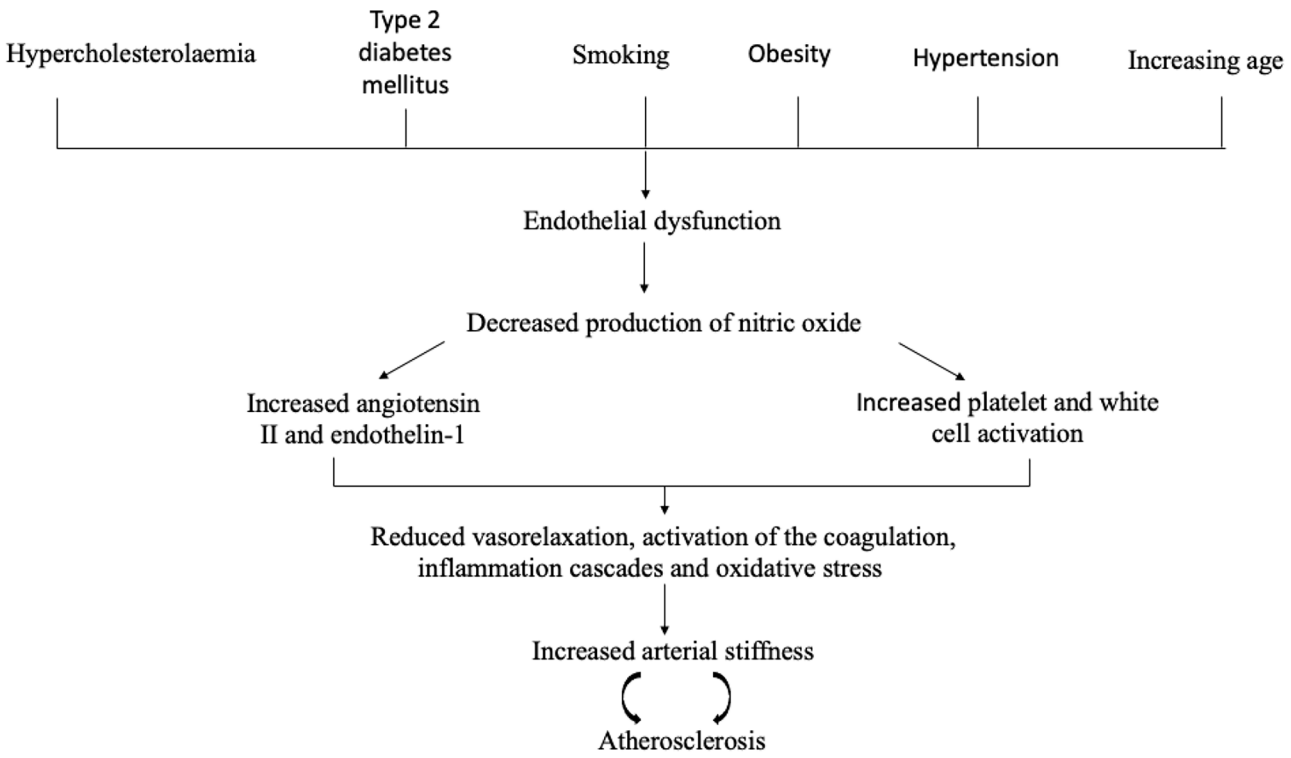

Fig.2 The pathophysiology underlying endothelial dysfunction and atherosclerosis

hypercholesterolaemia, increasing age [11–15], smoking [16••, 17], hypertension [18••, 19], type 2 diabetes mellitus (T2DM) and obesity [20–22]. Endothelial dysfunction is associated with decreased production of nitric oxide (NO); the latter plays a major role in regulating the tone of blood vessels by being the major vasodilator produced by the endothelium. NO acts to negate the actions of endothelium-derived contracting factors such as angiotensin II and endothelin-1. Moreover, NO inhibits platelet and white cell activation and maintains the vascular smooth muscle in a non-proliferative state. Therefore, reduced production of NO results in reduced vasorelaxation, activation of the coagulation and inflammation cascades and oxidative stress [23, 24], thus leading to the initiation and clinical manifestations of atherosclerosis [25]. Endothelial dysfunction causes contraction of vascular muscle cells, resulting in increased arterial stiffness [26–28].

Measurement of Arterial Stiffness

Advances in biomedical engineering have established non-invasive and reproducible methods for assessment of arterial stiffness. To date, measurement of arterial stiffness remains for the most part a research tool that has not entered routine clinical practice. However, growing evidence of clinical value and further advances in technology will likely involve measurement and interpretation of arterial stiffness in clinical care in the near future [29]. Techniques that have been used to assess aortic stiffness include point measurements, like magnetic resonance or ultrasound-derived distensibility, regional measures such as transit time pulse wave velocity (PWV) and indirect measures derived from analysis of features of pressure waveforms recorded in the arm using a standard blood pressure cuff. There are advantages and disadvantages of each technique; however, carotid femoral PWV and conventional pulse pressure are the best studied and have the strongest evidence supporting clinical value [29]. Furthermore, carotid femoral PWV is often cited as the gold standard measure of aortic stiffness [29]. Methods of assessment of arterial stiffness are outlined in Table 1. Studies demonstrating the impact of arterial stiffness on cardiovascular health will be discussed below.

Pulse pressure and arterial stiffness are strongly correlated because age-associated vascular calcification and elastin breakdown leads to arterial stiffening, which results in larger forward wave amplitude, earlier reflected wave arrival and a greater pulse pressure [30]. Although not a direct measure of arterial stiffness, pulse pressure is often used as a surrogate marker of arterial compliance. Interestingly, data from the Framingham Study suggested that a wide pulse pressure is a major risk factor of coronary heart disease [31].

Table 1 Methods of assessment of arterial stiffness

Method	Mode of measurement	Advantage	Disadvantage
Pulse pressure	The difference between systolic and diastolic pressures, measured either centrally or peripherally [32].	Easily available [30].	Influenced by heart rate, stroke volume, aortic geometry and peak aortic flow [30].
Ambulatory arterial stiffness index (AASI)	Derived from 24-h ambulatory BP measurements [34]. All BP recordings are plotted on a regression slope. AASI is determined as 1 minus the regression slope [41]. In subjects with increased arterial stiffness, an increase in mean arterial pressure results in a sharper increase in systolic than diastolic pressure [41].	Easily available [41].	Influenced by BP dipping at night and systolic and diastolic BP [41].
Augmentation index (AI)	Calculated as augmentation pressure divided by pulse pressure × 100, to give a percentage. The augmentation pressure is the measure of contribution that the wave reflection makes to the systolic arterial pressure. Augmentation index is calculated by applanation tonometry over the right radial artery or carotid artery, with the subject in the supine position [38–40]. With an increase in stiffness, there is a faster propagation of the forward pulse wave, as well as a more rapid reflected wave [36, 37].	Easily available [38].	Influenced by multiple factors, including heart rate, gender and height [40].
Carotid-femoral PWV	PWV is given by the Bramwell-Hill equation (below) [45]. Here, V is volume per unit length, ρ is the density (the mass per unit volume) and P is pressure. $PWV\sqrt{\frac{V \cdot dP}{\rho \cdot dV}}$	Gold standard for arterial stiffness [45].	Influenced by BP at time of measurement [45]. Skill needed to use probe-based devices correctly [51].
Brachial-ankle PWV	The ratio of the distance between the brachial and tibial artery, divided by the transit time between the two [49•].	Simple and easily measured using an office BP monitor [49•].	Influenced by BP at time of measurement Limited accuracy in measurement of distance between the two arteries [49•].
B	A property of a local segment of the artery. PWV, which measures a longer segment of the arterial tree, represents the average of the local β values from the measured segment. The equation for stiffness parameter β is log transformation of the pressure ratio divided by ratio of distension, $\beta = (Ddia/\Delta D)\ln(Psys/Pdia)$ [52]. Measured by simultaneously recording the first and second heart sound on a phonocardiogram with PW recordings using the brachial artery and the tibial artery [55].	Independent on the BP at the time of measurement [55].	Difficult to measure in clinical practice, as it is obtained by assessing only a local segment of the artery by simultaneous measurement of both pressure and diameter changes [53].
CAVI	Calculated by combining two indices the stiffness parameter: β and the Bramwell-Hill formula [54].	Independent of BP at time of measurement [55]. Easy to measure and highly reproducible [55].	The reference values for CAVI are based on a Japanese population and hence may not be applicable to different populations [58].

Furthermore, this data demonstrated that the measurement of aortic pulse pressure appears to be an independent marker of CV risk in elderly subjects and those with end-stage renal disease (ESRD) and is more predictive of arterial stiffness than peripheral pulse pressure [32, 33].

Ambulatory arterial stiffness index (AASI) is a measure derived from a 24-h ambulatory blood pressure monitoring and has also been shown to be an independent predictor of CV mortality, especially in normotensive patients and is actually more accurate than pulse pressure [35]. Moreover, it has been shown to be a better predictor of stroke than cardiac mortality [35]. Nonetheless, more studies are needed to support the use of AASI as a therapeutic target in clinical practice.

Augmentation index is a readily available indirect estimate of arterial stiffness. Augmentation index predicts the presence of CAD [41]. Of note, in a 2-year follow-up study of patients undergoing percutaneous coronary intervention, increased augmentation index was independently associated with an increased risk for death, myocardial infarction and restenosis [42]. Moreover, it has been shown to be predictive of CV and all-cause mortality in patients with ESRD [43].

The gold standard for evaluating arterial stiffness is by carotid-femoral PWV [44, 45]. This is the velocity at which the arterial pulse propagates along the arterial wall. PWV varies with blood pressure. PWV increases with pressure for two reasons; firstly, arterial compliance decreases with increasing pressure due to the curvilinear relationship between arterial pressure and volume. Secondly, volume increases with increasing pressure (as the artery dilates), directly increasing PWV. Therefore, PWV is proportional to arterial stiffness and inversely proportional to arterial compliance. In clinical practice, PWV is most commonly calculated as $PWV = \Delta L/\Delta T$, where ΔL is the distance between two sites and ΔT is the time taken for the arterial pulse to travel from the proximal to the distal measuring site [46]. As the aorta is the major vessel, aortic PWV is likely to represent the most accurate measurement. However, the most feasible, non-invasive method is the carotid-femoral PWV [47]. First, the arterial pulse wave is recorded through a tonometer applied on the skin surface from the carotid and femoral sites sequentially. The time delay between carotid and femoral waves is then calculated by comparing the two recordings with a continuous ECG tracing. The length between the recording points must be measured. The transit time is usually measured as the time between the start of the upward stroke of the pulse wave at the two measuring points. The rapidity of the transmission of the pressure wave is increased in stiffer vessels. Carotid femoral PWV is reliable due to the large body of evidence demonstrating its association with incident CV disease independently of traditional risk factors and in various populations. Therefore, it is the gold standard method to measure arterial stiffness [48, 49•]. Addition of carotid-femoral PWV to standard Framingham risk factors in the group at intermediate risk improved classification of those who experienced a CVD event in a 10-year follow-up period by 13%, thus suggesting that increased aortic stiffness, as assessed by carotid-femoral PWV, is a true risk factor, rather than just a marker of risk for CVD [50•]. Furthermore, a single assessment can provide important information regarding blood pressure (BP) progression and susceptibility to end-organ damage. This is useful in patients at intermediate CVD risk, including those with borderline hypertension [49•].

β is another measure of arterial stiffness. Stiffness parameter β has been shown to predict coronary atherosclerosis [51–53]. Recently, β has been applied to develop a new arterial stiffness index, the cardio-ankle vascular index (CAVI) [54]. CAVI is easy to measure and highly reproducible. Moreover, it is independent of BP at the time of measurement [55]. CAVI increases with age and is higher in males compared to females [56]. Studies have shown that CAVI is significantly related to coronary artery disease (CAD), cerebral infarction, carotid atherosclerosis, chronic kidney disease and factors linked to atherosclerosis including hypertension, diabetes mellitus, dyslipidaemia, smoking and metabolic syndrome [57–60]. Furthermore, weight loss is associated with CAVI reduction [57]. The main advantages of CAVI include BP independence at the time of measurement, inclusion of the ascending aorta in the area of measurement and hence arterial function that might have a closer relationship to cardiac function, relative simplicity of the test and low cost [57]. CAVI provides additional information in comparison to traditional risk factors [58], and in view of its ease in measurement, it could be applied to clinical practice as a new independent risk factor for outcomes in CVD [58]. This will be discussed in further detail hereunder.

Arterial Stiffness and CV Risk

Arterial stiffness is associated with a range of CV risk factors, including increasing age [61], hypertension [62–64], hypercholesterolaemia [65, 66•], smoking [67], T2DM [68], impaired glucose tolerance [69] and visceral adiposity [70]. Increased arterial stiffness has been correlated with the presence and extent of atherosclerosis in the general population [44, 71–74]. Thus, in the Framingham Heart Study, aortic PWV was found to be predictive of the development of cardiac events, following adjustment for gender, systolic BP, lipid profile, antihypertensive medication, smoking and diabetes mellitus [75•]. This study included 2232 participants (mean age 63 years, 58% women) who were followed up for a total of 7.8 years. Results showed that an elevated PWV was associated with a 48% relative risk increase in CV events (95% CI 1.16–1.91), which was highly statistically significant ($P = 0.002$). The observational nature of the

Framingham study resolved the controversy with regard to the cause-and-effect relation between hypertension and arterial stiffness. In fact, interestingly, this study demonstrated that a high aortic stiffness was associated with a significantly increased risk of developing hypertension in previously normotensive individuals [62, 75•, 76•]. Likewise, the Rotterdam study, an observational prospective study comprising 2835 subjects without established CVD who were followed up for 4.1 years, showed that PWV > 14.6 m/s in men and > 14.2 m/s in women was significantly associated with risk of CVD (HR 1.93, 95% CI 1.16–3.21, $P = 0.001$) and CAD (HR: 2.17, 95% CI 1.08–3.98, $P = 0.02$); however, no correlation with the risk of stroke and overall mortality was noted [77•].

Arterial stiffness is one of the leading risk markers for hypertension. Masked uncontrolled hypertension (MUCH), defined as the presence of normal office BP but elevated ambulatory BP, is a challenging condition. A study including a total of 155 hypertensive patients were divided into controlled hypertension (CH), MUCH and sustained uncontrolled hypertension (SUCH) groups, respectively. SUCH is diagnosed with both uncontrolled office and ambulatory BP. Both MUCH and SUCH groups had a significantly higher CAVI than the CH group ($p < 0.017$ and $p < 0.002$ respectively). Multinomial logistic regression analysis showed that, compared with the CH group, increased CAVI levels were positively associated with the presence of MUCH and SUCH after adjusting for confounders. Therefore, CAVI may be used as a non-invasive indicator to identify patients with MUCH [82••]. Moreover, aortic PWV was also shown to independently predict CV events and fatal stroke [79] in a cohort of 710 patients with essential hypertension. Furthermore, at any given age, aortic PWV was the best predictor of CV mortality in hypertensive patients.

The impact of arterial stiffness was studied in various patient cohorts. Thus, for example, Muhammad et al. (2017) showed that subjects with PWV values at the highest quartile (median PWV 12.3 m/s) had a significantly higher risk (HR 3.24 [95% CI 1.51–6.97]) of developing T2DM compared to those in the first quartile (median PWV 9.93 m/s), after adjustment for baseline characteristics and CV risk factors ($P = 0.002$) [84]. Interestingly, subjects with T2DM exhibit progressive stiffening of central, rather than peripheral arteries, after adjustment for other risk factors, as opposed to the effects of age and systolic BP, whereby both central and peripheral arteries exhibit stiffening [85]. Furthermore, in subjects with T2DM, arterial stiffness serves as prognosticator of survival as well as diabetes-associated microvascular complications. With regard to the former, arterial stiffness as assessed using aortic PWV and HbA1c were the only statistically significant predictors of CV event-free survival in 761 subjects with T2DM aged between 55 and 65 years and followed up for a total of 7.9 years [86]. With regard to microvascular complications, patients with T2DM and increased urinary albumin-to-creatinine ratio (UACR) exhibit significantly higher PWV compared to patients with T2DM and normal UACR [86]. Similarly, each 1 m/s increment in cf-PWV increased by 11% the incidence rate of the development or progression of diabetic neuropathy, underlying the significant prognostic value of arterial stiffness [87–89].

The assessment of arterial stiffness can also be applied in the setting of ESRD. A study including one hundred fifty patients with ESRD aged 52 ± 16 years were monitored for 51 ± 38 months. A decrease in BP in subjects with ESRD was accompanied by a decline in PWV. Furthermore, a decrease in PWV levels by 1 m/s was associated with a 29% decrease in the risk for total mortality (RR 0.71, 95% CI 0.60–0.86, $P = 0.00001$) and a 21% decrease in the risk for CV mortality (RR 0.79, 95% CI 0.69–0.93, $P = 0.00001$), independent of age and BP [83]. Interestingly, subjects with diabetes and ESRD exhibit higher PWV than non-diabetic subjects with ESRD; in this patient cohort with PWV also predicted CV and all-cause mortality [80, 81], thus suggesting that more advanced atherosclerotic changes in those with diabetic ESRD contribute to the higher cardiovascular mortality rate of this population.

A meta-analysis of studies analysing PWV including 17 longitudinal studies that evaluated 15,877 subjects over a mean period of 7.7 years showed similar results. Several populations such as patients with hypertension, diabetes, ESRD, coronary artery disease and subjects from the general population or ethnic minorities were included. Age, sex and cardiovascular risk factors were controlled for in most of the studies. Results showed that the relative risk for the development of CV events was linearly related from the first to the third tertile of aortic pulse wave velocity. The pooled RRs of total CV events, CV mortality and all-cause mortality were 2.26 (95% CI 1.89–2.70, $P < 0.01$, 14 studies), 2.02 (95% CI 1.68–2.42, $P < 0.01$, 10 studies) and 1.90 (95% CI 1.61–2.24, $P < 0.01$, 11 studies), respectively, for high versus low aortic PWV subjects. Additionally, an increase in aortic PWV by 1 m/s corresponded to an age-, sex- and risk factor–adjusted risk increase of 14%, 15% and 15% in total CV events, CV mortality and all-cause mortality respectively [78].

Interestingly, an association has been identified between COVID-19 and arterial stiffness. Patients hospitalised due to acute COVID-19 infection were found to have increased arterial stiffness compared with COVID negative individuals, both during the acute infection and at follow up [90••, 91••]. Arterial stiffness as assessed by either PWV or by augmentation index remained elevated even 48 weeks after COVID-19 infection compared to controls [92••, 93••, 94••]. Those patients complaining of fatigue 4 months post COVID-19 infection had more impaired values of PWV compared with those without fatigue [95••]. The increased arterial stiffness following severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is possibly due to impairment of vascular smooth muscle cell function and structural changes of the extracellular matrix of the vascular wall that occur after viral binding to ACE2 receptors [90••]. Furthermore, overactivation of the renin–angiotensin–aldosterone system mediates increased arterial stiffness [90••]. The Working Group on Atherosclerosis and Vascular Biology together with the Council of Basic Cardiovascular Science of the ESC provided a position statement on the importance of the endothelium in the underlying pathophysiology behind the clinical presentation in COVID-19 and identify key questions for future research to address. They suggest the need of more studies on endothelial function in this context [96••].

Effect of Medications on Arterial Stiffness

Various randomized controlled trials using different medications have been carried out to assess the effects on arterial stiffness and CV outcomes. These include antihypertensive treatment, body weight reduction agents, statins and antidiabetic drugs. Therefore, measuring arterial stiffness may not only identify patients at risk at an early stage, but also serve as a surrogate index for treatment monitoring, as discussed hereunder.

The impact of antihypertensive medication on arterial stiffness was assessed in a subset of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA). In this study, a total of 19,257 hypertensive individuals were randomised to one of two treatment arms. Amlodipine plus perindopril was compared to standard therapy, which included the cardioselective beta blocker atenolol plus diuretic therapy in a prospective controlled randomised trial design. The administration of amlodipine plus perindopril was significantly more efficacious in the reduction of CV events ($p < 0.0001$), fatal and non-fatal stroke ($p = 0.0003$) and all-cause mortality ($p = 0.025$) than standard therapy, despite relatively equal modification of BP. The study was stopped prematurely after 5.5 years [97]. The results of this trial implied that clinical benefit may be related to other factors independent of BP modification. Subset analysis was thus performed to potentially provide insight into the mechanism of CV benefit; the Conduit Artery Function Evaluation (CAFÉ) trial subsequently analysed 2199 subjects enrolled in the ASCOT-BPLA study with determination of arterial stiffness and central aortic pressure. The results of the CAFÉ study showed that the amlodipine-based regimen reduced central aortic systolic, diastolic and pulse pressure and augmentation index [98]. Potential mechanisms include the fact that heart rate reduction with beta-blockade prolongs the cardiac ejection time, but has no effect on PWV. On the other hand, drugs that block the renin–angiotensin–aldosterone system, especially angiotensin II-converting enzyme inhibitors (ACEIs), are of particular interest as the renin–angiotensin–aldosterone system contributes to the modulation of arterial stiffness. In fact, ACEIs have been recommended by recent Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as the preferred agents to reduce arterial stiffness in patients with ESRD [99]. In the REASON study including 471 hypertensive patients followed up for 1 year, only the perindopril/indapamide combination significantly decreased carotid wave reflections, resulting in a selective decrease in central systolic BP and pulse pressure (PP), leading to a related reduction in left ventricular hypertrophy (LVH), in contrast to the lack of reduction in carotid PP and LVH observed with atenolol [100].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have gained increasing interest over the past few years in view of the significant positive outcome data with regard to CVD, especially in patients with T2DM, such that the 2019 ESC Guidelines on diabetes, pre-diabetes and CV diseases strongly recommend their use in patients with T2DM and CVD to reduce CV events (class I, level of evidence A) [101••]. SGLT2 inhibitors improve vascular function by increasing the bioavailability of nitric oxide in the endothelium and modulating the proliferation, migration, survival and senescence of endothelial cells. They decrease endothelial cell activation, stimulate direct vasorelaxation and ameliorate endothelial dysfunction or expression of pro-atherogenic cells and molecules. This anti-oxidant and anti-inflammatory effect slows arterial stiffening process in patients with diabetes (Fig. 3) [102, 103••]. A study carried out in aged mice, that assessed the effect of SGLT2 inhibition on arterial dysfunction and proteins associated with oxidative stress, showed promising results. Mesenteric artery endothelial function and stiffness and aortic stiffness in empagliflozin treated versus control mice was assessed. Mice treated with empagliflozin exhibited improved mesenteric endothelial function compared with control and reduced mesenteric artery and aortic stiffness. The findings suggest that empagliflozin improves endothelial function and reduces arterial stiffness in a preclinical animal models [105]. Further studies are needed to assess whether SGLT2 inhibition is a potential therapeutic alternative to reduce the progression of CVD in older individuals. Data from a subanalysis of the EMPA-REG OUTCOME trial had favourable effects on markers of arterial stiffness. This showed that treatment with empagliflozin resulted in a significant decrease in pulse pressure ($P < 0.001$), with a trend towards a reduction in AASI ($P = 0.059$) [104].

There is accumulating evidence of a favourable effect of statin treatment on arterial stiffness. In patients with hypercholesterolaemia treated with pravastatin for 6 months, significant decreases in PWV were seen in those with ≥ 15% reduction in total cholesterol levels [106]. In a similar study

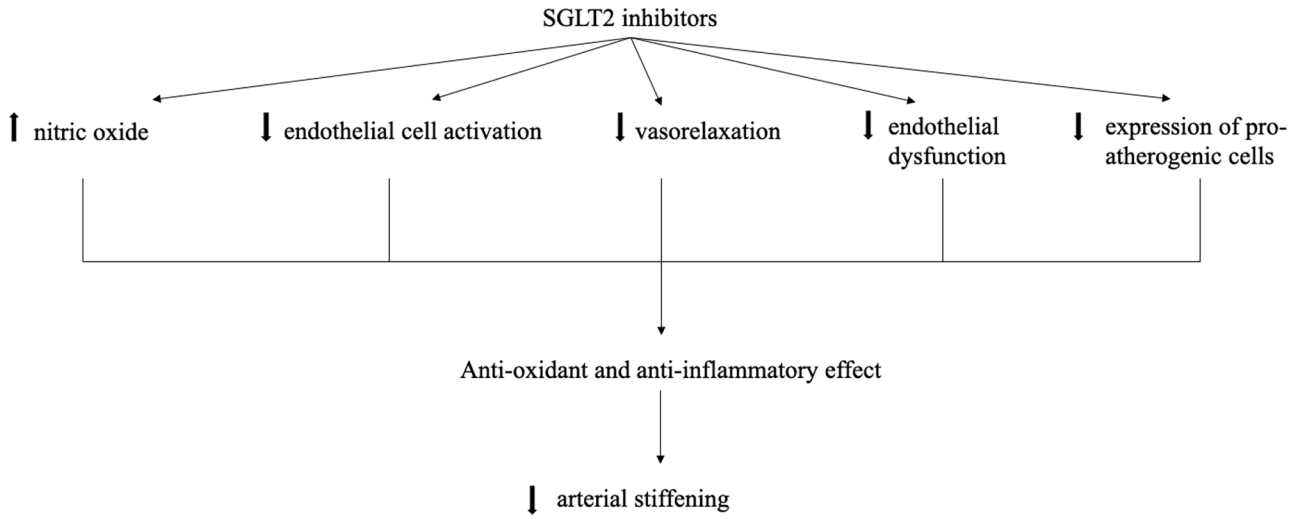

Fig.3 The role of SGLT2 inhibitors

group, the improvement in PWV with fluvastatin for 1 year correlated with the change in triglyceride levels [107]. Apart from the lipid lowering properties of statins, structural changes within the vessel wall may also contribute to their effects on arterial stiffness. Statins inhibit vascular smooth muscle cell proliferation which may decrease arterial stiffness [108, 109]. Interestingly, 3 months of atorvastatin therapy in patients with rheumatoid arthritis and relatively normal cholesterol levels improved systemic arterial compliance [110]. Another study showed that 3 months of atorvastatin therapy in patients with isolated systolic hypertension and normal lipid profiles resulted in a reduction in arterial stiffness [111]. Moreover, fluvastatin for 6 months reduced PWV in diabetic patients with ESRD undergoing haemodialysis [112]. However, neither ezetimibe monotherapy nor ezetimibe added to low-intensity simvastatin treatment had any effect on arterial stiffness [113, 114]. Interestingly, in patients with familial hypercholesterolaemia, addition of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-i) and ezetimibe to high-intensity statin improved lipid and PWV profiles. Patients with high-intensity statin, ezetimibe plus PCSK9-i versus high-intensity statin plus ezetimibe only were followed up for a total of six months. Patients in the PCSK9-i group had a greater LDL-C reduction (−51% vs −22.8% respectively, $P<0.001$) and a greater PWV reduction (−15% vs −8.5% respectively, $P<0.01$). Moreover, a decrease in PWV was associated with a decrease in LDL ($P=0.05$), and this relationship appeared to be stronger in patients with familial hypercholesterolaemia without CV events ($P=0.01$) [115].

Although measures of arterial 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 demonstrated. Importantly, it needs to be determined whether a reduction in PWV is associated with a concomitant reduction in CV events, independently of the normalisation of classical CV risk factors [116]. Hence, more studies are needed.

Conclusion

Arterial stiffness and its hemodynamic consequences are now established predictors of adverse CV outcomes. The measurement of arterial stiffness has been significantly refined and can be performed in an accurate and reproducible manner using a range of non-invasive techniques. Treatment options, which directly target the consequences of arterial stiffening, as opposed to arbitrary reduction of BP, have favourable outcomes. Hence, more emphasis should be given to the use of arterial stiffness for CV assessment and management in various patient populations, not only for research purposes but also in routine clinical practice to enable improved CV outcomes with reduced morbidity and mortality.

Compliance with Ethical Standards

Conflict of Interest The authors confirm that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Liao J, Farmer J. Arterial stiffness as a risk factor for coronary artery disease. Current Atherosclerosis Reports. 2014;16(2). https://doi.org/10.1007/s11883-013-0387-8.
2. Langille BL. Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix. J Cardiovasc Pharmacol. 1993;21(1):11–7. https://doi.org/10.1097/00005344-199321001-00003.
3. Gauthier-Bastien A, Ung R-V, Larivière R, Mac-Way F, Lebel M, Agharazii M. Vascular remodeling and media calcification increases arterial stiffness in chronic kidney disease. Clin Exp Hypertens. 2013;36(3):173–80. https://doi.org/10.3109/10641963.2013.804541.
4. London GM, Cohn JN. Prognostic application of arterial stiffness: task forces. Am J Hypertens. 2002;15(8):754–8. 6. https://doi.org/10.1016/s0895-7061(02)02966-7.
5. de Souza F, Muxfeldt ES, Salles GF. Prognostic factors in resistant hypertension: implications for cardiovascular risk stratification and therapeutic management. Expert Rev Cardiovasc Ther. 2012;10(6):735–45. https://doi.org/10.1586/erc.12.58.
6. Hooglugt A, Klatt O, Huveneers S. Vascular stiffening and endothelial dysfunction in atherosclerosis. Curr Opin Lipidol. 2022;33(6):353–63. https://doi.org/10.1097/MOL.0000000000000852.
7. Arribas SM, Hinek A, González MC. Elastic fibres and vascular structure in hypertension.Pharmacol Ther. 2006;111:771–791. https://doi.org/10.1016/j.pharmthera.2005.12.003.
8. Benetos A, Waeber B, Izzo J, Mitchell G, Lawrence R, Roland A, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. Am J Hypertens. 2002;15:1101–8. https://doi.org/10.1016/s0895-7061(02)03029-7.
9. •• Fantin F, Giani A, Trentin M, Rossi AP, Zoico E, Mazzali G, et al. The correlation of arterial stiffness parameters with aging and comorbidity burden. J Clin Med. 2022;11(19):5761.https://doi.org/10.3390/jcm11195761. **Recent study suggesting that arterial stiffness parameters can complement the characterization of patients affected by a remarkable comorbidity burden**.
10. Bonarjee VVS. Arterial stiffness: a prognostic marker in coronary heart disease. Available methods and clinical application. Front Cardiovasc Med. 2018;5:64. https://doi.org/10.3389/fcvm.2018.00064.
11. Ungvari Z, Gupte S, Recchia F, Batkai S, Pacher P. Role of oxidative-nitrosative stress and downstream pathways in various forms of cardiomyopathy and heart failure. Curr Vasc Pharmacol. 2005;3(3):221–9. https://doi.org/10.2174/1570161054368607.
12. Chowienczyk PJ, Watts GF, Cockcroft JR, Ritter JM. Impaired endothelium-dependent vasodilation of forearm resistance vessels in hypercholesterolaemia. Lancet. 1992;340(8833):1430–2. https://doi.org/10.1016/0140-6736(92)92621-l.
13. Britten MB, Zeiher AM, Volker Schächinger. Clinical importance of coronary endothelial vasodilator dysfunction and therapeutic options. J Intern Med. Wiley-Blackwell; 1999;245(4):315–27. https://doi.org/10.1046/j.1365-2796.1999.00449.x.
14. Zeiher AM, Drexler H, Saurbier B, Just H. Endothelium-mediated coronary blood flow modulation in humans. Effects of age, atherosclerosis, hypercholesterolemia, and hypertension. J Clin Invest. 1993;92(2):652–62. https://doi.org/10.1172/JCI116634.
15. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol. 2015;89:122–35. https://doi.org/10.1016/j.yjmcc.2015.01.021.
16. •• Hahad O, Arnold N, Prochaska JH, Panova-Noeva M, Schulz A, Lackner KJ, et al. Cigarette smoking is related to endothelial dysfunction of resistance, but not conduit arteries in the general population-results from the Gutenberg health study. Front Cardiovasc Med. 2021;8:674622. https://doi.org/10.3389/fcvm.2021.674622. **Findings from this study suggest that cigarette smoking is associated with altered endothelial function of resistance**.
17. Lavi S, Prasad A, Yang EH, Mathew V, Simari RD, Rihal CS, et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. Circulation. 2007;115(20):2621–7. https://doi.org/10.1161/CIRCULATIONAHA.106.641654.
18. •• Yang Q, Wang P, Cai Y, Cui Y, Cui J, Du X, et al. Circulating microRNA-505 may serve as a prognostic biomarker for hypertension-associated endothelial dysfunction and inflammation. Front Cardiovasc Med. 2022;9:834121. https://doi.org/10.3389/fcvm.2022.834121. **This study links for the first time miR-505 to endothelial dysfunction and inflammation under hypertensive conditions, supporting the translational value of miR-505 in prognosticating hypertension-associated endothelial impairment and inflammatory injuries in target organs such as the vessels and kidneys**.
19. Negro R. Endothelial effects of antihypertensive treatment: focus on irbesartan. Vasc Health Risk Manag. 2008;4(1):89–101. https://doi.org/10.2147/vhrm.2008.04.01.89.
20. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J Am Coll Cardiol. 1996;27(3):567–74. https://doi.org/10.1016/0735-1097(95)00522-6.
21. Bridger T. Childhood obesity and cardiovascular disease. Paediatr Child Health. 2009;14(3):177–82. https://doi.org/10.1093/pch/14.3.177.
22. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation. 2002;105(7):804–9. https://doi.org/10.1161/hc0702.104279.
23. Anderson TJ. Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. Can J Cardiol. 2006;22:72–80. https://doi.org/10.1016/s0828-282x(06)70990-4.
24. Wilkinson IB, MacCallum H, Cockcroft JR, Webb DJ. Inhibition of basal nitric oxide synthesis increases aortic augmentation index and pulse wave velocity in vivo. Br J Clin Pharmacol. 2002;53(2):189–92. https://doi.org/10.1046/j.1365-2125.2002.1528adoc.x.
25. McVeigh GE, Allen PB, Morgan DR, Hanratty CG, Silke B. Nitric oxide modulation of blood vessel tone identified by arterial waveform analysis. Clin Sci (Lond). 2001;100(4):387–93 PMID: 11256976.
26. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003;108(17):2054–9. https://doi.org/10.1161/01.CIR.0000089191.72957.ED.
27. Hadi HA, Carr CS, Al SJ. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag. 2005;1(3):183–98 PMID: 17319104.
28. Wilkinson IB, Mäki-Petäjä KM, Mitchell GF. Uses of arterial stiffness in clinical practice. Arterioscler Thromb Vasc Biol. 2020;40(5):1063–7. https://doi.org/10.1161/atvbaha.120.313130.
29. Verdecchia P, Angeli F, Taddei S. At the beginning of stiffening: endothelial dysfunction meets "pulsology." Hypertension. 2006;48(4):541–2. https://doi.org/10.1161/01.HYP.0000239236.12524.d3.
30. Bonarjee VVS. Arterial stiffness: a prognostic marker in coronary heart disease. Available Methods and Clinical Application.

Front Cardiovasc Med. 2018;5:64. https://doi.org/10.3389/fcvm.2018.00064.
31. Segers P, Rietzschel ER, Chirinos JA. Brief review on how to measure arterial stiffness in humans. Arterioscler Thromb Vasc Biol. 2019;40:1034–43. https://doi.org/10.1161/ATVBAHA.119.313132.
32. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang JG, Wilkinson IB, Williams B, Vlachopoulos C. Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension. 2007;50(1):154–60. https://doi.org/10.1161/HYPERTENSIONAHA.107.090068.
33. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. Hypertension. 2002;39(3):735–8. https://doi.org/10.1161/hy0202.098325.
34. Dolan E, Thijs L, Li Y, Atkins N, McCormack P, McClory S, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. Hypertension. 2006;47:365–70. https://doi.org/10.1161/01.HYP.0000200699.74641.c5.
35. Hansen TW, Li Y, Staessen JA, Jeppesen J, Rasmussen S, Wang JG, et al. Independent prognostic value of the ambulatory arterial stiffness index and aortic pulse wave velocity in a general population. J Hum Hypertens. 2008;22:214–6. https://doi.org/10.1038/sj.jhh.1002295.
36. Fantin F, Mattocks A, Bulpitt CJ, Banya W, Rajkumar C. Is augmentation index a good measure of vascular stiffness in the elderly? Age Ageing. 2007;36(1):43–8. https://doi.org/10.1093/ageing/afl115.
37. Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P, et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. Hypertension. 1996;27(2):168–75. https://doi.org/10.1161/01.hyp.27.2.168.
38. Franklin SS. Ageing and hypertension: the assessment of blood pressure indices in predicting coronary heart disease. J Hypertens Suppl. 1999;17(5):S29-36 PMID: 10706323.
39. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension. 2001;38(4):932–7. https://doi.org/10.1161/hy1001.096106.
40. Hayashi T, Nakayama Y, Tsumura K, Yoshimaru K, Ueda H. Reflection in the arterial system and the risk of coronary heart disease. Am J Hypertens. 2002;15(5):405–9. https://doi.org/10.1016/s0895-7061(02)02260-4.
41. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37(5):1236–41. https://doi.org/10.1161/01.hyp.37.5.1236.
42. Weber T, Auer J, O'rourke MF, Kvas E, Lassnig E, Lamm G, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. Eur Heart J. 2005;26(24):2657–63. https://doi.org/10.1093/eurheartj/ehi504.
43. London GM, Blacher J, Pannier B, Guérin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension. 2001;38(3):434–8. https://doi.org/10.1161/01.hyp.38.3.434.
44. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999;33(5):1111–7. https://doi.org/10.1161/01.hyp.33.5.1111.
45. Kim HL, Kim SH. Pulse wave velocity in atherosclerosis. Front Cardiovasc Med. 2019;6:41. https://doi.org/10.3389/fcvm.2019.00041.
46. Niiranen TJ, Kalesan B, Mitchell GF, Vasan RS. Relative contributions of pulse pressure and arterial stiffness to cardiovascular disease. Hypertension. 2019;73(3):712–7. https://doi.org/10.1161/HYPERTENSIONAHA.118.12289.
47. Bramwell JC, Hill AV. The velocity of pulse wave in man. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character. 1922;93(652):298–306.
48. Cheng HM, Chen CH. Measuring arterial stiffness in clinical practice: moving one step forward. J Clin Hypertens. 2020;22:1824–6. https://doi.org/10.1111/jch.13965.
49.• Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004;43(6):1239–45. https://doi.org/10.1161/01.HYP.0000128420.01881.aa. **Findings from this study suggest that in a healthy cohort with a minimal burden of cardiovascular disease risk factors, an age-related increase in aortic stiffness, as compared with peripheral arterial stiffness, is associated with increasing forward wave amplitude and pulse pressure and reversal of the arterial stiffness gradient**.
50.• Mendis S. The contribution of the Framingham Heart Study to the prevention of cardiovascular disease: a global perspective. Prog Cardiovasc Dis. 2010;53(1):10–4. https://doi.org/10.1016/j.pcad.2010.01.001. **The Framingham Heart Study has also been in the forefront of the development of cardiovascular risk prediction equations for assessment of absolute risk. The Framingham Study provided insights into the prevalence, incidence, prognosis, predisposing factors and determinants of CVD**.
51. Hasegawa M. Fundamental research on human aortic pulse wave velocity. Jikei Med J. 1970;85:742–60.
52. Emoto M, Nishizawa Y, Kawagishi T, Maekawa K, Hiura Y, Kanda H, et al. Stiffness indexes beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. Diabetes Care. 1998;21(7):1178–82. https://doi.org/10.2337/diacare.21.7.1178.
53. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb. 2006;13:101–7. https://doi.org/10.5551/jat.13.101.
54. Wohlfahrt P, Cífková R, Movsisyan N, Kunzová Š, Lešovský J, Homolka M, et al. Reference values of cardio-ankle vascular index in a random sample of a white population. J Hypertens. 2017;35:2238–44. https://doi.org/10.1097/HJH.0000000000001437.
55. Miyoshi T, Ito H. Assessment of arterial stiffness using the cardio-ankle vascular index. Pulse. 2016;4(1):11–23. https://doi.org/10.1159/000445214.
56. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. European network for non-invasive investigation of large arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588–2605. https://doi.org/10.1093/eurheartj/ehl254.
57. Dobsak P, Soska V, Sochor O, Jarkovsky J, Novakova M, Homolka M, et al. Increased cardio-ankle vascular index in hyperlipidemic patients without diabetes or hypertension. J Atheroscler Thromb. 2015;22(3):272–83. https://doi.org/10.5551/jat.24851.
58. Nagayama D, Watanabe Y, Saiki A, Shirai K, Tatsuno I. Lipid parameters are independently associated with cardio-ankle vascular index (CAVI) in healthy Japanese subjects. J Atheroscler Thromb. 2018;25(7):621–33. https://doi.org/10.5551/jat.42291.
59. Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H. Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. Circ J. 2008;72(4):598–604. https://doi.org/10.1253/circj.72.598.
60. Satoh N, Shimatsu A, Kato Y, Araki R, Koyama K, Okajima T, et al. Evaluation of the cardio-ankle vascular index, a new indicator of arterial stiffness independent of blood pressure, in obesity and metabolic syndrome. Hypertens Res. 2008;31(10):1921–30. https://doi.org/10.1291/hypres.31.1921.

61. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler Thromb Vasc Biol. 1998;18(1):127–32. https://doi.org/10.1161/01.atv.18.1.127.
62. Kaess BM, Rong J, Larson MG, Hamburg N, Vita J, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012;308(9):875–81. https://doi.org/10.1001/2012.jama.10503.
63. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37:1236–41. https://doi.org/10.1161/01.hyp.37.5.1236.
64. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, et al. Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. Circulation. 2002;105(10):1202–7. https://doi.org/10.1161/hc1002.105135.
65. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, et al. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. J Am Coll Cardiol. 2002;39(6):1005–11. https://doi.org/10.1016/s0735-1097(02)01723-0.
66.• Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. Circulation. 2007;115(20):2628–36. https://doi.org/10.1161/CIRCULATIONAHA.106.667733. **Findings from this study suggest that the prevalence of abnormal aortic stiffness increases steeply with advancing age, especially in the presence of obesity or diabetes**.
67. Stefanadis C, Tsiamis E, Vlachopoulos C, Stratos C, Toutouzas K, Pitsavos C, Marakas S, Boudoulas H, Toutouzas P. Unfavorable effect of smoking on the elastic properties of the human aorta. Circulation. 1997;95(1):31–8. https://doi.org/10.1161/01.cir.95.1.31.
68. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation. 1995;91(5):1432–43. https://doi.org/10.1161/01.cir.91.5.1432.
69. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation. 2002;106(16):2085–90. https://doi.org/10.1161/01.cir.0000033824.02722.f7.
70. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation. 2006;113(5):664–70. https://doi.org/10.1161/CIRCULATIONAHA.105.579342.
71. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005;111(25):3384–90. https://doi.org/10.1161/CIRCULATIONAHA.104.483628.
72. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113(5):657–63. https://doi.org/10.1161/CIRCULATIONAHA.105.555235.
73. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circ J. 2005;69(3):259–64. https://doi.org/10.1253/circj.69.259.
74. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002;39(1):10–5. https://doi.org/10.1161/hy0102.099031.
75.• Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study Circulation. 1999;100(4):354–60. https://doi.org/10.1161/01.cir.100.4.354. **Findings from this study suggest that higher pulse pressure is an important component of cardiovascular risk**.
76.• Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasan RS, Keaney JF Jr, et al. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation. 2004;109(5):613–9. https://doi.org/10.1161/01.CIR.0000112565.60887.1E. **Findings from this study suggest that increasing age, systolic blood pressure, and smoking are associated with lower flow-mediated dilation, whereas prior exercise and increasing heart rate were associated with higher flow-mediated dilation**.
77.• Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113(5):657–63. https://doi.org/10.1161/CIRCULATIONAHA.105.555235. **This study concluded that aortic pulse wave velocity is an independent predictor of coronary heart disease and stroke in healthy individuals**.
78. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318–27. https://doi.org/10.1016/j.jacc.2009.10.061.
79. Liao J, Farmer J. Arterial stiffness as a risk factor for coronary artery disease. Curr Atheroscler Rep. 2014;16(2):387. https://doi.org/10.1007/s11883-013-0387-8.
80. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999;99(18):2434–9. https://doi.org/10.1161/01.cir.99.18.2434.
81. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol. 2001;12(10):2117–24. https://doi.org/10.1681/ASN.V12102117.
82.•• Wang N, Guo Y, Li X, Dong Y, Liu Q, Wang G, et al. Association between cardio-ankle vascular index and masked uncontrolled hypertension in hypertensive patients: a cross-sectional study. J Atheroscler Thromb. 2022;2022(2):1–8. https://doi.org/10.1155/2022/3167518. **Findings of this study support, for the first time, the novel notion that cardio-ankle vascular index, as an arterial stiffness parameter, is an independent risk factor for masked uncontrolled hypertension**.
83. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation. 2001;103(7):987–92. https://doi.org/10.1161/01.cir.103.7.987.
84. Muhammad IF, Borné Y, Östling G, Kennbäck C, Gottsäter M, Persson M, et al. Arterial stiffness and incidence of diabetes: a population-based cohort study. Diabetes Care. 2017;40(12):1739–45. https://doi.org/10.2337/dc17-1071.
85. Kimoto E, Shoji T, Shinohara K, Inaba M, Okuno Y, Miki T, et al. Preferential stiffening of central over peripheral arteries in type 2 diabetes. Diabetes. 2003;52(2):448–52. https://doi.org/10.2337/diabetes.52.2.448.
86. Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. J Am Soc Nephrol. 2005;16(4):1069–75. https://doi.org/10.1681/ASN.2004090769.

87. Cardoso CR, Moran CB, Marinho FS, Ferreira MT, Salles GF. Increased aortic stiffness predicts future development and progression of peripheral neuropathy in patients with type 2 diabetes: the Rio de Janeiro Type 2 Diabetes Cohort Study. Diabetologia. 2015;58(9):2161–8. https://doi.org/10.1007/s00125-015-3658-9.
88. Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar ME, Ouerdane S, et al. Aortic stiffness and cardiovascular risk in type 2 diabetes. J Hypertens. 2013;31(8):1584–92. https://doi.org/10.1097/HJH.0b013e3283613074.
89. Wijkman M, Länne T, Östgren CJ, Nystrom FH. Aortic pulse wave velocity predicts incident cardiovascular events in patients with type 2 diabetes treated in primary care. J Diabetes Complications. 2016;30(7):1223–8. https://doi.org/10.1016/j.jdiacomp.2016.06.008.
90.•• Mavraganis G, Dimopoulou MA, Delialis D, Bampatsias D, Patras R, Sianis A, Maneta E, Stamatelopoulos K, Georgiopoulos G. Clinical implications of vascular dysfunction in acute and convalescent COVID-19: a systematic review. Eur J Clin Invest. 2022;52(11):e13859. https://doi.org/10.1111/eci.13859. **Recent study, suggesting a detrimental effect of COVID-19 on markers of endothelial function and arterial stiffness that could persist for months after the resolution of the infection**.
91.•• Schnaubelt S, Oppenauer J, Tihanyi D, et al. Arterial stiffness in acute COVID-19 and potential associations with clinical outcome. J Intern Med. 2021;290(2):437–43. https://doi.org/10.1111/joim.13275. **Findings from this study suggest that COVID-19 is related to enhanced pulse wave velocity, reflecting an increase in arterial stiffness**.
92.•• Ratchford SM, Stickford JL, Province VM, et al. Vascular alterations among young adults with SARS-CoV-2. Am J Physiol Heart Circ Physiol. 2021;320(1):404-410. https://doi.org/10.1152/ajpheart.00897. **This study was the first to investigate the vascular implications of contracting SARS-CoV-2 among young, otherwise healthy adults. The main findings from this study are a strikingly lower vascular function and a higher arterial stiffness compared with healthy controls. This suggests significant vascular effects seen weeks after contracting SARS-CoV-2 in young adults**.
93.•• Jud P, Gressenberger P, Muster V, et al. Evaluation of endothelial dysfunction and inflammatory vasculopathy after SARS-CoV-2 infection-a cross-sectional study. Front Cardiovasc Med. 2021;8:750887. https://doi.org/10.3389/fcvm.2021.750887. **Recent study suggesting that COVID-19 affects arterial stiffness, capillary morphology and selected parameters of arginine, kynurenine and homocysteine metabolism**.
94.•• Szeghy RE, Province VM, Stute NL, et al. Carotid stiffness, intima-media thickness and aortic augmentation index among adults with SARS-CoV-2. Exp Physiol. 2022;107(7):694-707. https://doi.org/10.1113/ep089481. **This study found that carotid stiffness and aortic augmentation index were greater in young adults who tested positive for SARS-CoV-2 compared with healthy young adults. These findings provide additional evidence for detrimental effects of SARS-CoV-2 on young adult vasculature, which might have implications for cardiovascular health**.
95.•• Zanoli L, Gaudio A, Mikhailidis DP, et al. Vascular dysfunction of COVID-19 is partially reverted in the long-term. Circ Res. 2022;130(9):1276-1285. https://doi.org/10.1161/circresaha.121.320460. **Recent study suggesting that COVID-19-related arterial stiffening involves several arterial tree portions and is partially resolved in the long-term**.
96.•• Evans PC, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Bäck M. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. Cardiovasc Res. 2020;116(14):2177–2184. https://doi.org/10.1093/cvr/cvaa230. **The Working Group on Atherosclerosis and Vascular Biology together with the Council of Basic Cardiovascular Science of the European Society of Cardiology provide a Position Statement on the importance of the endothelium in the underlying pathophysiology behind the clinical presentation in COVID-19 and identify key questions for future research to address. This position paper proposes that endothelial biomarkers and tests of function should be evaluated for their usefulness in the risk stratification of COVID-19 patients**.
97. Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet. 2005;366(9489):907–13. https://doi.org/10.1016/S0140-6736(05)67186-3.
98. Williams B, Lacy PS; CAFE and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Investigators. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. J Am Coll Cardiol. 2009;54(8):705–13. https://doi.org/10.1016/j.jacc.2009.02.088.
99. Mallareddy M, Parikh CR, Peixoto AJ. Effect of angiotensin-converting enzyme inhibitors on arterial stiffness in hypertension: systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2006;8(6):398–403. https://doi.org/10.1111/j.1076-7460.2006.05418.x.
100. Asmar RG, London GM, O'Rourke ME, Safar ME; REASON Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension. 2001;38(4):922–6.https://doi.org/10.1161/hy1001.095774.
101.••Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. https://doi.org/10.1093/eurheartj/ehz486. **The emphasis in these guidelines is to provide information on the current state of the art in how to prevent and manage the effects of diabetes mellitus on the heart and vasculature**.
102. Adam CA, Anghel R, Marcu DTM, Mitu O, Roca M, Mitu F. Impact of sodium–glucose cotransporter 2 (SGLT2) inhibitors on arterial stiffness and vascular aging—what do we know so far? (a narrative review). Life. 2022;12:803. https://doi.org/10.3390/life12060803.
103.••Patoulias D, Papadopoulos C, Stavropoulos K, Zografou I, Doumas M, Karagiannis A. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. The Journal of Clinical Hypertension. 2020;22(4):562–71. https://doi.org/10.1111/jch.13831. **This paper summarised knowledge regarding the prognostic role of arterial stiffness in type 2 diabetes mellitus, along with the presentation of retrieved data on the potential role of sodium-glucose co-transporter-2 inhibitors**.
104. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab. 2015;17(12):1180–93. https://doi.org/10.1111/dom.12572.
105. Soares RN, Ramirez-Perez FI, Cabral-Amador FJ, Morales-Quinones M, Foote C, Ghiarone T, et al. SGLT2 inhibition attenuates arterial dysfunction and decreases vascular F-actin content and expression of proteins associated with oxidative stress in aged mice. GeroScience. 2022;44:1657–75. https://doi.org/10.1007/s11357-022-00563-x.

106. Muramatsu J, Kobayashi A, Hasegawa N, Yokouchi S. Hemodynamic changes associated with reduction in total cholesterol by treatment with the HMG-CoA reductase inhibitor pravastatin. Atherosclerosis. 1997;130(1–2):179–82. https://doi.org/10.1016/s0021-9150(96)06024-8.
107. Yokoyama H, Kawasaki M, Ito Y, Minatoguchi S, Fujiwara H. Effects of fluvastatin on the carotid arterial media as assessed by integrated backscatter ultrasound compared with pulse-wave velocity. J Am Coll Cardiol. 2005;46(11):2031–7. https://doi.org/10.1016/j.jacc.2005.06.084.
108. Laufs U, Marra D, Node K, Liao JK. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of p27(Kip1). J Biol Chem. 1999;274(31):21926–31. https://doi.org/10.1074/jbc.274.31.21926.
109. Yang Z, Kozai T, van der Loo B, Viswambharan H, Lachat M, Turina MI, et al. HMG-CoA reductase inhibition improves endothelial cell function and inhibits smooth muscle cell proliferation in human saphenous veins. J Am Coll Cardiol. 2000;36(5):1691–7. https://doi.org/10.1016/s0735-1097(00)00924-4.
110. Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Ann Rheum Dis. 2004;63(12):1571–5. https://doi.org/10.1136/ard.2003.018333.
111. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, Kingwell BA. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol. 2002;39(6):1020–5. https://doi.org/10.1016/s0735-1097(02)01717-5.
112. Adams SP, Sekhon SS, Tsang M, Wright JM. Fluvastatin for lowering lipids. Cochrane Database Syst Rev. 2018;3(3):CD012282. https://doi.org/10.1002/14651858.CD012282.pub2.
113. Efrati S, Averbukh M, Dishy V, Faygenzo M, Friedensohn L, Golik A. The effect of simvastatin, ezetimibe and their combination on the lipid profile, arterial stiffness and inflammatory markers. Eur J Clin Pharmacol. 2007;63(2):113–21. https://doi.org/10.1007/s00228-006-0238-4.
114. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Endothelial function, arterial stiffness and lipid lowering drugs. Expert Opin Ther Targets. 2007;11(9):1143–60. https://doi.org/10.1517/14728222.11.9.1143.
115. Mandraffino G, Scicali R, Rodríguez-Carrio J, Savarino F, Mamone F, Scuruchi M, et al. Arterial stiffness improvement after adding on PCSK9 inhibitors or ezetimibe to high-intensity statins in patients with familial hypercholesterolemia: A Two-Lipid Center Real-World Experience. J Clin Lipidol. 2020;14(2):231–40. https://doi.org/10.1016/j.jacl.2020.01.015.
116. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. Am J Hypertens. 2002;15(5):445–52. https://doi.org/10.1016/s0895-7061(01)02326-3.